



# Effective Health Care Program

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Comparative Effectiveness Review  
Number 116

## **Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism Among Special Populations**



Agency for Healthcare Research and Quality  
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## **Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism Among Special Populations**

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## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see [www.effectivehealthcare.ahrq.gov/reference/purpose.cfm](http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm)

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

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# Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism Among Special Populations

## Structured Abstract

**Background.** Venous thromboembolism (VTE) is a prevalent and avoidable complication of hospitalization. Patients hospitalized with trauma, traumatic brain injury, burns, or liver disease; patients on antiplatelet therapy; obese or underweight patients; those having obesity surgery; or with acute or chronic renal failure have unequal risks for bleeding and thrombosis and may benefit differently from prophylactic therapy medication.

**Objectives.** To systematically review the comparative effectiveness and safety of pharmacological and mechanical methods of prophylaxis of VTE in these special populations.

**Data sources.** We searched MEDLINE<sup>®</sup>, Embase<sup>®</sup>, SCOPUS, CINAHL<sup>®</sup>, www.clinicaltrials.gov, International Pharmaceutical Abstracts (IPA), and the Cochrane Library in July 2012. This was complemented by hand searches from the reference lists and unpublished studies provided by sponsors.

**Review methods.** We included randomized controlled trials on these special populations. Since these populations may be excluded from trials, we also included controlled observational studies of pharmacologic agents, and uncontrolled observational studies and case series of inferior vena cava (IVC) filter use. Two reviewers evaluated studies for eligibility, serially abstracted data using standardized forms, and independently evaluated the risk of bias in the studies and strength of evidence for major outcomes and comparisons. We qualitatively synthesized the evidence and also pooled the relative risks from the controlled studies.

**Results.** After a review of 30,902 unique citations, we included 101 studies of which just 6 were trials. The majority of observational studies had a high risk of bias. The strength of evidence is low that IVC filter placement is associated with a lower incidence of pulmonary embolism and fatal pulmonary embolism in hospitalized patients with trauma compared with no IVC filter placement. The strength of evidence is low that enoxaparin reduces deep vein thrombosis and that unfractionated heparin reduces mortality in patients with traumatic brain injury when compared with patients without anticoagulation. Low-grade evidence supports the idea that IVC filters with usual care are associated with increased mortality and do not decrease the risk of pulmonary embolism in patients undergoing bariatric surgery compared with usual care alone. All other comparisons, for all of the Key Questions, had insufficient evidence to permit conclusions.

**Conclusions.** Our systematic review demonstrates that there is a paucity of high-quality evidence to inform treatment of these special populations. Future research using robust observational studies that control for confounding by indication and disease severity are needed as randomized controlled trials typically exclude or do not report on these populations.

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# Executive Summary

## Introduction

## Background

Pulmonary embolism (PE) and deep vein thrombosis (DVT) are collectively known as venous thromboembolism (VTE). VTE affects an estimated 900,000 Americans every year, resulting in significant morbidity and mortality.<sup>1,2</sup> Although the average annual incidence of DVT currently ranges from 48 to 122 per 100,000 in the United States,<sup>1,2</sup> rates will rise with the aging population. There are significant adverse consequences of DVT and PE,<sup>1</sup> including an estimated 300,000 fatalities annually and hundreds of thousands of hospitalizations in nonfatal cases.<sup>1,2</sup> In addition, a diagnosis of DVT or of PE in the hospital increases the costs of the hospitalization by roughly \$10,000 and \$20,000, respectively.<sup>3</sup> Thus, VTE is an important patient safety issue with significant morbidity, mortality, and health care costs.<sup>4</sup> Accordingly, the comparative effectiveness and safety of interventions for the prevention and treatment of VTE are among the national priorities for comparative effectiveness research.<sup>5</sup> In this review, we describe the evidence about prevention of DVT in “special populations.” Special populations are those patients for whom the benefit and risk of VTE prophylaxis are uncertain, or patients for whom there is decisional uncertainty about the optimal choice, timing, and dose of VTE prophylaxis, or significant practice variation. The burden of VTE is higher among some patient populations, including patients who have experienced recent trauma,<sup>6-11</sup> traumatic brain injury or burns;<sup>12-14</sup> patients undergoing bariatric surgery;<sup>15-21</sup> and patients with acute renal failure, chronic renal failure, or end-stage renal disease.<sup>22-25</sup> Some of these patient groups have a high risk of bleeding, the most important complication of VTE prophylaxis. Therefore, the risk-benefit ratio of prophylactic medications in these populations is uncertain and is similarly unclear for patients with altered clearance of medications.<sup>26-30</sup>

## Therapies of Interest

In this review, we describe the evidence for drugs and devices that are currently available in the United States, and are either FDA approved for VTE prophylaxis or are used off label by clinicians for this indication. We included studies of unfractionated heparin (UFH) and low molecular weight heparins (LMWH) delivered subcutaneously,<sup>26-29</sup> as well as fondaparinux, a synthetic pentasaccharide. Similarly, we included antiplatelet agents aspirin and clopidogrel; as well as the anticoagulant warfarin, which clinicians may use off label for this indication. We also included dabigatran, a recently approved oral anticoagulant that directly inhibits thrombin; the FDA-approved dabigatran for the prevention of stroke in patients with atrial fibrillation, but it also has the potential for off-label use for prophylaxis of VTE. Rivaroxaban was included; it is an oral factor Xa inhibitor that the FDA approved in July 2011 for VTE prophylaxis for patients undergoing elective hip and knee arthroplasty. This drug also has the potential for off-label use in other patient populations. We also included sequential compression devices, venous foot pumps, and various types of IVC filters.<sup>4</sup>

## **Key Questions**

This report includes our review of the evidence on the efficacy, effectiveness, and safety of pharmacological and mechanical methods of prophylaxis in our defined special populations. The Key Questions (KQs) we explored are as follows:

KQ 1. What are the comparative effectiveness and safety of IVC filters to prevent PE in hospitalized patients with trauma?

KQ 2a. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with traumatic brain injury?

KQ 2b. What is the optimal timing of initiation and duration of pharmacologic prophylaxis to prevent VTE in hospitalized patients with traumatic brain injury?

KQ 3. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns?

KQ 4. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with liver disease?

KQ 5. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients receiving antiplatelet therapy?

KQ 6. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in patients having bariatric surgery?

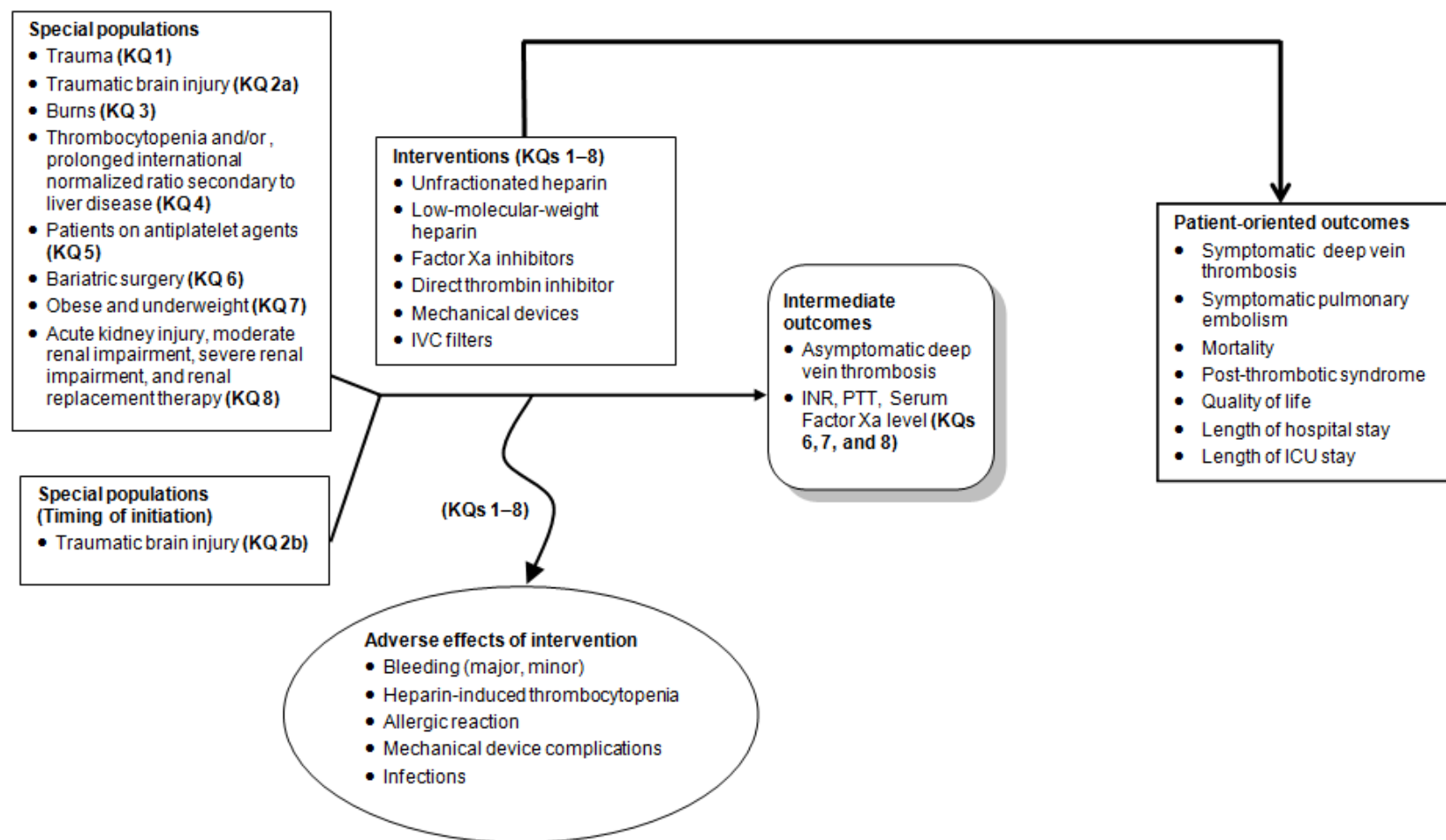
KQ 7. What are the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of obese and underweight patients?

KQ 8. What are the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis?

## Framework

Our conceptual model for the systematic review is presented in Figure A. The figure illustrates the special populations of interest, therapies, and intermediate and clinical outcomes we reviewed, as well as the adverse consequences associated with these prophylactic regimens.

**Figure A. Analytic framework: Pharmacologic and mechanical prophylaxis of venous thromboembolism among special populations**



INR = international normalized ratio; IVC = inferior vena cava; KQ = Key Question; PTT = partial thromboplastin time

## Methods

The methods for this comparative effectiveness review (CER) follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) “Methods Guide for Effectiveness and Comparative Effectiveness Reviews” ([www.effectivehealthcare.ahrq.gov/methods-guide.cfm](http://www.effectivehealthcare.ahrq.gov/methods-guide.cfm)).

## Search Strategy

We searched the following databases for primary studies through July 2012: MEDLINE<sup>®</sup>, Embase<sup>®</sup>, SCOPUS, CINAHL<sup>®</sup>, International Pharmaceutical Abstracts, [clinicaltrials.gov](http://clinicaltrials.gov), and the Cochrane Library. We developed a search strategy for MEDLINE, accessed via PubMed<sup>®</sup>, based on medical subject headings (MeSH<sup>®</sup>) terms and text words of key articles that we identified a priori (Appendix B). We reviewed the reference lists of all included articles, relevant review articles, and related systematic reviews to identify articles that may have been missed in the original search. In addition, we requested and reviewed Scientific Information Packets (SIPs) provided by the pharmaceutical manufacturers.

## Study Selection

We reviewed titles followed by abstracts to identify randomized controlled trials (RCTs) or observational studies with comparison groups reporting on the effectiveness or safety of venous thromboembolism prevention in our populations. Two investigators independently reviewed abstracts; we excluded abstracts only if both investigators agreed that the article met one or more of the exclusion criteria. We resolved disagreements by consensus. The inclusion and exclusion criteria are shown in Table A. The population, intervention, comparator, outcome, timing, and setting are shown in Table B.

## Data Abstraction and Data Management

We used DistillerSR (Evidence Partners, 2010) to manage the screening and review process. DistillerSR is a Web-based database management program that manages all levels of the review process.

## Assessment of Methodological Quality of Individual Studies

We conducted the risk of bias assessment in duplicate using the Downs and Black instrument for observational studies and trials.<sup>31</sup> We found that 10 items were most relevant to this review and we prioritized them in our assessment of risk of bias. We did not consider any study without randomization to have a low risk of bias.

## Data Synthesis and Analysis

For each KQ, we created a detailed set of evidence tables containing all information abstracted from eligible studies, and grouped the information by comparison interventions and qualitatively synthesize the results. For studies amenable to pooling quantitatively, we conducted meta-analysis using relative risks by using a DerSimonian and Laird random effects model.<sup>32</sup> Since most of the outcomes were rare and several studies had zero events, we used the treatment arm continuity correction to estimate the relative risk.<sup>33</sup> We conducted sensitivity analysis using alternative continuity corrections (0.5, 0.1), as well as no continuity correction (Peto Odds

Ratio).<sup>33</sup> All analyses were conducted using Stats Direct and Stata version 11.0. When there was substantial statistical and clinical heterogeneity we did not report pooled results but displayed the relative risks with 95% confidence intervals for the individual studies. For KQ 1, we calculated 95% exact binomial confidence intervals surrounding the proportions of patients experiencing events in each of the observational studies. These were plotted ordered by the year of the study, with the size of the box representing the number of individuals in the denominator.

## Grading the Evidence for Each KQ

After synthesizing the evidence, we graded the quantity, quality, and consistency of the best available evidence addressing KQs 1 to 8 by adapting an evidence grading scheme recommended in the “Methods Guide for Comparative Effectiveness Reviews.”<sup>34</sup> In assigning evidence grades, we considered the four recommended domains: risk of bias in the included studies, directness of the evidence, consistency across studies, and precision of the pooled estimate or the individual study estimates. We found that few of the studies reported precision, although we were able to calculate confidence intervals for some of the outcomes. We classified evidence pertaining to KQs 1 to 8 into four categories:

1. *High* grade (indicating high confidence that the evidence reflects the true effect, and further research is very unlikely to change our confidence in the estimate of the effect)
2. *Moderate* grade (indicating moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of the effect and may change the estimate)
3. *Low* grade (indicating low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate)
4. *Insufficient* grade (evidence is unavailable). A single high risk or moderate risk of bias study was considered to be insufficient evidence.

## Assessing Applicability

We assessed applicability of the evidence separately for the outcomes of benefit (reduction in VTE) and harm (increased risk of bleeding) as recommended in the “Methods Guide for Comparative Effectiveness Reviews of Interventions.”<sup>34</sup> We evaluated whether the included populations in these studies were representative of participants in the real world. We assessed whether the concomitant interventions administered in these studies were also representative of real-world management strategies for these special populations. We assessed whether there were features of the individual studies that limited the applicability of the study’s findings, including whether studies excluded patients with comorbidities, whether studies allowed or disallowed the concomitant use of nonmedical co-interventions (early ambulation), and the choice and dosing of comparators.

## Peer Review and Public Comment

A full draft report was reviewed by experts and posted for public commentary from August 2, 2012, through August 30, 2012. Comments received from either invited reviewers or through the public comment Web site were compiled and addressed. A disposition of comments will be posted on the Effective Health Care Program Web site 3 months after the release of the evidence report.

**Table A. Study inclusion and exclusion criteria**

Category	Inclusion Criteria	Exclusion Criteria
<b>Populations</b>	<ul style="list-style-type: none"> <li>• Human subjects (only)</li> <li>• Adults in special patient populations, including: <ul style="list-style-type: none"> <li>○ Trauma</li> <li>○ Traumatic brain injury</li> <li>○ Burns</li> <li>○ Liver disease</li> <li>○ Antiplatelet therapy</li> <li>○ Bariatric surgery</li> <li>○ Obese and underweight</li> <li>○ Acute kidney injury, moderate renal impairment,</li> <li>○ severe renal impairment, renal replacement therapy</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Animal studies/models</li> <li>• Children</li> <li>• Pediatric</li> <li>• Adolescent</li> <li>• Adults in the following patient populations: <ul style="list-style-type: none"> <li>○ Treatment of VTE</li> <li>○ Secondary prophylaxis</li> <li>○ Catheter thrombosis</li> <li>○ Antiphospholipid antibodies/other autoimmune diseases</li> <li>○ Cancer (malignancy, chemotherapy, radiotherapy)</li> <li>○ Cardiovascular (coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty) patients on full-dose anticoagulation</li> <li>○ Pregnancy</li> <li>○ Disseminated intravascular coagulation</li> <li>○ Heparin-induced thrombocytopenia</li> <li>○ Congenital platelet disorders</li> <li>○ VTE prophylaxis for long distance travel</li> <li>○ Abdominal surgery</li> <li>○ Vascular surgery</li> <li>○ Urological surgery</li> <li>○ Gynecological surgery</li> </ul> </li> </ul>
<b>Intervention</b>	Studies that evaluate interventions or mechanical devices	Studies of agents that have not been approved for thromboprophylaxis in the United States or interventions not available in the United States will not be evaluated
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Symptomatic deep vein thrombosis</li> <li>• Symptomatic pulmonary embolism</li> <li>• Mortality</li> <li>• Post-thrombotic syndrome</li> <li>• Quality of life</li> <li>• Length of hospital stay</li> <li>• Length of ICU stay</li> <li>• Bleeding (major, minor)</li> <li>• Heparin-induced thrombocytopenia</li> <li>• Allergic reaction</li> <li>• Mechanical device complications</li> <li>• Infections</li> <li>• Asymptomatic deep vein thrombosis</li> </ul> <p>INR, PTT, factor Xa level (KQs 6, 7 and 8)</p>	No data on relevant outcomes of interest



**Table A. Study inclusion and exclusion criteria (continued)**

Category	Inclusion	Exclusion
<b>Type of Study</b>	<p>We included the following study designs</p> <ul style="list-style-type: none"> <li>• Randomized controlled trials</li> <li>• Prospective cohort studies</li> <li>• Retrospective cohort studies</li> <li>• Case-control studies</li> <li>• Uncontrolled case-series for devices</li> <li>• Case reports of device complications in the relevant special populations</li> <li>• Case reports of pharmacologic therapies other than the known complications of bleeding and heparin-induced thrombocytopenia</li> </ul>	<ul style="list-style-type: none"> <li>• Case reports of efficacy</li> <li>• Case reports of bleeding or heparin-induced thrombocytopenia associated with pharmacologic strategies</li> <li>• In vitro studies</li> <li>• Animal studies</li> <li>• Cost-effectiveness studies</li> <li>• Modeling studies</li> <li>• Risk assessment studies</li> <li>• Registries without descriptions of interventions</li> <li>• Diagnostic studies</li> <li>• Ecologic study designs</li> <li>• Time-series designs</li> <li>• No original data, commentary, or editorial</li> </ul> <p>Systematic reviews and meta-analysis</p>

ICU = intensive care unit; INR = international normalized ratio; PTT = partial thromboplastin time; VTE = venous thromboembolism

**Table B. PICOTS (population, intervention, comparator, outcome, timing, and setting) for each Key Question**

PCIOTS	KQ 1	KQ 2	KQ 3–KQ 5	KQ 6	KQ 7–KQ 8
<b>Population(s)</b>	<ul style="list-style-type: none"> <li>Trauma</li> </ul>	<ul style="list-style-type: none"> <li>Traumatic brain injury</li> </ul>	<ul style="list-style-type: none"> <li>Burns (KQ 3)</li> <li>Liver disease (KQ 4)</li> <li>Antiplatelet therapy (KQ 5)</li> </ul>	<ul style="list-style-type: none"> <li>Bariatric surgery</li> </ul>	<ul style="list-style-type: none"> <li>Obese and underweight patients (KQ 7)</li> <li>Patients with acute kidney injury or moderate or severe renal impairment (KQ 8)</li> <li>Patients receiving dialysis (KQ 8)</li> </ul>
<b>Interventions</b>	<ul style="list-style-type: none"> <li>IVC filters</li> </ul>	<ul style="list-style-type: none"> <li>Mechanical devices</li> <li>Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors)</li> <li>IVC filters</li> </ul>	<ul style="list-style-type: none"> <li>Mechanical devices</li> <li>Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors)</li> </ul>	<ul style="list-style-type: none"> <li>Pharmacologic (UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors)</li> <li>Mechanical devices</li> <li>IVC filters</li> </ul>	<ul style="list-style-type: none"> <li>Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors)</li> <li>Mechanical devices</li> </ul>
<b>Comparators</b>	<ul style="list-style-type: none"> <li>No IVC filters. (Studies that included usual care or those that did not use IVC filters as active controls including mechanical prophylaxis (e.g., SCDs, compression stockings) and pharmacologic controls)</li> </ul>	<ul style="list-style-type: none"> <li>Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis</li> <li>Placebo-controlled studies, studies that used active controls, and uncontrolled studies</li> </ul>	<ul style="list-style-type: none"> <li>Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis</li> <li>Placebo-controlled studies, studies that used active controls, and uncontrolled studies</li> </ul>	<ul style="list-style-type: none"> <li>Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis</li> <li>Placebo-controlled studies, or studies that used active controls, and uncontrolled studies</li> </ul>	<ul style="list-style-type: none"> <li>Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis</li> <li>Placebo-controlled studies, studies that used active controls, and uncontrolled studies</li> </ul>

**Table B. PICOTS (population, intervention, comparator, outcome, timing, and setting) for each Key Question (continued)**

PICOTS	KQ 1	KQ 2	KQ 3–KQ 5	KQ 6	KQ 7–KQ 8
<b>Outcomes measures</b>	<ul style="list-style-type: none"> <li>• Symptomatic DVT</li> <li>• Symptomatic PE</li> <li>• Asymptomatic DVT</li> <li>• Bleeding</li> <li>• Mortality</li> <li>• Post-thrombotic syndrome</li> <li>• Quality of life</li> <li>• Length of stay</li> <li>• Allergic reaction</li> <li>• Mechanical device complications</li> <li>• Infections</li> </ul>	<ul style="list-style-type: none"> <li>• Symptomatic DVT</li> <li>• Symptomatic PE</li> <li>• Asymptomatic DVT</li> <li>• Bleeding</li> <li>• Mortality</li> <li>• Post-thrombotic syndrome</li> <li>• Quality of life</li> <li>• Length of stay</li> <li>• Length of ICU stay</li> <li>• Heparin-induced thrombocytopenia</li> <li>• Allergic reaction</li> <li>• Mechanical device complications</li> <li>• Infections</li> </ul>	<ul style="list-style-type: none"> <li>• Symptomatic DVT</li> <li>• Symptomatic PE</li> <li>• Asymptomatic DVT</li> <li>• Bleeding</li> <li>• Mortality</li> <li>• Post-thrombotic syndrome</li> <li>• Quality of life</li> <li>• Length of stay</li> <li>• Heparin-induced thrombocytopenia</li> <li>• Allergic reaction</li> <li>• Mechanical device complications</li> <li>• Infections</li> </ul>	<ul style="list-style-type: none"> <li>• Symptomatic DVT</li> <li>• Symptomatic PE</li> <li>• Asymptomatic DVT</li> <li>• Bleeding</li> <li>• Mortality</li> <li>• Post-thrombotic syndrome</li> <li>• Quality of life</li> <li>• Length of stay</li> <li>• Heparin-induced thrombocytopenia</li> <li>• Allergic reaction</li> <li>• Mechanical device complications</li> <li>• Infections</li> </ul>	<ul style="list-style-type: none"> <li>• Symptomatic DVT</li> <li>• Symptomatic PE</li> <li>• Asymptomatic DVT</li> <li>• Bleeding</li> <li>• Mortality</li> <li>• INR, PTT, Factor Xa level (<b>KQs 7 and 8</b>)</li> <li>• Post-thrombotic syndrome</li> <li>• Quality of life</li> <li>• Length of stay</li> <li>• Bleeding (major, minor)</li> <li>• Heparin-induced thrombocytopenia</li> <li>• Allergic reaction</li> <li>• Mechanical device complications</li> <li>• Infections</li> </ul>
<b>Adverse effects of intervention(s) and treatment burden</b>	<ul style="list-style-type: none"> <li>• Major bleeding defined as including: fatal bleeding; clinically overt bleeding causing a fall in hemoglobin of <math>\geq 2</math> g/dL or leading to transfusion of two or more units of packed cells or whole blood; or bleeding into critical organs (retroperitoneal or intracranial)</li> <li>• In surgical patients: an assessment of the amount of blood loss, minor bleeding, surgical site bleeding, and complications from mechanical IVC filters (e.g., device migration, perforation, fractures, filter thrombosis, infections, prolonged hospitalization, mortality)</li> </ul>				
<b>Timings</b>	<ul style="list-style-type: none"> <li>• Studies with all durations of followup</li> </ul>				
<b>Settings</b>	• Hospital setting	• Hospital setting	• Hospital setting	• Hospital setting	• Hospital setting

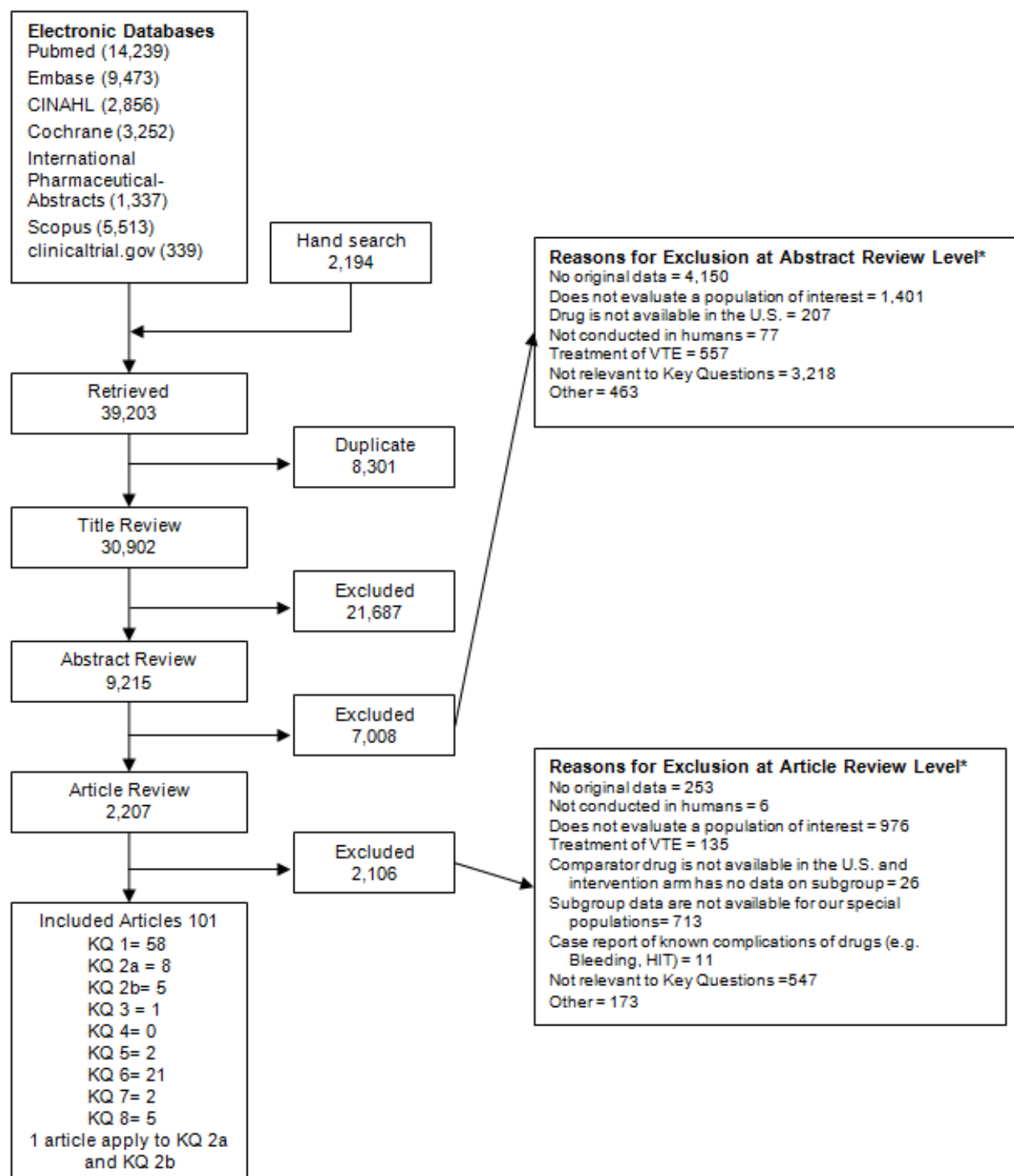
DVT = deep vein thrombosis; INR = international normalized ratio; IVC = inferior vena cava; KQ = Key Question; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PTT = partial thromboplastin time; SCD = sequential circumferential compression device; UFH = unfractionated heparin

## Results

### Search Results

Figure B summarizes the search results. The literature search identified 30,902 unique citations. We excluded 21,687 of these citations during title screening, and 7,008 during abstract screening. An additional 2,106 articles were excluded at the article screening level because they did not meet one or more of the inclusion criteria (Table A). One hundred and one articles were included in the review. Only six were randomized controlled trials. Of the included studies, 58 studies compared the effects of IVC filter use in patients with trauma, 12 studies compared the effects of pharmacoprophylaxis in patients with traumatic brain injury, and one study reported on patients with burns. We did not identify any studies among patients with liver failure. Twenty-one studies reported on patients with obesity surgery, two reported on antiplatelet therapy, and five reported on patients with renal failure.

**Figure B. Summary of the literature search**



HIT = heparin induced thrombocytopenia; KQ = Key Question; VTE = venous thromboembolism

\*Total exceeds the number in the exclusion box because reviewers were allowed to mark more than one reason for exclusion.

## Results by Population

### KQ 1. Patient With Trauma

Fifty-eight studies addressed this KQ. Most studies had a high risk of bias except five observational studies that had a moderate risk of bias (Table C).

- The strength of evidence is low that IVC filter placement is associated with a lower incidence of PE compared with no IVC filter placement.
- The strength of evidence is low that IVC filter placement is associated with a lower incidence of fatal PE compared with no IVC filter placement.
- The strength of evidence is insufficient that IVC filter placement is associated with less mortality compared with no IVC filter placement.
- The strength of evidence is insufficient that IVC filter placement is associated with a higher incidence of DVT compared with no IVC filter placement.
- The strength of evidence is insufficient that IVC filter placement is associated with filter related thrombosis.
- The strength of evidence is insufficient that IVC filter placement is associated with filter tilt/migration.

### KQ 2a. Patients With Traumatic Brain Injury

There were eight studies that evaluated the effectiveness and safety of pharmacological and mechanical strategies in patients with traumatic brain injury. Most studies had a high risk of bias (Table C). The insufficient strength of evidence rating was based on either inconsistency in the body of evidence, our inability to assess consistency (consistency unknown), imprecision in the outcomes reported, or a high risk of bias in the included studies.

- The strength of evidence is low that enoxaparin reduces the rates of DVT compared with no pharmacoprophylaxis.
- The strength of evidence is low that UFH reduces total mortality compared with no pharmacoprophylaxis.
- The strength of evidence is insufficient to comment on the comparative effectiveness and safety of any other pharmacological and mechanical strategies on VTE outcome and bleeding.

### KQ 2b. Patients With Traumatic Brain Injury

Five studies evaluated the effectiveness and safety of early (<72 hrs) versus late pharmacoprophylaxis (>72 hrs) in patients with traumatic brain injury (Table C). All studies were rated to be at high risk of bias. Estimates were often imprecise and inconsistent leading to conclusions of insufficient strength of evidence.

- The strength of evidence was insufficient to comment on the effectiveness of early (< 72 hours) versus late (> 72 hours) pharmacoprophylaxis with enoxaparin, UFH, or any heparin on the outcomes of VTE, DVT, PE, fatal PE, total mortality, major and minor bleeding.

### **KQ 3. Patients With Burns**

There was just one study for this Key Question, which received a high risk of bias rating due to methodologic limitations in design and reporting, sample size, and the absence of a control group.

- The strength of evidence is insufficient to comment on the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns.

### **KQ 4. Patients With Liver Disease**

We found no studies that directly addressed the comparative effectiveness and safety of pharmacologic strategies for VTE prevention in patients with liver disease.

### **KQ 5. Patients Receiving Antiplatelet Therapy**

We found two studies addressing this question.

- The strength of evidence is insufficient to comment on differences in rates of major bleeding comparing prophylactic rivaroxaban with enoxaparin in patients concomitantly treated with antiplatelet agents.
- The strength of evidence is insufficient to comment on differences in rates of major bleeding comparing prophylactic dabigatran with enoxaparin in patients concomitantly treated with aspirin.

### **KQ 6. Patient Having Bariatric Surgery**

There were 21 observational studies on this question. Most studies had a high risk of bias, with either inconsistent or unknown consistency of findings across studies (Table C).

In hospitalized patients having bariatric surgery:

- The strength of evidence is low that prophylactic IVC filters do not decrease the risk of PE relative to no filter use, in patients also receiving noninvasive mechanical measures.
- The strength of evidence is low that prophylactic inferior vena cava filters increase the risk of all-cause death relative to no filter use, in patients also receiving noninvasive mechanical measures.
- The strength of evidence is insufficient that prophylactic inferior vena cava filters increase the risk of postoperative DVT relative to no filter use, in patients also receiving noninvasive mechanical measures and pharmacological prophylaxis.
- The strength of evidence is insufficient that prophylactic inferior vena cava filters decrease the risk of fatal PE relative to no filter use, in patients also receiving noninvasive mechanical measures.
- The strength of evidence is insufficient to support the comparative effectiveness and safety of any pharmacological strategies.

## **KQ 7. Hospitalized Patients Who Are Obese or Underweight**

We included two studies on this Key Question. We rated the strength of evidence as insufficient for all outcomes because of unknown consistency and imprecision.

- The strength of evidence is insufficient to comment on the effectiveness of prophylaxis with fixed-dose dalteparin over placebo in reducing VTE in hospitalized obese patients.
- The strength of evidence is insufficient to comment on the effectiveness of prophylaxis with fixed-dose dalteparin over placebo in reducing major bleeding and mortality in hospitalized obese patients.
- The strength of evidence is insufficient to comment on whether fixed-dose enoxaparin at 40 mg dose compared with various weight-based dosing regimens (0.4 mg/kg or 0.5 mg/kg of enoxaparin) differ in achieving target anti-factor Xa level in obese hospitalized patients.
- There were no studies that specifically evaluated underweight patients.

## **KQ 8. Patients With Renal Insufficiency or Failure**

We included five studies on this Key Question (Table C).

- The strength of evidence is insufficient to know the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis. We found no studies that directly assessed this question.



**Table C. Summary of the strength of evidence by Key Question**

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Strength of Evidence, Evidence Statement, and Magnitude of Effect
<b>KQ 1</b>								
IVC filter vs. no filter	PE	6	966	High	Direct	Precise	Consistent	Low that IVC filter placement is associated with a lower incidence of PE in hospitalized patients with trauma compared with no IVC filter placement. RR 0.20 (95% CI = 0.06 to 0.70; $I^2=0\%$ )
	Fatal PE	3	570	High	Direct	Precise	Consistent	Low that IVC filter placement is associated with a lower incidence of fatal PE in hospitalized patients with trauma compared with no IVC filter placement. RR 0.09 (0.01 to 0.81; $I^2=0\%$ )
	Mortality	3	478	High	Direct	Imprecise	Inconsistent	Insufficient that IVC filter placement is associated with less mortality in hospitalized patients with trauma compared with no IVC filter placement RR 0.70 (0.40 to 1.23; $I^2=6.7\%$ )
	DVT	3	266	High	Direct	Imprecise	Inconsistent	Insufficient that IVC filter placement is associated with a higher incidence of DVT compared with no IVC filter placement RR 1.76 (95% CI = 0.49 to 6.18; $I^2=56.8\%$ ): $p=0.38$
	Filter related thrombosis	1	324	High	Direct	Imprecise	Unknown	Insufficient to support that IVC filter placement is associated with a higher incidence of filter related thrombosis compared with no IVC filter placement 1.8 % vs 0 %
<b>KQ 2a</b>								
Enoxaparin vs. dalteparin	VTE	1	287	Moderate	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. dalteparin in reducing total VTE in TBI patients 7% vs. 7.5%; $p=0.868$
	Progression of ICH	1	287	Moderate	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs dalteparin in reducing progression of ICH in TBI patients

**Table C. Summary of the strength of evidence by Key Question (continued)**

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Strength of Evidence, Evidence Statement, and Magnitude of Effect
<b>KQ 2a (continued)</b>								
Enoxaparin vs. UFH	DVT	1	329	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. UFH in reducing Total DVT in TBI patients 1% vs. 1%
	PE	1	329	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. UFH in reducing total PE in TBI patients 0% vs. 4% ; p<0.05
	Mortality	1	329	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. UFH in reducing total mortality in TBI patients 5% vs. 15.8%;p<0.05
	Progression of ICH	1	329	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs UFH in reducing progression of ICH in TBI patients; 5% vs. 12%; p<0.05
Enoxaparin vs. IPC/control	VTE	1	480	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. IPC/control in reducing total VTE in TBI patients. 3.9% vs. 2.2%;p=0.29
	DVT	3	397	Moderate	Direct	Imprecise	Consistent	Low grade evidence to suggest that enoxaparin reduces DVT in TBI patients when compared with IPC/control
	PE	3	397	Moderate	Direct	Imprecise	Inconsistent	Insufficient evidence to comment on effectiveness of enoxaparin vs. IPC/control in reducing total PE in TBI patients
	Fatal PE	1	120	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. IPC/control in reducing Fatal PE in TBI patients; 6.6% vs. 3.3%;p=0.04
	Mortality	2	182	Moderate	Direct	Imprecise	Inconsistent	Insufficient evidence to comment on effectiveness of enoxaparin vs. IPC/control in reducing total mortality in TBI patients
	Progression of ICH	2	182	Moderate	Direct	Imprecise	Inconsistent	Insufficient evidence to comment on effectiveness of enoxaparin vs IPC/control/placebo in reducing Exacerbation of epidural hematoma in TBI patients

**Table C. Summary of the strength of evidence by Key Question (continued)**

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Strength of Evidence, Evidence Statement, and Magnitude of Effect
<b>KQ 2a (continued)</b>								
UFH vs. control	VTE	1	812	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of UFH vs. control in reducing total VTE in TBI patients 1% vs. 3%;p=0.019
	DVT	1	228	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of UFH vs. control in reducing total DVT in TBI patients 1% vs. 2%*
	PE	1	228	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of UFH vs. control in reducing total PE in TBI patients 4% vs. 2%*
	Mortality	2	1040	High	Direct	Precise	Consistent	Low grade evidence to suggest that UFH reduces mortality in TBI compared with controls
Dalteparin vs. control	VTE	1	122	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of dalteparin vs control in reducing Total VTE in TBI patients 0% vs 0%*
	Progression of ICH	1	122	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of dalteparin vs control in reducing progression of ICH in TBI patients 0% vs 0%*
IPC vs. control	VTE	1	32	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of IPC vs. control in reducing total VTE in TBI patients 28.6% vs. 22.2%: p=0.7
	PE	1	32	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of IPC vs. control in reducing total PE in TBI patients 28.6% vs. 11.1%*

**Table C. Summary of the strength of evidence by Key Question (continued)**

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Strength of Evidence, Evidence Statement, and Magnitude of Effect
<b>KQ 2b</b>								
Enoxaparin <72 hrs. vs. >72 hrs.	VTE	1	255	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin started <72 hrs. vs. >72 hrs. in reducing VTE in TBI patients 5.6% vs. 2.7%;p=0.26
	DVT	1	669	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin started <72 hrs. vs. >72 hrs. in reducing proximal DVT in TBI patients 1.5% vs. 3.5%;p= 0.12
Enoxaparin <72 hrs. vs. >72 hrs.	PE	1	669	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin started <72 hrs. vs. >72 hrs. in reducing PE in TBI patients 1.5% vs. 2.2%; p=0.49
	Fatal PE	1	669	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin started <72 hrs. vs. >72 hrs. in reducing fatal PE in TBI patients 0% vs. 0.3% *
	Progression of ICH	2	924	High	Direct	Imprecise	Inconsistent	Insufficient evidence to comment on effectiveness of enoxaparin started <72 hrs vs >72 hrs in reducing progression of ICH in TBI patients
UFH <72 hrs. vs. >72 hrs.	DVT	1	64	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of UFH started <72 hrs. vs. >72 hrs. in reducing DVT in TBI patients 4.3% vs. 5.9%;p=1.00
	PE	1	64	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of UFH started <72 hrs. vs. >72 hrs. in reducing PE in TBI patients;4.3% vs. 0%; p=0.96
	Mortality	1	64	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of UFH started <72 hrs. vs. >72 hrs. in reducing total mortality in TBI patients; 8.5% vs. 5.9% ; p=1.00

**Table C. Summary of the strength of evidence by Key Question (continued)**

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Strength of Evidence, Evidence Statement, and Magnitude of Effect
<b>KQ 5</b>								
Rivaroxaban vs. enoxaparin	Major bleeding	1	1089	Low	Direct	Imprecise	Unknown	Insufficient evidence to comment on difference in rates of major bleeding with prophylactic rivaroxaban or enoxaparin in patients concomitantly treated with antiplatelet agents 3.6% vs. 3.25%*
Dabigatran vs. enoxaparin	Major bleeding	1	258	Low	Direct	Imprecise	Unknown	Insufficient evidence to comment on difference in rates of major bleeding with prophylactic dabigatran or enoxaparin in patients concomitantly treated with aspirin 1.6% vs. 3.0%, risk ratio 0.68 (95% C.I. 0.22 to 2.1)*
<b>KQ 6</b>								
Enoxaparin vs. Unfractionated Heparin	PE	1	476	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. unfractionated heparin in reducing PE in patients undergoing bariatric surgery; 0% vs. 0.4%; p=0.99
	DVT	1	476	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. unfractionated heparin in reducing DVT in patients undergoing bariatric surgery; 0% vs. 0%*
	Major bleeding	1	476	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. unfractionated heparin in reducing major bleeding in patients undergoing bariatric surgery; 5.9% vs. 1.3%; p=0.011
	Mortality	1	476	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. unfractionated heparin in reducing mortality in patients undergoing bariatric surgery; 0% vs. 0%*

**Table C. Summary of the strength of evidence by Key Question (continued)**

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Strength of Evidence, Evidence Statement, and Magnitude of Effect
<b>KQ 6 (continued)</b>								
Enoxaparin vs. extended duration of Enoxaparin	PE	1	308	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. extended duration enoxaparin in reducing PE in patients undergoing bariatric surgery; 2.3 % vs. 0%*
	VTE	1	308	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. extended duration enoxaparin in reducing VTE in patients undergoing bariatric surgery; 4.6% vs. 0% ;P=0.006
	DVT	1	308	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. extended duration enoxaparin in reducing DVT in patients undergoing bariatric surgery; 2.3% vs. 0%*
	Major bleeding	1	308	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. extended duration enoxaparin in reducing major bleeding in patients undergoing bariatric surgery; 4.5% vs. 0%, p= 0.06
	Mortality	1	308	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin vs. extended duration enoxaparin in reducing mortality in patients undergoing bariatric surgery 0% vs. 0%; p = NS
Enoxaparin at standard dosing vs. augmented dosing	PE	3	1319	High	Direct	Unknown	Inconsistent	Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs. augmented dosing in reducing PE in patients undergoing bariatric surgery
	DVT	3	1319	High	Direct	Unknown	Inconsistent	Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs. augmented dosing in reducing DVT in patients undergoing bariatric surgery
	VTE	1	481	High	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs. augmented dosing in reducing VTE in patients undergoing bariatric surgery 5.4% vs. 0.6% ; p <0.01
	Bleeding	3	1319	High	Direct	Unknown	Inconsistent	Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs. augmented dosing in reducing bleeding in patients undergoing bariatric surgery

**Table C. Summary of the strength of evidence by Key Question (continued)**

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Strength of Evidence, Evidence Statement, and Magnitude of Effect
<b>KQ 6 (continued)</b>								
Filter vs. no filter	PE	4	99960	High	Direct	Precise	Consistent	Low grade evidence to support that prophylactic IVCs do not reduce PE in patients undergoing bariatric surgery compared with controls RR = 0.91 (95% CI = 0.32 to 2.57; p=0.858; $I^2=16.3\%$ )
	Fatal PE	1	409	High	Direct	Imprecise	Unknown	Insufficient to comment on effectiveness of IVCF in reducing fatal PE in bariatric surgery 0% vs. 11.1%*
	DVT	4	99960	High	Direct	Imprecise	Consistent	Insufficient evidence to support that IVCs increase DVT in patients undergoing bariatric surgery compared with controls RR = 2.77 (95% CI=0.87 to 8.85; p=0.086; $I^2=62.6\%$ )
	Mortality	4	106006	High	Direct	Precise	Consistent	Low grade evidence to support that IVCs are associated with increased mortality in patients undergoing bariatric surgery RR =3.63 (95% CI=1.99 to 6.61; p<0.05; $I^2=0.0\%$ )
<b>KQ 7</b>								
Dalteparin vs. Placebo	VTE	1	1118	Moderate	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of dalteparin vs placebo in reducing total VTE in obese patients; 2.8% vs 4.3%; (RR, 0.64; 95% CI 0.32-1.28)
	Mortality	1	1118	Moderate	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of dalteparin vs placebo in reducing mortality in obese patients; 9.9% vs 8.6%, p=0.36
	Major bleeding	1	1118	Moderate	Direct	Imprecise	Unknown	Insufficient evidence to comment on safety of dalteparin vs placebo in reducing major bleeding in obese patients; 0% vs 0.7%, p>0.99
Enoxaparin 40 mg daily vs. 0.4 mg/kg	Percentage of patients achieving target anti-Factor Xa level	1	20	Moderate	Indirect	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin 40 mg daily versus 0.4 mg/kg in achieving peak anti-Factor Xa level in obese patients; 19% vs 32%, p=NR

**Table C. Summary of the strength of evidence by Key Question (continued)**

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Strength of Evidence, Evidence Statement, and Magnitude of Effect
<b>KQ 7 (continued)</b>								
Enoxaparin 40 mg daily vs. 0.5 mg/kg	Percentage of patients achieving target anti-Factor Xa level	1	22	Moderate	Indirect	Precise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin 40 mg daily versus 0.5 mg/kg in achieving peak anti-Factor Xa level in obese patients; 19% vs 86%, p<0.001
Enoxaparin 0.4 mg/kg vs. 0.5 mg/kg	Percentage of patients achieving target anti-Factor Xa level	1	20	Moderate	Indirect	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin 0.4 mg/kg versus 0.5 mg/kg in achieving peak anti-Factor Xa level in obese patients; 32% vs. 86%, p=NR
<b>KQ 8</b>								
Tinzaparin vs. enoxaparin	VTE	1	55	High	Direct	Imprecise	Unknown	Insufficient on reducing VTE in patients with renal insufficiency 0/27 vs. 0/28*
	Bleeding	1	55	High	Direct	Imprecise	Unknown	Insufficient on bleeding in patients with renal insufficiency 5 /27 vs. 4/28 (p=0.67)
Dabigatran vs. enoxaparin	VTE	1	632	Moderate	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of dabigatran in reducing VTE in severe renal compromise patients vs. enoxaparin (4.3% vs. 6.4%, OR: 0.68, 95% CI: 0.31-1.48, p=0.334)
	Bleeding	1	632	Moderate	Direct	Precise	Unknown	Insufficient evidence to comment on the safety of dabigatran vs. enoxaparin in terms of reducing major bleeding episodes in patients with renal compromise 0 vs. 4.7%, p=0.039
Desirudin vs. enoxaparin	VTE	1	2047	Moderate	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of desirudin in reducing VTE in severe renal compromise patients vs. enoxaparin 4.9% vs. 7.6%, p=0.019
	Bleeding	1	2047	Moderate	Direct	Imprecise	Unknown	Insufficient evidence to comment on the safety of desirudin vs. enoxaparin in terms of reducing major bleeding episodes in patients with renal compromise.; 0.8% vs 0.2%, p=0.109



**Table C. Summary of the strength of evidence by Key Question (continued)**

Intervention	Outcome	Studies N	Enrolled Participants	Risk of Bias	Directness	Summary Precision	Consistency	Strength of Evidence, Evidence Statement, and Magnitude of Effect
<b>KQ 8 (continued)</b>								
Enoxaparin vs. unfractionated heparin	Bleeding	1	323	High	Direct	Precise	Unknown	Insufficient evidence to comment on the safety of unfractionated heparin vs. enoxaparin in terms of reducing major bleeding episodes in patients with renal compromise 13.5% vs. 4.1%, RR: 0.31, 95% CI: 0.14 to 0.71
UHF in severe renal compromise vs. all other renal status (undifferentiated)	VTE	1	2615	Moderate	Direct	Imprecise	Unknown	Insufficient on reducing VTE in severe renal compromise patients vs. all other renal patients 2.6% of patients had a VTE event
	Bleeding	1	2615	Moderate	Direct	Imprecise	unknown	Insufficient evidence to comment on effectiveness of UFH in increasing bleeding in severe renal compromise patients vs. all other renal patients Insufficient evidence; 13 events in 92 patients

CI = confidence interval; DVT = deep vein thrombosis; ICH = intracranial hemorrhage; IPC = intermittent pneumatic compression; IVCF = inferior vena cava filters;

PE = pulmonary embolism; RR = ; TBI = traumatic brain injury, UFH = unfractionated heparin; VTE = venous thromboembolism

\*P-values or tests of statistical significance not reported.

## Discussion

Our systematic review summarizes the current state of the evidence on the role of pharmacologic and mechanical prophylaxis for the prevention of VTE among these special populations. Our review demonstrates a paucity of evidence from high-quality studies to inform several of these Key Questions for these special populations.

## Summary of Studies

### Patients With Trauma

The strength of evidence is low that prophylactic IVC filter placement when compared with no filter use is associated with a lower incidence of PE and fatal PE in hospitalized patients with trauma. We also found insufficient evidence that prophylactic IVC filter placement is associated with an increased incidence of DVT in hospitalized patients with trauma when compared with no use of filters. We found insufficient evidence to comment on mortality associated with prophylactic IVC filter placement in hospitalized patients with trauma.

We identified only a single RCT addressing prophylaxis in this population and it had significant methodological limitations. This pilot trial randomized patients to usual care plus IVC filters versus usual care but was underpowered for all outcomes. Most studies in our database were assessed as having a high risk of bias except five observational studies that were assessed as having a moderate risk of bias. There was significant heterogeneity among the included studies in design and eligibility, and inconsistency in efficacy and safety outcome assessment methods. Although many of the studies reported on the VTE outcomes, most did not provide details about anatomic locations of the DVTs or PEs. There were also differences in reporting and duration of followup. The included studies lacked adequate details about enrolled patient characteristics, such as race and gender, and details of the extent and severity of the trauma limiting our ability to generalize findings from these studies to other ethnic groups or age categories. There has been a wide variation in the use of IVCs in trauma centers which cannot be explained by patient characteristics.<sup>41</sup> This variation could lead to selection bias for any observational studies of IVCs.

Several uncontrolled observational studies provided information on the rare occurrences of filter complications such as strut fracture, insertion site thrombosis, arterial-venous fistulas, filter misplacement, filter tilt, filter migration and IVC thrombosis. The low rates of such complications, the significant risks of bias in the included studies, and the lack of control groups precluded any definitive assessment of the comparative safety of different filter types in patients with trauma.

Our current findings should be interpreted in the context of other systematic reviews on this topic. A recent review conducted a qualitative synthesis of data from 24 studies and found increasing use of retrievable filters and low rates of filter-related complications.<sup>35</sup> The authors concluded there was a lack of high-quality data, and therefore the true efficacy of prophylactic IVC filters for prevention of PE in trauma patients remains unclear. A review from 2006, endorsed by the American Venous Forum, found the evidence on optional IVC filters was not sufficient to support evidence-based recommendations.<sup>36</sup>

There are conflicting guidelines on this topic. The practice guideline from the Eastern Association for the Surgery of Trauma states that insertion of a prophylactic IVC filters *should be considered* in very high-risk trauma patients.<sup>37</sup> A recent American College of Chest

Physicians (ACCP) review suggested that that placement of an IVC filter probably reduces the risk of PE over the short term, but notes that the complications are “frequent” and long term outcomes are unclear.<sup>38</sup> This group noted that removable filters may mitigate the long-term complication rate, but also noted that they are often not removed. Thus the ACCP guidelines *recommend against* IVC filters for primary VTE prevention in patients with trauma (Grade 2C).<sup>38</sup>

## **Patients With Traumatic Brain Injury**

We identified two RCTs that addressed DVT prophylaxis in patients with traumatic brain injury. The remaining studies were single-center cohort studies, the majority of which were retrospective. The majority of the cohort studies were assessed as having a high risk of bias. Due to lack of high-quality studies having minimal risk of bias, we were unable to comment on the comparative effectiveness of pharmacological and mechanical prophylaxis of venous thromboembolism in hospitalized patients with traumatic brain injury. However, we found low-grade evidence to support the idea that enoxaparin reduces the rates of DVT compared with no pharmacoprophylaxis in hospitalized patients with traumatic brain injury. We also found low-grade evidence to support the idea that UFH reduces the rates of total mortality compared with no pharmacoprophylaxis in hospitalized patients with traumatic brain injury.

Five retrospective cohort studies evaluated the timing of pharmacologic prophylaxis in patients with traumatic brain injury. The lack of high-quality studies precludes definitive conclusions about the timing and initiation of prophylaxis in patients with brain trauma.

The two organizations, EAST and the Traumatic Brain Foundation, that provide guidelines for the care of the patients with trauma and patients with traumatic brain injury, respectively, do not make specific recommendations about DVT prophylaxis in patients with traumatic brain injury due to the paucity of evidence.<sup>37</sup> Additionally, the ACCP guidelines do not specifically address DVT prophylaxis in these patients.<sup>38</sup>

## **Patients With Burns**

We did not find any studies that evaluated the comparative effectiveness and safety of pharmacologic strategies in the prevention of VTE among patients with burns. The only included cohort study of IVC filter placement had a high risk of bias with significant methodological limitations. It included just 20 patients and did not have a control group. The very high mortality rate in this study (9 out of 20 participants) was likely related to multi-organ failure.<sup>39</sup> The ACCP 2012 guidelines do not provide specific recommendations for preventing VTE in patients with burns.<sup>40</sup>

## **Patients With Liver Disease**

We found no studies that directly address the comparative effectiveness and safety of pharmacologic strategies among patients with liver disease.

## **Patients on Antiplatelet Therapy**

We identified two studies that directly addressed the comparative effectiveness and safety of pharmacologic strategies among hospitalized patients receiving antiplatelet therapy. We found insufficient evidence about difference in rates of major bleeding with prophylactic rivaroxaban or enoxaparin in patients concomitantly treated with antiplatelet agents. We also found

insufficient evidence to support differences in rates of major bleeding with prophylactic dabigatran or enoxaparin in patients concomitantly treated with aspirin.

## **Patients Having Bariatric Surgery**

There was marked practice variation in filter use for VTE prophylaxis among hospitalized patients undergoing bariatric surgery, beyond what could be explained by differences in the patient populations. Regardless, the process of selecting patients for filters based on real or perceived VTE risk may bias toward a lack of filter efficacy, or the appearance of harm.<sup>42</sup> In each of the studies that we included that specifically noted retrieval rates, physicians ultimately removed more than two-thirds of the retrievable filters placed.

In the absence of high-quality studies, we were unable to determine the comparative effectiveness and safety, or the optimal timing and duration, of prophylactic pharmacotherapy. The observational studies did not provide a clear association between the use of preoperative initiation of pharmacologic prophylaxis and perioperative bleeding, or between postoperative initiation of pharmacologic prophylaxis and thrombosis. A study of extended prophylaxis versus inpatient prophylaxis suggested that continuing enoxaparin therapy for 10 days after discharge may be associated with a lower risk of VTE, when compared with shorter therapy.<sup>43</sup> The rate of fatal PE appears to be low in patients receiving pharmacologic prophylaxis. Consistent with current practice, the majority of the studies emphasized the use of compression devices, compression stockings, and early ambulation. Additionally, the studies that focused on IVC filters generally included patients receiving concurrent pharmacologic prophylaxis.

Pharmacokinetic data from two studies suggest that “subtherapeutic” anti-Xa levels are common when patients receive standard prophylactic doses of enoxaparin, particularly 30 mg twice daily, and that “supratherapeutic” levels are common when patients receive doses of 60 mg twice daily. However, the extent to which anti-Xa levels predict bleeding in obese patients undergoing bariatric surgery is unknown.<sup>44,45</sup>

In contrast to our comparative effectiveness review, which evaluated only comparative studies of pharmacologic regimens, Becattini et al. also included uncontrolled single-arm studies of pharmacologic prophylaxis.<sup>46</sup> They concluded that the incidence of symptomatic postoperative VTE appeared to be less than 1 percent with either prophylactic strategy, but that with screening for events, the rate was approximately 2 percent. Using a standardized definition of bleeding, bleeding rates were approximately 1 percent for standard-dose regimens, and 1.6 percent for weight-adjusted (augmented) pharmacological prophylaxis. The authors concluded that there might be a higher rate of bleeding with augmented dosing regimens with no evidence of increased efficacy, similar to our findings.

## **Obese or Underweight Hospitalized Patients**

We identified two studies that reported on this Key Question. One subgroup analysis of an RCT reported on the comparative effectiveness and safety of fixed low-dose dalteparin 5,000 IU/day versus placebo among hospitalized obese patients with a BMI less than 40kg/m<sup>2</sup>. The strength of evidence was insufficient to comment on the effectiveness of prophylaxis with fixed dose dalteparin over placebo in reducing VTE in hospitalized obese patients. The strength of evidence was insufficient to comment on the effectiveness of prophylaxis with fixed dose dalteparin over placebo in reducing major bleeding and mortality in hospitalized obese patients. We also found that strength of evidence was insufficient to comment on whether fixed dose enoxaparin at 40 mg dose compared with various weight-based dosing regimens (0.4 mg/kg or

0.5 mg/kg of enoxaparin) differed in achieving target anti-factor Xa level in obese hospitalized patients. We did not find any evidence about the role of other pharmacologic or mechanical strategies among hospitalized obese patients. There were no studies among patients who are underweight.

## **Patients With Renal Insufficiency or Failure**

Five studies evaluated the effectiveness and safety of pharmacologic prophylaxis for prevention of VTE in patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis or patients receiving dialysis.<sup>30,47-50</sup> Although patients with compromised renal function who require pharmacologic VTE prophylaxis are common, we found insufficient evidence to guide treatment decisions. Our findings are consistent with other recently published reviews. The ACCP guidelines make dosing recommendations for the *therapeutic* use of LMWH.<sup>51,52</sup> However, their assessment is that the data are insufficient to make direct recommendations about prophylaxis. Their assessment of the indirect evidence regarding bioaccumulation and increased anti-Xa levels are consistent with ours. The ACCP guidelines also suggest that decreased clearance of LMWHs has been associated with increased risk of bleeding events for patients with severe renal insufficiency. However, the cited study compares patients with and without severe renal dysfunction who received the same therapy. Therefore, it is not possible to determine the additional risk conveyed by LMWH therapy, that is, above the baseline increased risk of bleeding among patients with renal insufficiency.

## **Limitations**

Our systematic review identified important weaknesses in the literature. We did not identify high quality RCTs on any of these KQs. The RCTs identified were small and had methodological limitations. The majority of observational studies had either at high or moderate risk of bias and did not report on several quality items of interest. The greatest risk to their validity was confounding by indication in that the sicker patients received more intense prophylaxis than the less sick patients, with no or inadequate adjustment for differences between treatment groups. The studies were heterogeneous in definitions of VTE and bleeding outcomes. We also did not find data on several pharmacologic comparisons of interest or details about appropriate dosing strategies in these special populations.

Our systematic review has several limitations. Although our search strategy was comprehensive, we may have missed studies. Although we included study designs other than randomized controlled trials in our review, the identification and indexing of observational studies is far more challenging than that of randomized controlled trials. It is possible we may have missed a few observational studies. The potential impact of this on the strength of our inference is unknown. We were unable to assess the possibility of publication bias or selective outcomes reporting and its impact on our findings, and it is difficult to determine the impact of unpublished data on the findings of the systematic review.

## **Future Research**

Our report highlights the need for additional research on the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE among these special populations. For many of the questions, multicenter clinical trials may be prohibitively expensive or impossible. We describe here options for observational research as well as trials.

There remains a significant research gap regarding the efficacy and safety for IVC filters for PE prophylaxis in trauma patients. The American Venous Forum and the Society of Interventional Radiology Multidisciplinary Consensus Conference have placed a high priority on studies of filters in trauma.<sup>36</sup> If feasible, a large, multicenter RCT could definitively answer the question on the efficacy and safety of IVC filters in patients with trauma including patients with traumatic brain injury.<sup>36</sup> We recognize that this may be prohibitively complex and expensive; therefore, answering this question with well-designed observational research may be optimal. These observational studies could be prospective cohort studies with the exposed group defined as individuals with trauma receiving filters and with a carefully matched comparison group of individuals—having comparable injuries and comorbid conditions—who do not receive filters. Additionally, observational research could be facilitated with use of registry data, such as from the National Trauma Data Bank.<sup>55</sup> Although presently there is insufficient detail about filter placement in this registry, this could be rectified. This would then allow cohort studies to be nested within this registry. The information that would need to be captured would be filter-related information including timing, indication, type of filter, as well as complications from placement. Retrospective cohort studies may also be valuable for this question but there needs to be much better control for confounding by indication than was done in the studies included in this review. With careful risk adjustment through regression or the use of other methods such as propensity score matching or instrumental variable analyses, valid inferences can be drawn from retrospective studies. Future studies should also attempt to determine the reasons for low filter retrieval rates.

Additional studies among patients with traumatic brain injury may include trials, including trials about the timing of initiation of prophylaxis. The level of detail about timing of dosing in observational data may be limited. Studies should also determine how to better risk stratify patients to inform decisions about pharmacologic prophylaxis. This could be addressed with observational studies describing outcomes of patients in different strata of risk.

For this systematic review, we searched for studies that measured the effect of pharmacologic strategies on anti-Xa concentration, which is a reasonable surrogate for bleeding risk, for the Key Questions addressing patients with renal insufficiency and obesity and underweight. Pharmacokinetic studies are needed in other patient populations to determine whether altered pharmacokinetics of enoxaparin may result in inadequate dosing in burn patients, and whether dose-adjustment of enoxaparin based on serum anti-Xa monitoring is warranted.<sup>53</sup> More broadly, additional research is needed to better understand what raises VTE risk in patients with burns. Electronic health record data should provide sufficient information about exposures to pharmacologic and mechanical interventions in burned patients, as well as the patients' outcomes; and would allow for the control of confounding by indication with information about comorbid conditions, burn severity and surface area affected. Given that there are likely important institutional differences in practice patterns regarding prophylaxis of burns, the use of the institution as an instrumental variable is conceivable (assuming that the patient mix is comparable across institutions).

Future research should include high-quality observational studies to determine the comparative effectiveness and safety of various pharmacological and mechanical strategies among patients with liver disease. Such studies should characterize the relative risks of bleeding and thrombosis across stages of liver disease, which will require clinical information such as from electronic health records.

The question of elevated risk of bleeding with dual therapy with prophylactic anticoagulation and aspirin therapy remains unanswered. Rare events such as bleeding from prophylactic doses of anticoagulant are difficult to answer in trials; this question too will require high-quality observational studies that control for confounding by indication with the use of propensity score methods or possibly instrumental variables.

Trials of IVC filters in patients undergoing bariatric surgery might not be warranted. There is established value of pharmacologic prophylaxis in this patient population, so that RCTs that do not allow pharmacological treatment might be considered to be unethical. Similarly, because the rates of events are so low in patients with pharmacological treatment, exposing individuals to filter placement in an RCT may expose them to complication risk while there is little opportunity to demonstrate improvement in PE rates over the existing low rates. Such trials should include only those patients deemed to be at highest risk for VTE complications, such as those with prior VTE. RCTs might address whether standard doses of prophylaxis that have been proven safe and effective in other types of surgery (such as 5,000 units of subcutaneous unfractionated heparin three times daily, enoxaparin 30 mg twice daily, or enoxaparin 40 mg once daily) are adequate for patients undergoing bariatric surgery. We suggest that weight-based dosing compared with fixed-dosing, rather than BMI-based dosing compared with fixed-dosing, is the more relevant scientific question.

RCTs should evaluate the comparative effectiveness and safety of LMWHs in obese patients. Such trials need to ensure that those at both extremes of weight the underweight ( $\text{BMI} < 18 \text{ kg/m}^2$ ) and severely obese ( $\text{BMI} > 40 \text{ kg/m}^2$ ) are adequately represented in these trials. RCTs of VTE prevention will ideally report data on subgroups of obese and overweight patients, as well as subgroups of patients defined by renal impairment status. Future trials should seek to enroll a subpopulation of patients with renal insufficiency to add to this body of evidence. Observational analyses may be useful for this question as well. We propose that large trials that have been completed should report subgroup results, including subgroups that were not specified at the start of the trial, so that this information is available to researchers doing meta-analysis.<sup>54</sup> Whereas the results in these subgroups might be considered exploratory in the context of the parent trial, when pooled across studies, the added power may allow for stronger, yet cautious, conclusions.

Even with evidence for the above, it still may not be clear what is the best practice as this may depend on patients' preferences for the possible outcomes. An individual's tolerance of risk without an intervention may exceed his tolerance of a different risk with an intervention, and this has importance for decisionmaking. These questions are best answered with qualitative methods or possibly with quantitative methods designed for learning patients' preferences. These can then be used in decision-analytic models that may be informative to clinicians and patients.

## Conclusions

Our systematic review summarizes the current state of the evidence on the role of pharmacologic and mechanical prophylaxis for the prevention of VTE among these special populations. Our review demonstrates a paucity of evidence from high-quality studies to inform these Key Questions for these special populations. Our systematic review identified important weaknesses in the literature. Future research using high-quality observational studies that control for confounding by indication, such as provider and practice patterns, and confounding by disease severity may be needed as RCTs typically exclude or do not report on these special populations.

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# Introduction

## Background

Pulmonary embolism (PE) resulting from deep vein thrombosis (DVT), collectively known as venous thromboembolism (VTE), affects an estimated 900,000 Americans every year, resulting in significant morbidity and mortality.<sup>1,2</sup> Although the average annual incidence of DVT currently ranges from 48 to 122 per 100,000 in the United States,<sup>1,2</sup> rates will likely rise along with the country's aging population. There are significant adverse consequences of DVT and PE<sup>1</sup>, including an estimated 300,000 fatalities annually, and hundreds of thousands of hospitalizations in nonfatal cases.<sup>1,2</sup> In addition, a diagnosis of DVT or PE in the hospital increases the costs of index hospitalization by approximately \$10,000 and \$20,000, respectively.<sup>3</sup> Thus, VTE is an important patient safety issue with significant morbidity, mortality, and health care costs.<sup>4</sup> Accordingly, the comparative effectiveness and safety of interventions for the prevention and treatment of VTE are among the national priorities for comparative effectiveness research.<sup>5</sup> In this review, we describe the evidence about prevention of DVT in "special populations," which we define below. For most of these populations, there are no guidelines that provide recommendations regarding care. Additionally, for most, there is considerable decisional uncertainty about the best option for thromboprophylaxis. The results of this comparative effectiveness review will inform those developing guidelines, and clinicians and patients who are making decisions about the best approach to prophylaxis.

Special populations include those patients for whom the benefit or risk of VTE prophylaxis is uncertain, or patients for whom there is decisional uncertainty about the optimal choice, timing, and dose of VTE prophylaxis, or significant practice variation. The burden of VTE is higher among some patient populations including patients who have experienced recent trauma<sup>6-11</sup> or burns;<sup>12-14</sup> patients undergoing bariatric surgery;<sup>15-21</sup> and patients with acute renal failure, chronic renal failure, or end-stage renal disease.<sup>22-25</sup> Not only do these patients have an increased risk of DVT and PE, but most are also at high risk for bleeding, the most important complication of VTE prophylaxis. Therefore, the risk-benefit ratio of prophylactic medications in these populations is uncertain, and is similarly unclear in populations of patients with altered clearance of medications.<sup>26-30</sup>

## Special Populations

### General Traumatic Injury

Trauma is known to be a major risk factor for VTE. A prospective study reported rates of DVT as high as 58 percent among those who experienced severe trauma (injury severity score >9) without thromboprophylaxis.<sup>6</sup> Among hospitalized trauma patients, PE occurs in one of every 25 patients and studies have linked PE to considerable mortality.<sup>6</sup> Some patients with special types of trauma, such as those with spinal trauma, are at the highest risk of DVT, with rates approximating 80 percent.<sup>4</sup> There appear to be significant practice variation and clinical uncertainty around the role of pharmacologic versus mechanical prophylaxis among patients with trauma. Although clinicians commonly recommend pharmacologic prophylaxis, some may consider it to be contraindicated in certain trauma patients, such as those with: solid organ injury (i.e., liver, spleen, or kidney); pelvic or retroperitoneal hematoma; ocular injury with hemorrhage; or thrombocytopenia (platelet count <50,000). In these cases, there is debate about

the placement of prophylactic inferior vena cava (IVC) filters to prevent PE. Some authors suggest that using this intervention among patients at very high risk may prevent the most dramatic and life-threatening cases of PE, although evidence for this is uncertain. Other studies associate IVC filters with significant complications,<sup>31,32</sup> such as the occurrence of DVT,<sup>57</sup> and recommend against their use. Other studies show that placement of IVC filters do not lower the rate of PE and may not be of benefit in the trauma setting<sup>34</sup> or among other patient populations.<sup>34</sup> Ongoing uncertainty exists about whether clinicians should use prophylactic IVC filters in trauma patients for whom anticoagulation is relatively contraindicated. The concept of temporary (also known as “retrievable” or “optional”) IVC filters is appealing but further complicates the picture. Current guidelines from the American College of Chest Physicians (ACCP) recommend against the use of IVC filters for primary prevention in patients without proven VTE.<sup>4</sup> The Eastern Association for the Surgery of Trauma guidelines suggest that clinicians can consider using prophylactic IVC filters in patients who have certain significant injury patterns, are at very high risk for VTE, and cannot receive pharmacologic prophylaxis.<sup>35</sup>

## **Patients With Traumatic Brain Injury**

There is considerable practice variation and clinical uncertainty about the choice of a prophylaxis modality (pharmacologic or mechanical), and about the optimal pharmacologic agent, dose, timing of initiation, and duration among patients with traumatic brain injury.<sup>36</sup> This population has an increased risk for VTE due to a combination of factors (i.e., the brain injury itself, other injuries, intensive care unit admission, immobilization, major surgery, etc.). This risk should prompt routine thromboprophylaxis; however, the associated elevated risk of bleeding in patients with traumatic brain injury often leads physicians to withhold anticoagulant thromboprophylaxis. The concern about anticoagulant thromboprophylaxis in this population is progression of intracranial bleeding that may result in clinical deterioration and possibly worse long-term outcomes. There is ongoing clinical uncertainty and wide variations in practice regarding the appropriate time to initiate pharmacologic prophylaxis.

## **Patients With Burns**

Patients hospitalized with burns are at an increased risk for VTE, but there is no consensus about the most appropriate prophylactic strategy for prophylaxis of VTE among these patients.<sup>37</sup> DVT has a reported incidence of 1 to 23 percent in a series of burn patients.<sup>14</sup> The ACCP guidelines recommend thromboprophylaxis if possible for burn patients who have additional risk factors for VTE such as advanced age, morbid obesity, extensive burns, burns to the lower extremities, concomitant trauma to the lower extremities, use of a femoral venous catheter, and/or prolonged immobility (Grade 1C).<sup>4</sup> However, concerns about the potential risk of heparin-associated bleeding may have resulted in very low rates of heparin use and considerable uncertainty about the optimal choice of therapy among burn centers.<sup>13</sup> There is considerable uncertainty around specific drugs, dosing regimens, and the risk-benefit tradeoff for these particular subpopulations of patients.

## **Patients With Liver Disease**

Patients with liver diseases such as cirrhosis may be simultaneously at increased risk for both bleeding and thrombosis, thus complicating the decisions related to VTE prevention.<sup>38</sup> Patients with thrombocytopenia, platelet dysfunction, and a prolonged international normalized ratio

(INR), secondary to liver disease, are at increased risk for both minor and major bleeding secondary to altered hemostasis.<sup>39</sup> However, patients with these specific conditions often remain at risk for venous thromboembolism, particularly since many of the illnesses that lead to defects in hemostasis—such as cirrhosis—can directly precipitate thrombosis as a result of activated hemostasis and may also precipitate thrombosis indirectly through complications such as infection. There is clinical uncertainty about the optimal choice of VTE prophylaxis in this patient population and about the optimal threshold of thrombocytopenia and the prolonged INR value at which bleeding increases with anticoagulant thromboprophylaxis. There are no specific reviews or guidance documents that clarify the role of thromboprophylaxis in these patients.

## **Individuals Receiving Antiplatelet Therapy**

Patients receiving antiplatelet therapy with acetylsalicylic acid or thienopyridines, such as clopidogrel, ticlopidine, and prasugrel, are at increased risk for bleeding. These patients constitute a large proportion of patients hospitalized for various medical conditions.<sup>38</sup> There is clinical uncertainty about the optimal choice of VTE prophylaxis in this patient population. There are no specific guidance documents that clarify the role of thromboprophylaxis in patients receiving chronic long term antiplatelet therapy.

## **Individuals Having Bariatric Surgery**

There is clinical uncertainty about venous thromboprophylaxis in patients who undergo bariatric surgery. In an analysis of a large cohort in the Bariatric Outcomes Longitudinal Database,<sup>20</sup> the incidence of VTE after bariatric surgery was 0.42 percent within 90 days after surgery. Although these obese patients were at risk of VTE, their hospitalizations were short, and they were able to ambulate early. The risk of VTE was greater in the patients who underwent gastric bypass than in those who underwent adjustable gastric banding (0.55 vs. 0.16 percent). The risk of VTE was also greater in patients who had an IVC filter placed (hazard ratio 7.7; 95% confidence interval 4.5–13). The ACCP guidelines recommend low dose unfractionated heparin (UFH) and low-molecular-weight heparins (LMWH) or fondaparinux at higher than usual doses for patients undergoing bariatric surgery.<sup>4</sup> A recent survey of bariatric surgeons reported that nearly 60 percent of bariatric surgeons preferred LMWH for prophylaxis.<sup>15</sup> However, many were uncertain about the best choice of therapy and about the timing and duration of VTE prophylaxis.<sup>15</sup> Therefore, there is much practice variation, ranging from no prophylaxis to multimodality thromboprophylaxis that might also include preoperative placement of an IVC filter.

## **Obese or Underweight Hospitalized Patients**

Studies associate obesity, including severe obesity, with an increased risk of VTE.<sup>40</sup> It is uncertain if fixed doses of pharmacologic agents such as UFH, LMWH, and factor Xa inhibitors provide optimal prophylaxis in this special population. The pharmacokinetics of several agents may be different among obese patients requiring dose adjustments.<sup>41</sup> Although LMWH and other pharmacologic agents may require dosage adjustments, the optimal dosing strategy (including duration of therapy) for these patients is not clear. Similarly, the optimal choice and dosing regimens for patients who are underweight (body mass index <18.5 kg/m<sup>2</sup>) is unclear.

## Patients With Acute or Chronic Renal Failure

The optimal treatment choice and dosing strategy for thromboprophylaxis for patients with acute or chronic renal failure and chronic kidney disease (CKD) remains uncertain. In a prospective community-based cohort, patients with stage 3 or 4 CKD had a higher risk of VTE than those with normal kidney function.<sup>22</sup> The rates of VTE among patients with end-stage renal disease were also high. Generally, the burden of VTE among patients with CKD falls disproportionately on Hispanics and African Americans.<sup>42</sup> Patients with advanced CKD also have a tendency to bleed because of platelet dysfunction.<sup>43</sup> Fondaparinux and LMWHs are primarily eliminated via the renal pathway and may accumulate in patients with renal failure. This accumulation is dependent in part on the chain lengths of the LMWHs and their subsequent renal clearance, thereby resulting in different pharmacokinetic and pharmacodynamics effects.<sup>30</sup> Consequently, patients with diminished renal function may be at an increased risk for bleeding. Although there appear to be differences between the LMWHs with regard to accumulation risk, the relationship between their use and the incidence of bleeding is not well established. ACCP guidelines recommend that clinicians should dose adjust, monitor, or simply avoid anticoagulant medications that bioaccumulate (Grade 1C). Cook et al.,<sup>25</sup> argued that LMWHs may be the optimal choice, given the lower incidence of thrombocytopenia in patients with CKD. There are similar concerns about the optimal strategies for VTE prophylaxis among patients with acute kidney injury.

## Therapies of Interest

In this review, we describe the evidence for drugs and devices that currently are available in the United States and that are either FDA approved for VTE prophylaxis or that clinicians may use without an indication (“off-label”) for this purpose (Table 1).

The pharmacologic agents of interest include UFH and LMWH delivered subcutaneously.<sup>26-29</sup> The anticoagulant action of unfractionated heparin occurs due to binding to antithrombin, and resulting inactivation of Factor IIa, Xa, IXa, XIa, XIIa.<sup>44</sup> Low molecular weight heparins primarily promote Factor Xa inhibition.<sup>44</sup> Fondaparinux, a synthetic pentasaccharide, is also available as an option for thromboprophylaxis. We also included dabigatran, a recently approved oral anticoagulant that directly inhibits thrombin; the FDA approved it for the prevention of stroke in patients with atrial fibrillation, but it has the potential for off-label use for prophylaxis of VTE. Rivaroxaban is an oral factor Xa inhibitor that the FDA approved in July 2011 for VTE prophylaxis for patients undergoing elective hip and knee arthroplasty; this drug also has the potential for off-label use in other patient populations. Similarly, we included antiplatelet agents, such as aspirin and clopidogrel, as well as the anticoagulant warfarin, which clinicians may use off-label for this indication.

We also included sequential compression devices, venous foot pumps, and various types of IVC filters, in this review.<sup>4</sup> They are all devices that clinicians use for VTE prophylaxis.

## Key Questions

This report includes our review of the evidence about the efficacy, effectiveness, and safety of pharmacological and mechanical methods of prophylaxis in our defined special populations. The Key Questions (KQs) we explored are as follows:

KQ 1. What are the comparative effectiveness and safety of IVC filters to prevent PE in hospitalized patients with trauma?

KQ 2. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with traumatic brain injury? What is the optimal timing of initiation and duration of pharmacologic prophylaxis to prevent VTE in hospitalized patients with traumatic brain injury?

KQ 3. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns?

KQ 4. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with liver disease?

KQ 5. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients receiving antiplatelet therapy?

KQ 6. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in patients having bariatric surgery?

KQ 7. What are the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of obese and underweight patients?

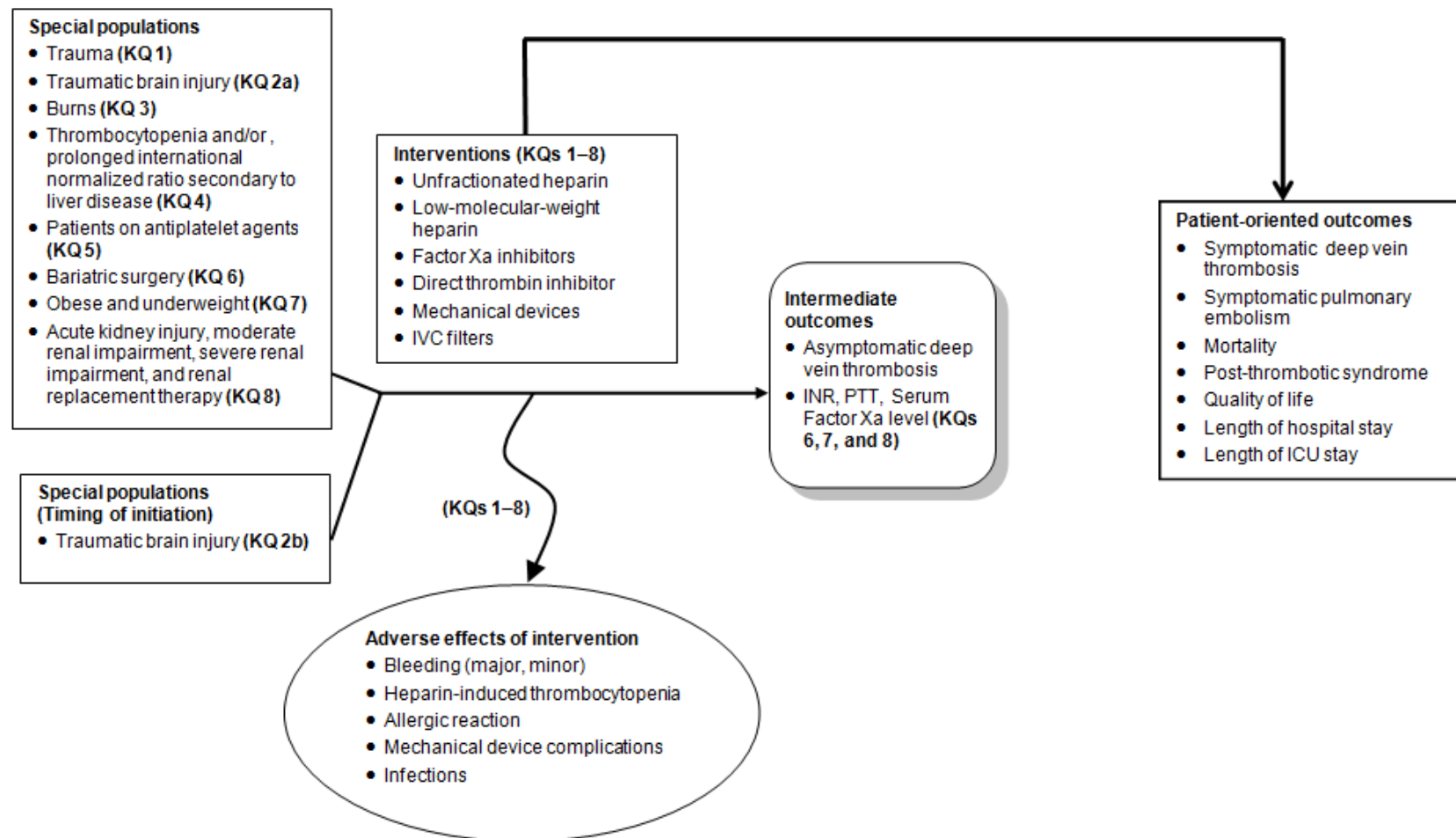
KQ 8. What are the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis?

## **Framework**

Figure 1 presents the analytic framework for this systematic review. It illustrates the KQs, special populations of interest, therapies, and intermediate and clinical outcomes included in our review, as well as the adverse consequences associated with the specified prophylactic regimens.



**Figure 1. Analytic framework: Pharmacologic and mechanical prophylaxis of venous thromboembolism among special populations**



INR = international normalized ratio; IVC = inferior vena cava; KQ = Key Question; PTT = partial thromboplastin time

**Table 1. Pharmacologic agents and medical devices approved in the United States for some indication and that may be considered for VTE prophylaxis**

<b>Pharmacologic Agent</b>	<b>Intervention</b>	<b>Route</b>	<b>Dose</b>	<b>Manufacturer</b>	<b>U.S. Availability</b>	<b>Comments</b>
<b>Antiplatelets</b>	<i>Aspirin</i>	Oral	Various	Various	Yes	NA
	<i>Clopidogrel (Plavix®)</i>	Oral	75 or 300 mg base	Sanofi Aventis/ Bristol-Myers Squibb	Yes	NA
	<i>Ticlopidine (Ticlid®)</i>	Oral	125 or 250 mg	Hoffman-La Roche Inc.		NA
	<i>Prasugrel (Effient®)</i>	Oral	EQ 5 or 10 mg base	Roche Palo	Yes	NA
	<i>Ticagrelor (Brilinta®)</i>	Oral	90 mg	AstraZeneca LP	Yes	NA
	<i>Dipyridamole (Persantine®)</i>	Oral	25, 50, or 75 mg	Boehringer Ingelheim	Yes	NA
	<i>Cilostazol (Pletal®)</i>	Oral	50 or 100 mg	Otsuka	Yes	NA
<b>Dextran sulphate</b>	<i>Dextran sulphate</i>	Intravenous	Various	PKC	Yes	NA
<b>Vitamin K Antagonists</b>	<i>Warfarin (Coumadin®)</i>	Oral	1–10 mg	Various generics; Bristol-Myers Squibb	Yes	NA
	<i>Dicumarol</i>	Oral	Various			
<b>Low-Dose Unfractionated Heparins</b>	<i>Heparin</i>	Subcutaneous	5,000 Units BID or TID	Several	Yes	NA
<b>Low-Molecular-Weight Heparins</b>	<i>Enoxaparin sodium (Lovenox®)</i>	Subcutaneous	40 mg QD or 30 mg BID (30 mg for renal impairment)	Sanofi-Aventis; generic from Sandoz (2010)	1993	Dosing indication for abdominal surgery and acutely ill medical patients
	<i>Dalteparin sodium (Fragmin®)</i>	Subcutaneous	5,000 IU QD	Eisai/Pfizer	1994	Indicated for surgery prophylaxis
	<i>Tinzaparin sodium (Innohep®)</i>	Subcutaneous	3,500 IU QD to 4,500 IU SC daily	LEO Pharma/Celgene	2000	Indicated for surgery prophylaxis
<b>Factor Xa Inhibitors</b>	<i>Fondaparinux (Arixtra®)</i>	Subcutaneous	2.5 mg QD	GSK	2001	Indicated for abdominal surgery prophylaxis
	<i>Rivaroxaban (Xarelto®)</i>	Oral	10 mg QD	Johnson and Johnson	2011	Indicated for elective hip/knee arthroplasty
<b>Direct Thrombin Inhibitors</b>	<i>Argatroban (Argatroban®)</i>	Intravenous Infusion	100 mg/mL	Pfizer	2000	Prophylaxis with active HIT
	<i>Dabigatran (Pradaxa®)</i>	Oral	75 and 150 mg	Boehringer Ingelheim	2010	Prevent stroke and systemic embolism in AF
	<i>Bivalirudin (Angiomax®)</i>	Intravenous	250 mg/Vial	The Medicines Company	2000	NA
	<i>Lepirudin (Refludin®)</i>	Intravenous Infusion	50 mg/Vial	Bayer	1998	Anticoagulation with HIT to prevent further thromboembolic complications

**Table 1. Pharmacologic agents and medical devices approved in the United States for some indication and that may be considered for VTE prophylaxis (continued)**

<b>Mechanical Device</b>	<b>Intervention</b>	<b>Name</b>	<b>Manufacturer</b>	<b>Comments</b>
	Intermittent Pneumatic compression	Aircast VenaFlow	DJO	Apply intermittent application of pressure to a patient's calf, thigh or foot for the purpose of assisting blood flow in the veins.
		SCD Express	Tyco/Kendall	DVT prophylaxis
	Graduated compression stockings	Jobst T.E.D.® Others	Jobst	To prevent pooling of blood in legs
	Venous Foot Pumps	A-V Impulse System Venodyne	Novamedix	DVT prophylaxis
<b>Inferior Vena Caval Filters</b>	<b>Name</b>	<b>Type</b>	<b>Manufacturer</b>	<b>Comments</b>
	Greenfield Stainless Steel®	Permanent	Boston Scientific	Prevention of PE with venous thrombosis or pulmonary thromboembolism when anticoagulants are contraindicated
	Simon Nitinol®	Permanent	Bard Peripheral Vascular	Preventing PE from migrating to the pulmonary arteries
	TRAPEASE®	Permanent	Cordis	Prevention of recurrent PE when anticoagulants are contraindicated
	Greenfield Titanium®	Permanent	Boston Scientific	No information available
	Vena Tech LP®	Permanent	B. Braun	Partial interruption of IVC to prevent PE when anticoagulants are contraindicated
	Gianturco-Roehm Bird's Nest®	Permanent	Cook	Prevention of recurrent PE when anticoagulants are contraindicated
	Celect®	Retrievable	Cook	Prevention of recurrent PE when anticoagulants are contraindicated
	Gunther Tulip®	Retrievable	Cook	Prevention of recurrent PE when anticoagulants are contraindicated
	G2®	Retrievable	Bard Peripheral Vascular	Prevention of recurrent PE
	G2x®	Retrievable	Bard Peripheral Vascular	Prevention of recurrent PE when anticoagulants are contraindicated
	Eclipse®	Retrievable	Bard Peripheral Vascular	Prevention of recurrent PE when anticoagulants are contraindicated
	VenaTech LGM®	No longer sold	B. Braun	Partial interruption of IVC to prevent PE when anticoagulants are contraindicated
	Tempofilter®	Retrievable	B. Braun	NA

**Table 1. Pharmacologic agents and medical devices approved in the United States for some indication and that may be considered for VTE prophylaxis (continued)**

Inferior Vena Caval Filters	Name	Type	Manufacturer	Comments
	ALN IVC <sup>®</sup>	Retrievable	ALN Implants	Prevention of recurrent PE when anticoagulants are contraindicated
	Option IVC <sup>®</sup>	Retrievable	Rex/Angio Tech	Prevention of recurrent PE when anticoagulants are contraindicated
	Safeflo <sup>®</sup>	Permanent	Rafael Medical	Prevention of recurrent PE when anticoagulants are contraindicated
	OPTEASE <sup>®</sup>	Retrievable	Cordis Corp	Prevention of recurrent PE when anticoagulants are contraindicated

AF = atrial fibrillation; BID = twice a day; DVT = deep vein thrombosis; EQ = equivalent; HIT = heparin-induced thrombocytopenia; IU = international unit; IVC = inferior vena cava; PE = pulmonary embolism; QD = once a day; SC = subcutaneous; TID = three times a day

## Methods

The methods for this comparative effectiveness review (CER) follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) “Methods Guide for Effectiveness and Comparative effectiveness Reviews” ([www.effectivehealthcare.ahrq.gov/methods-guide.cfm](http://www.effectivehealthcare.ahrq.gov/methods-guide.cfm)) The main sections of this chapter reflect the elements of the protocol established for the CER; certain methods map to the PRISMA checklist. This systematic review was carried out according to a prespecified protocol registered at the AHRQ Web site.<sup>45</sup>

Our Evidence-based Practice Center (EPC) established a team and a work plan to develop this evidence report. The project involved recruiting key informants and technical experts, formulating and refining the questions, performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence, and submitting the report for peer review and public comment.

### Topic Refinement

The topic for this report was nominated via the EHC Web site. We recruited a panel of key informants to give input on key steps including the selection and refinement of the questions to be examined. The panel included local experts with expertise in bariatric surgery and external informants including expertise in burns, hematology, trauma, payer, and patient representatives.

With the input of the key informants, and staff of AHRQ and the Scientific Resources Center, we developed the Key Questions (KQs). Our draft KQs were posted on Effective Health Care Program Web site for public comment on August 16, 2011. We then refined the KQs based on the feedback received.

We recruited a Technical Expert Panel (TEP) which included experts in the prevention of venous thrombosis, on burn care, on trauma management, on bariatric surgery perioperative care, and hematologists. These technical experts provided high-level expertise to the Evidence-based Practice Center (EPC) during our development of the protocol for the comparative effectiveness review. Additionally, the Effective Health Care Program posted the KQs on its Web site for public comment and we discussed the KQs with the TEP. With input from the technical expert panel and representatives from AHRQ, we finalized the protocol. The protocol was posted on the Effective Health Care Program Web site on January 12th, 2012.<sup>45</sup>

### Search Strategy

We searched the following databases for primary studies through July 2012: MEDLINE<sup>®</sup>, Embase<sup>®</sup>, SCOPUS, CINAHL<sup>®</sup>, International Pharmaceutical Abstracts, and the Cochrane Library. We searched the [clinicaltrials.gov](http://clinicaltrials.gov) in addition to these databases. We developed a search strategy for MEDLINE, accessed via PubMed<sup>®</sup>, based on medical subject headings (MeSH<sup>®</sup>) terms and text words of key articles that we identified a priori (Appendix B). We reviewed the reference lists of all included articles, relevant review articles, and related systematic reviews to identify articles which may have been missed in the original search. In addition, we requested and reviewed Scientific Information Packets (SIPs) provided by the pharmaceutical manufacturers. Our search did not have any language restrictions; we included non-English articles in our review but did not find any non-English article applicable to our project.

We conducted an updated literature search (of the same databases searched initially) concurrently with the peer review process. Any literature suggested by peer reviewers was

investigated and, if appropriate, incorporated into the final review. We determined the appropriateness of all additional literature by the same methods described in this chapter.

## Study Selection

We reviewed titles followed by abstracts to identify randomized controlled trials (RCTs) or observational studies and case reports reporting on the effectiveness or safety of venous thromboembolism prevention in our selected populations (Table 2).

Two investigators independently reviewed abstracts and we excluded the abstracts if both investigators agreed that the article met one or more of the exclusion criteria. We resolved disagreements by consensus. We recognized that much of the evidence about use of IVC filters would be from observational studies without comparison groups; therefore in our review of titles and abstracts we were inclusive of any design, including uncontrolled observational studies, case series and case reports, which described unanticipated harms from use of IVC filters.

For inclusion in this review, we required that studies enrolled or reported on patients who were members of our special populations. This included patients with traumatic brain injury, with burns requiring burn unit care, individuals with liver disease, patients receiving antiplatelet therapy, patients undergoing bariatric surgery, obese and underweight hospitalized medical patients, and patients with any degree of renal impairment. If the studies included a mixed population that included one of our special populations, the study either needed to report results separately for our population, or our population needed to comprise 80 percent or more of the total population. We excluded studies that were predominantly describing outcomes for children, adolescents, or pregnant women. We also excluded studies specifically evaluating any of our excluded patient populations: patients with antiphospholipid antibodies, cancer, disseminated intravascular coagulation, treatment of heparin-induced thrombocytopenia, or congenital platelet disorders. We excluded studies that used pharmacotherapy for treatment of venous thrombosis or that were evaluating secondary prevention of venous thrombosis outside of our stated patient populations. For our KQ 8 we excluded studies occurring among renal transplant recipients or those with nephrotic syndrome.

We included trials if the comparators were pharmacotherapies for prevention of venous thrombosis available in the United States, vena cava filters available in the United States, or mechanical devices or usual care practices. We did not require that observational studies about vena cava filters have comparison groups. We resolved differences regarding article inclusion through consensus adjudication, and a third reviewer audited a random sample to ensure consistency in the reviewing process.

At the point of full article review, we excluded studies that did not report on at least one of our outcomes of interest. These were: symptomatic or asymptomatic deep vein thrombosis or pulmonary embolism, fatal pulmonary embolism, mortality, post-thrombotic syndrome, quality of life, length of hospital stay or intensive care unit stay, bleeding, heparin-induced thrombocytopenia, allergic reactions, mechanical device complications, infections for all KQs. For KQ 7 and KQ 8 we also considered additional outcomes such as international normalized ratio, prothrombin time, or factor Xa levels (Table 3).

**Table 2. Study inclusion and exclusion criteria**

Category	Inclusion Criteria	Exclusion Criteria
Populations	<ul style="list-style-type: none"> <li>• Human subjects (only)</li> <li>• Adults in special patient populations, including:               <ul style="list-style-type: none"> <li>○ Trauma</li> <li>○ Traumatic brain injury</li> <li>○ Burns</li> <li>○ Liver disease</li> <li>○ Antiplatelet therapy</li> <li>○ Bariatric surgery</li> <li>○ Obese and underweight</li> <li>○ Acute kidney injury, moderate renal impairment,</li> <li>○ severe renal impairment, renal replacement therapy</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Animal studies/models</li> <li>• Children</li> <li>• Pediatric</li> <li>• Adolescent</li> <li>• Adults in the following patient populations:               <ul style="list-style-type: none"> <li>○ Treatment of VTE</li> <li>○ Secondary prophylaxis</li> <li>○ Catheter thrombosis</li> <li>○ Antiphospholipid antibodies/other autoimmune diseases</li> <li>○ Cancer (malignancy, chemotherapy, radiotherapy)</li> <li>○ Cardiovascular (coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty) patients on full-dose anticoagulation</li> <li>○ Pregnancy</li> <li>○ Disseminated intravascular coagulation</li> <li>○ Heparin-induced thrombocytopenia</li> <li>○ Congenital platelet disorders</li> <li>○ VTE prophylaxis for long distance travel</li> <li>○ Abdominal surgery</li> <li>○ Vascular surgery</li> <li>○ Urological surgery</li> <li>○ Gynecological surgery</li> </ul> </li> </ul>
Intervention	Studies that evaluate interventions or mechanical devices	Studies of agents that have not been approved for thromboprophylaxis in the United States or interventions not available in the United States will not be evaluated
Outcomes	<ul style="list-style-type: none"> <li>• Symptomatic deep vein thrombosis</li> <li>• Symptomatic pulmonary embolism</li> <li>• Mortality</li> <li>• Post-thrombotic syndrome</li> <li>• Quality of life</li> <li>• Length of hospital stay</li> <li>• Length of ICU stay</li> <li>• Bleeding (major, minor)</li> <li>• Heparin-induced thrombocytopenia</li> <li>• Allergic reaction</li> <li>• Mechanical device complications</li> <li>• Infections</li> <li>• Asymptomatic deep vein thrombosis</li> </ul> INR, PTT, factor Xa level (KQs 6, 7 and 8)	No data on relevant outcomes of interest

**Table 2. Study inclusion and exclusion criteria (continued)**

Category	Inclusion	Exclusion
Type of Study	<p>We included the following study designs</p> <ul style="list-style-type: none"> <li>• Randomized controlled trials</li> <li>• Prospective cohort studies</li> <li>• Retrospective cohort studies</li> <li>• Case-control studies</li> <li>• Uncontrolled case-series for devices</li> <li>• Case reports of device complications in the relevant special populations</li> <li>• Case reports of pharmacologic therapies other than the known complications of bleeding and heparin-induced thrombocytopenia</li> </ul>	<ul style="list-style-type: none"> <li>• Case reports of efficacy</li> <li>• Case reports of bleeding or heparin-induced thrombocytopenia associated with pharmacologic strategies</li> <li>• In vitro studies</li> <li>• Animal studies</li> <li>• Cost-effectiveness studies</li> <li>• Modeling studies</li> <li>• Risk assessment studies</li> <li>• Registries without descriptions of interventions</li> <li>• Diagnostic studies</li> <li>• Ecologic study designs</li> <li>• Time-series designs</li> <li>• No original data, commentary, or editorial</li> <li>• Systematic reviews and meta-analysis</li> </ul>

ICU = intensive care unit; INR = international normalized ratio; PTT = partial thromboplastin time; VTE = venous thromboembolism



## **Data Abstraction and Data Management**

We used DistillerSR (Evidence Partners, 2010) to manage the screening and review process. DistillerSR is a Web-based database management program that manages all levels of the review process.

Two independent reviewers conducted title scans. For a title to be eliminated at this level, both reviewers had to indicate that the study was ineligible. If the reviewers disagreed, we advanced the article to the next level, abstract review. Two investigators independently reviewed abstracts and we excluded the abstracts if both investigators agreed that the article meets one or more of the exclusion criteria. We tracked and resolved differences between investigators regarding abstract inclusion or exclusion through consensus adjudication. Articles promoted on the basis of abstract review had an independent parallel review to determine if they should be included in review. We resolved the differences by consensus adjudication.

We created standardized forms for data extraction (Appendix C). We pilot tested the forms prior to the beginning the process of data extraction. Each article had double review by study investigators for data abstraction. The second reviewer confirmed the first reviewer's data abstraction for completeness and accuracy. Reviewer pairs included personnel with both clinical and methodological expertise. We tracked and resolved differences between investigators regarding data through consensus adjudication. A third reviewer audited a random sample of articles selected by the first two reviewers to ensure consistency in the abstraction of data from the articles. We did not mask reviewers from the authors, institution, or journal for each article.

Reviewers extracted information on general study characteristics, study participants, eligibility criteria, interventions, outcome measures, the method of ascertainment, and the outcomes, including measures of variability where available. We entered all information from the article review process into the DistillerSR database. We used the DistillerSR database maintain the data, which we then exported into Excel for the preparation of evidence tables.

## **Assessment of Methodological Quality of Individual Studies**

We conducted the risk of bias independently and in duplicate. This was done independently by two reviewers. Disagreements between the two reviewers were resolved through consensus and adjudication by a third reviewer.

Although the original protocol planned to use different tools for trials and observational studies in the protocol, we chose a single instrument the Downs and Black instrument (Appendix E).<sup>46</sup> The need to standardize the rating of risk of bias across heterogeneous study designs including case reports, case-series, uncontrolled cohort studies, case-control studies, prospective and retrospective cohort studies and randomized trials prompted this change. We categorized the trials as having low risk of bias, moderate risk of bias, or high risk of bias and observational studies as having moderate risk of bias and high risk of bias.

We found that 10 items were most relevant to this review and we prioritized them in our assessment of risk of bias. We considered studies to have a low risk of bias if all of the following were true: the article completely described the hypothesis, the outcomes (in the introduction or methods section), the characteristics of the included subjects, the distribution of the potential confounders in each group, the interventions and comparisons (if relevant), the main findings, adverse events, and characteristics of the subjects lost to followup. Additionally, we judged studies to be at low risk of bias if they randomized subjects to the intervention and concealed the assignment until randomization was complete, and if they attempted to blind the study

participants and to blind those who measured the main outcomes. By this system, we could not consider any study without randomization to have a low risk of bias. Such nonrandomized studies could only be at moderate or high risk of bias. We rated studies as having a moderate risk of bias if one of those items was not true, even if all of the others were true, or if the reporting on the distribution of potential confounders in each group was at least partially done. If we found two of the elements were not true, we considered the study to have a high risk of bias.

Low risk of bias studies had the least bias and the results were considered valid. Moderate risk of bias studies was susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies. High risk of bias studies had significant flaws that might have invalidated the results.

## **Data Synthesis and Analysis**

For each KQ, we created a detailed set of evidence tables containing all information abstracted from eligible studies. We grouped the information for each KQ by comparison interventions. We conducted narrative synthesis of the evidence since the population, intervention and outcome characteristics across studies were heterogeneous. For studies amenable to pooling with meta-analysis we conducted meta-analysis using relative risks by using a DerSimonian and Laird Random effects model.<sup>47</sup> We identified substantial statistical heterogeneity in the trials as an I-squared statistic with a value greater than 50 percent. Since most of the outcomes were rare and several studies had zero events, with an imbalance in treatment arms we used the treatment arm continuity correction approach to estimate the relative risk.<sup>48</sup> We conducted sensitivity analysis using alternative continuity corrections (0.5, 0.1) as well as no continuity correction (Peto Odds Ratio). All analyses were conducted using Stats Direct and Stata version 11.0.<sup>48</sup> For KQ 1, we calculated 95% exact binomial confidence intervals surrounding the proportions of patients experiencing events in each of the observational studies. These were plotted ordered by the year of the study with the size of the box representing the number of individuals in the denominator.

## **Grading the Evidence for Each Key Question**

After synthesizing the evidence, two reviewers graded the quantity, quality, and consistency of the best available evidence addressing KQs 1 to 8 by adapting an evidence grading scheme recommended in the “Methods Guide for Conducting Comparative Effectiveness Reviews.”<sup>49</sup> In assigning evidence grades, we considered the four recommended domains, including risk of bias in the included studies, directness of the evidence, consistency across studies, and precision of the pooled estimate or the individual study estimates. We were unable to assess for publication bias or selective outcomes reporting because the tests for publication bias were underpowered when the number of studies is low (<10).

The risk of bias for an individual study was derived from the algorithm described above. We assessed the aggregate risk of bias of studies and integrated these assessments into a qualitative assessment of the summary risk of bias score. Since the majority of studies in our evidence based were at high risk of bias, most aggregate scores resulted in a high risk of bias rating. A small minority of trials were rated as low to moderate risk of bias.

Precision of individual studies was assessed by evaluating the statistical significance of a comparison. We found that few of the studies reported effect sizes and 95% confidence intervals. We estimated the confidence intervals for some of the outcomes, and also visually examined the

Forest plots to assess precision for certain outcomes. We also examined the summary estimates to assess precision for certain outcomes when meta-analysis was possible. If all studies in an evidence base were precise then the evidence base was rated to be precise. Studies whose effect size overlapped with the line of no difference were designated as imprecise. When studies did not report measures of dispersion or variability we rated the precision as unknown.

We rated the evidence as being direct if the intervention was directly linked to the patient oriented outcomes of interest in our analytic framework. We rated the evidence as indirect for intermediate outcomes (anti-Xa) when direct evidence linking the intervention to the ultimate health outcome was lacking.

We used an algorithm for assigning consistency based on the number of studies with similar directions of effect. If all the studies in an evidence base showed a similar direction of effect, we rated the evidence base as consistent. Single studies were rated as having unknown consistency.

To incorporate multiple domains into an overall grade to the strength of the body of evidence we used the estimate of the summary risk of bias score, directness, and consistency along with precision to provide support for an intervention. We used a qualitative approach to incorporating these multiple domains into an overall grade. Since the majority of observational studies were at high risk of bias, we initially assigned a low strength of evidence for outcomes from such studies. Consistent, precise and direct evidence from such high risk of bias studies was rated as low strength of evidence. The strength of evidence was downgraded to insufficient when consistency was unknown (i.e. single study) or inconsistent. The strength of evidence was downgraded to insufficient when evidence was indirect. Imprecision or unknown precision also led to a downgrade in the strength of evidence from low to insufficient. We also had a small minority of trials that were at low or moderate risk of bias in the updated search. Evidence from such studies was initially assigned a high or moderate strength of evidence based on the risk of bias ratings. Each further weakness in the SOE domain, such as indirectness, imprecision or inconsistency led to a further downgrade in their SOE ratings. A single study of high or moderate risk of bias was considered insufficient evidence. We classified evidence pertaining to KQs 1 to 8 into four categories: (1) “high” grade (indicating high confidence that the evidence reflects the true effect, and further research is very unlikely to change our confidence in the estimate of the effect); (2) “moderate” grade (indicating moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of the effect and may change the estimate); (3) “low” grade (indicating low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) “insufficient” grade (evidence is not sufficient to draw a conclusion).

## **Assessing Applicability**

Two reviewers assessed applicability separately for the outcomes of benefit (reduction in VTE) and harm (increased risk of bleeding) for the entire body of evidence guided by the PICOTS framework as recommended in the “Methods Guide for Comparative Effectiveness Reviews.”<sup>49</sup> We evaluated whether the include populations in these studies were representative of participants in the real world. We assessed whether the concomitant interventions administered in these studies were also representative of real world management strategies for these special populations. We assessed whether there were features of the individuals studies which limited the applicability of the study’s findings including whether studies excluded patients with comorbidities, whether studies allowed or disallowed the concomitant use of

nonmedical co-interventions (early ambulation), and the choice and dosing of comparators. We assessed whether findings were applicable to various ethnic groups.

## **Peer Review and Public Comment**

A full draft report was reviewed by experts and posted for public commentary from August 2, 2012, through August 30, 2012. Comments received from either invited reviewers or through the public comment website were compiled and addressed. A disposition of comments will be posted on the Effective Health Care Program Web site 3 months after the release of the evidence report.

**Table 3. PICOTS (population, intervention, comparator, outcome, timing, and setting) for each Key Question**

<b>PICOTS</b>	<b>KQ 1</b>	<b>KQ 2</b>	<b>KQ 3–KQ 5</b>	<b>KQ 6</b>	<b>KQ 7–KQ 8</b>
<b>Population(s)</b>	<ul style="list-style-type: none"> <li>• Trauma</li> </ul>	<ul style="list-style-type: none"> <li>• Traumatic brain injury</li> </ul>	<ul style="list-style-type: none"> <li>• Burns (KQ 3)</li> <li>• Liver disease (KQ 4)</li> <li>• Antiplatelet therapy (KQ 5)</li> </ul>	<ul style="list-style-type: none"> <li>• Bariatric surgery</li> </ul>	<ul style="list-style-type: none"> <li>• Obese and underweight patients (KQ 7)</li> <li>• Patients with acute kidney injury or moderate or severe renal impairment (KQ 8)</li> <li>• Patients receiving dialysis (KQ 8)</li> </ul>
<b>Interventions</b>	<ul style="list-style-type: none"> <li>• IVC filters</li> </ul>	<ul style="list-style-type: none"> <li>• Mechanical devices</li> <li>• Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors)</li> <li>• IVC filters</li> </ul>	<ul style="list-style-type: none"> <li>• Mechanical devices</li> <li>• Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors)</li> </ul>	<ul style="list-style-type: none"> <li>• Pharmacologic (UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors)</li> <li>• Mechanical devices</li> <li>• IVC filters</li> </ul>	<ul style="list-style-type: none"> <li>• Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors)</li> <li>• Mechanical devices</li> </ul>
<b>Comparators</b>	<ul style="list-style-type: none"> <li>• No IVC filters. (Studies that included usual care or those that did not use IVC filters as active controls including mechanical prophylaxis (e.g., SCDs, compression stockings) and pharmacologic controls)</li> </ul>	<ul style="list-style-type: none"> <li>• Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis.</li> <li>• Placebo- controlled studies, studies that used active controls, and uncontrolled studies.</li> </ul>	<ul style="list-style-type: none"> <li>• Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis.</li> <li>• Placebo- controlled studies, studies that used active controls, and uncontrolled studies.</li> </ul>	<ul style="list-style-type: none"> <li>• Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis.</li> <li>• Placebo- controlled studies, or studies that used active controls, and uncontrolled studies.</li> </ul>	<ul style="list-style-type: none"> <li>• Low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis.</li> <li>• Placebo- controlled studies, studies that used active controls, and uncontrolled studies.</li> </ul>

**Table 3. PICOTS (population, intervention, comparator, outcome, timing, and setting) for each Key Question (continued)**

PICOTS	KQ 1	KQ 2	KQ 3–KQ 5	KQ 6	KQ 7–KQ 8
<b>Outcomes measures</b>	<ul style="list-style-type: none"> <li>• Symptomatic DVT</li> <li>• Symptomatic PE</li> <li>• Asymptomatic DVT</li> <li>• Bleeding</li> <li>• Mortality</li> <li>• Post-thrombotic syndrome</li> <li>• Quality of life</li> <li>• Length of stay</li> <li>• Allergic reaction</li> <li>• Mechanical device complications</li> <li>• Infections</li> </ul>	<ul style="list-style-type: none"> <li>• Symptomatic DVT</li> <li>• Symptomatic PE</li> <li>• Asymptomatic DVT</li> <li>• Bleeding</li> <li>• Mortality</li> <li>• Post-thrombotic syndrome</li> <li>• Quality of life</li> <li>• Length of stay</li> <li>• Length of ICU stay</li> <li>• Heparin-induced thrombocytopenia</li> <li>• Allergic reaction</li> <li>• Mechanical device complications</li> <li>• Infections</li> </ul>	<ul style="list-style-type: none"> <li>• Symptomatic DVT</li> <li>• Symptomatic PE</li> <li>• Asymptomatic DVT</li> <li>• Bleeding</li> <li>• Mortality</li> <li>• Post-thrombotic syndrome</li> <li>• Quality of life</li> <li>• Length of stay</li> <li>• Heparin-induced thrombocytopenia</li> <li>• Allergic reaction</li> <li>• Mechanical device complications</li> <li>• Infections</li> </ul>	<ul style="list-style-type: none"> <li>• Symptomatic DVT</li> <li>• Symptomatic PE</li> <li>• Asymptomatic DVT</li> <li>• Bleeding</li> <li>• Mortality</li> <li>• Post-thrombotic syndrome</li> <li>• Quality of life</li> <li>• Length of stay</li> <li>• Heparin-induced thrombocytopenia</li> <li>• Allergic reaction</li> <li>• Mechanical device complications</li> <li>• Infections</li> </ul>	<ul style="list-style-type: none"> <li>• Symptomatic DVT</li> <li>• Symptomatic PE</li> <li>• Asymptomatic DVT</li> <li>• Bleeding</li> <li>• Mortality</li> <li>• INR, PTT, Factor Xa level (<b>KQs 7 and 8</b>)</li> <li>• Post-thrombotic syndrome</li> <li>• Quality of life</li> <li>• Length of stay</li> <li>• Bleeding (major, minor)</li> <li>• Heparin-induced thrombocytopenia</li> <li>• Allergic reaction</li> <li>• Mechanical device complications</li> <li>• Infections</li> </ul>
<b>Adverse effects of intervention(s) and treatment burden</b>	<ul style="list-style-type: none"> <li>• Major bleeding defined as including: fatal bleeding; clinically overt bleeding causing a fall in hemoglobin of <math>\geq 2</math> g/dL or leading to transfusion of two or more units of packed cells or whole blood; or bleeding into critical organs (retroperitoneal or intracranial)</li> <li>In surgical patients: an assessment of the amount of blood loss, minor bleeding, surgical site bleeding, and complications from mechanical IVC filters (e.g., device migration, perforation, fractures, filter thrombosis, infections, prolonged hospitalization, mortality)</li> </ul>				
<b>Timings</b>	<ul style="list-style-type: none"> <li>• Studies with all durations of followup</li> </ul>				
<b>Settings</b>	<ul style="list-style-type: none"> <li>• Hospital setting</li> </ul>	<ul style="list-style-type: none"> <li>• Hospital Setting</li> </ul>	<ul style="list-style-type: none"> <li>• Hospital setting</li> </ul>	<ul style="list-style-type: none"> <li>• Hospital setting</li> </ul>	<ul style="list-style-type: none"> <li>• Hospital setting</li> </ul>

DVT = deep vein thrombosis; INR = international normalized ratio; IVC = inferior vena cava; KQ = Key Question; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PTT = partial thromboplastin time; SCD = sequential circumferential compression device; UFH = unfractionated heparin

# Results

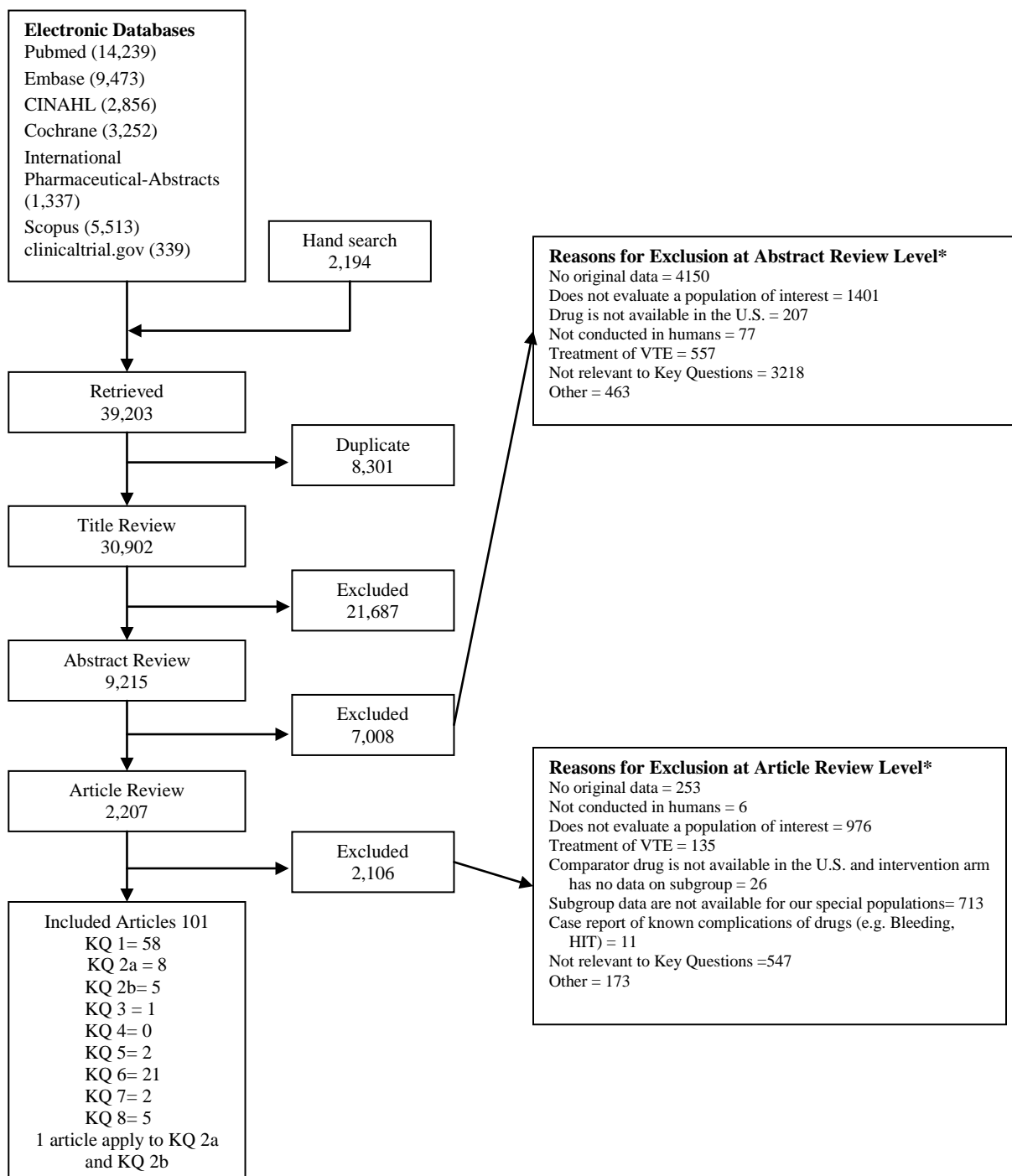
## Results of the Search

Figure 2 summarizes the search results. The literature search identified 30,902 unique citations. During the title screening, we excluded 21,687 citations. During the abstract screening, we excluded 7,008 citations that met at least one of the exclusion criteria. During article screening, we excluded an additional 2106 articles that did not meet one or more of the inclusion criteria. (Appendix D) One hundred and one articles were included in the review.

## Description of Types of Studies Retrieved

Of the 101 articles, only 6 were randomized controlled trials. Of the included studies, 58 studies addressed Key Question (KQ) 1 (patients with trauma), 8 studies addressed KQ 2a (patients with traumatic brain injury), 5 studies addressed KQ 2a (patients with traumatic brain injury–timing of initiation and duration of pharmacological prophylaxis), 1 study addressed KQ 3 (patients with burns), 2 studies addressed KQ 5 (patients receiving antiplatelet therapy), 21 studies addressed KQ 6 (patients having bariatric surgery), 2 study addressed KQ 7 (obese and underweight patients), and 5 studies addressed KQ 8 (patients with acute kidney injury and renal impairment). There were no studies identified that addressed KQ 4 (patients with liver failure).

**Figure 2. Summary of the literature search**



HIT = heparin induced thrombocytopenia; KQ = Key Question; VTE = venous thromboembolism

\*Total exceeds the # in the exclusion box because reviewers were allowed to mark more than 1 reason for exclusion.



## Scientific Information Packets (SIPs)

As part of the grey literature search, pharmaceutical companies with drugs or devices included in this review were asked to provide information about pertinent studies conducted with their products (published, unpublished, and clinical trials). Three companies responded with letters indicating that no relevant studies had been conducted. Four companies provided comprehensive scientific information packets (SIP), which identified potentially relevant studies; these citations were carefully crosschecked against our existing reference database (to avoid redundancy), yielding six new references, none of which were applicable to this review. One additional SIP was submitted by the American Association of Neurological Surgeons; however, this was a chemoprophylaxis protocol and therefore did not meet the eligibility criteria for this review (Appendix F).

## Clinical Trials

The U.S. clinical trials registry (clinicaltrials.gov) was used to identify additional trials pertinent to this review. Using search terms “venous thromboembolism prophylaxis” and “inferior vena cava filter”, we identified 339 clinical trials in adults and seniors until July 2012. Two national IVC filter registries who were recruiting participants were also identified. (Appendix I) Many of the trials were still recruiting participants. Only 15 trials were eligible for review. Five trials were completed. However, results were available for only two trials included in our review.<sup>50,51</sup>

## Key Question 1

What are the comparative effectiveness and safety of inferior vena cava filters to prevent pulmonary embolisms in hospitalized patients with trauma?

## Key Points and Evidence Grades

In hospitalized patients with trauma:

- The strength of evidence is low that IVC filter placement is associated with a lower incidence of PE compared with no IVC filter placement.
- The strength of evidence is low that IVC filter placement is associated with a lower incidence of fatal PE in hospitalized patients with trauma compared with no IVC filter placement.
- The strength of evidence is insufficient that IVC filter placement is associated with less mortality in hospitalized patients with trauma compared with no IVC filter placement.
- The strength of evidence is insufficient that IVC filter placement is associated with a higher incidence of DVT compared with no IVC filter placement
- The strength of evidence is insufficient that IVC filter placement is associated with filter related thrombosis in hospitalized patients with trauma
- The strength of evidence is insufficient that IVC filter placement is associated with filter tilt/migration in hospitalized patients with trauma

## Study Characteristics

### Randomized Controlled Trials and Controlled Observational Studies

Eight controlled studies evaluated the effect of IVC filters versus no filters on VTE events in adult trauma patients<sup>52-59</sup> (Table 4). Two controlled studies also compared IVC filters with IVC filters<sup>60,61</sup> (Table 5).

One was an RCT,<sup>52</sup> three were prospective cohort studies with concurrent comparison groups,<sup>53,56,59</sup> three were prospective cohort studies with historical controls,<sup>54,55,58</sup> and one was a retrospective cohort study.<sup>57</sup> The duration of follow up was 6 months in the RCT. All studies were within single institutions in North America. Only one study reported their funding source. This study was funded by industry.

### Uncontrolled Studies

Forty-eight uncontrolled studies evaluated the use of IVC filters in hospitalized patients with trauma.<sup>34,62-108</sup> They were conducted in North America,<sup>34,62-64,66,67,70-72,75-80,82-108</sup> Europe,<sup>73,74,81</sup> Asia,<sup>69</sup> and Australia.<sup>65,68</sup> Of these 48 studies, there were 36 cohort studies.<sup>34,62,64,65,67,69-72,74-84,87,89,91,94-97,99-104,106-108</sup> There were 13 prospective cohort studies, and the remaining were retrospective cohorts. There was one combined retrospective review and prospective study.<sup>104</sup> There were six case series<sup>66,68,73,90,92,98</sup> and six case reports.<sup>63,85,86,88,93,105</sup> These studies enrolled a median of 99 patients (range, 3 to 310) in the cohort studies, 30 patients (range, 8 to 249) in the case series, and one patient (range, 1 to 2) in the case reports. Four studies enrolled men only,<sup>85,86,93,103</sup> and two studies enrolled women only.<sup>65,105</sup> The majority followed participants during the period of hospitalization until discharge, with only a few cohorts following patients beyond discharge (Table 6).

## Participant Characteristics

### Randomized Controlled Trials and Controlled Observational Studies

The mean age of participants in the RCT was 53.7 years and 41.2 years in the control and IVC filter groups, respectively.<sup>52</sup> Of the enrolled patients, 62.5 and 72.2 percent were men, respectively. The patients in the controlled observational studies were largely aged 35 to 50 years old, with men comprising roughly 60 to 75 percent of the studied population.

Only two studies reported exclusion criteria. The trial excluded pregnant patients, patients with previously placed IVC filters, those with a contraindication to filter placement, and patients that were terminally ill or not expected to survive for more than 24 hours.<sup>52</sup> A second study excluded elderly patients with isolated rib fractures.<sup>54</sup> The remaining studies did not report exclusion criteria. Most studies did not describe the race of the patients.

### Uncontrolled Studies

The mean age of patients in the uncontrolled studies was roughly 40 years. The majority of studies enrolled both men and women with a preponderance of men in each study population. The mean injury severity scores were variable and ranged from 23.1<sup>95</sup> to 38<sup>74</sup> across studies, reflecting varying degrees of trauma severity. The inclusion and exclusion criteria varied widely (Table 6).

## Intervention Characteristics

### Randomized Controlled Trials and Controlled Observational Studies

Eight studies evaluated the comparative effectiveness of IVC filters versus no IVC filters in trauma patients.<sup>52-59</sup> All studies analyzed patients in two groups. One group of patients received “standard” therapy alone, and the other group received IVC filters in addition to “standard” therapy. The definitions of standard therapy varied. The most common standard therapy was a combination of venous compression devices with subcutaneous LMWH.<sup>52,55-58</sup> Two studies defined standard therapy as venous compression devices alone.<sup>53,54</sup> One study provided various VTE prophylaxis regimens (some venous compression devices and others LMWH).<sup>59</sup>

Two retrospective cohort studies compared the effectiveness of different kinds of IVC filters on the prevention of VTE in hospitalized patients with trauma.<sup>60,61</sup> One study compared the Gunther Tulip filter with the Celect filter.<sup>60</sup> Both of these filters are temporary and clinicians placed them bedside in the ICU. The second study compared the Gunther Tulip filter with the Optease filter.<sup>61</sup> Both of these filters are temporary and interventional radiologists placed them in angiography suites.

### Uncontrolled Studies

The uncontrolled IVC filter studies varied in the protocol used for VTE prophylaxis. Thirty-three studies used IVC filters only<sup>34,62,65-67,69-73,76-79,83-86,88-91,93,96-98,101-103,105-108</sup> and 15 studies involved the use of concurrent therapy with a pharmacological agent,<sup>63,64,81,99</sup> a mechanical agent,<sup>104</sup> or a combination of a pharmacological agent and a mechanical agent.<sup>68,74,75,80,82,87,92,94,95,100</sup> The brand of filters varied and included Bard Recovery, Celect®, Cook Bird’s nest, G2®, Gianturco-Roehm Bird’s Nest®, Greenfield Stainless Steel®, Greenfield Titanium®, Gunther Tulip®, OPTEASE®, Poliser, Recovery, Simon Nitinol®, TRAPEASE®, VenaTech LGM®, and Vena Tech LP® types. One retrospective, single-center, uncontrolled study compared outcomes by the specific filter type, which included both permanent (Greenfield, VenaTech, TrapEase) and retrievable (Gunther Tulip, and Recovery IVC) filters.<sup>108</sup> The multi-center study compared three retrievable IVC filters (Gunter-Tulip, Recovery, and OPTEASE).<sup>107</sup> The type of filter was retrievable in 16 studies,<sup>64,65,67-71,73,75-77,79,82,88,103,107</sup> permanent in three studies,<sup>66,95,105</sup> and both permanent and retrievable in five studies.<sup>34,74,81,106,108</sup> Twenty-four studies did not specify the type of filters used.<sup>62,63,72,78,80,83-87,89-94,96-102,104</sup> Two uncontrolled studies also reported data on outcomes by different types of IVC devices.<sup>107,108</sup>

## Ascertainment

### Randomized Controlled Trials and Controlled Observational Studies

Most studies relied on duplex ultrasonography for diagnosis of DVT, although some older studies used outdated modalities such as impedance plethysmography (IPG).<sup>53,55</sup> For the diagnosis of PE, most studies used computed tomography angiography. Some studies used angiography for the diagnosis of PE. Infrequently, studies used ventilation/perfusion scans for PE diagnosis.

### Uncontrolled Studies

Most of the uncontrolled studies used objective measures typically applied in clinical practice to document the occurrence of these events (duplex ultrasonography of DVT, computed

tomography angiography, ventilation-perfusion for PE), while only few reports used other measures, such as plethysomography, venography, and autopsy, when possible.

## Outcomes

Our results for the relative risk meta-analysis on the outcome of PE, fatal PE, mortality, DVT and filter related thrombosis among filters vs no filters in patients with trauma in controlled studies are shown in Figures 3–6. The results for the proportion and 95% Confidence intervals on the outcome of PE, mortality and DVT in uncontrolled studies in patients with trauma are shown in Figures 7–9.

## Pulmonary Embolism

### Inferior Vena Cava Filter Versus No Inferior Vena Cava Filter

We excluded the two studies conducted by Rogers et al from the meta-analysis and strength of evidence ratings as we considered them to have fatal flaws.<sup>53,54</sup> The first Rogers study<sup>54</sup> was excluded because of concerns about data-duplication. Rogers et al 1997<sup>53</sup> may have contained overlapping participants with another study by the same authors.<sup>54</sup> Another study by Rogers study was excluded from the meta-analysis and strength of evidence ratings because of severe prognostic imbalance in Injury Severity Scores (ISS) (mean ISS 22.8 vs. 9.3 in filter vs. control group).<sup>53</sup> In the only included small RCT, there was no statistical difference in the incidence of PE between the two groups.<sup>52</sup> There were no PEs in the IVC filter group and one PE among patients without filters. Five of the seven observational studies reported lower PE rates with IVC filter placement;<sup>54-56,58,59</sup> four of these were statistically significant findings. Two studies reported higher PE rates with IVC filter use.<sup>53,57</sup> However, one had a non-significant finding with a single PE in each group (but many more patients in its control arm).<sup>53</sup> One study of spinal cord injury patients found a single patient who had a PE diagnosed after a clinician placed an IVC filter<sup>57</sup> (Table 7).

We included six controlled studies for the meta-analysis on PE outcomes.<sup>52,55-59</sup> Our meta-analysis showed a precise and consistent evidence of reduction in PE with IVC filters compared with no IVC filters without any evidence of statistical heterogeneity (Figure 3, RR:0.20, 95% CI:0.06-0.70;  $I^2=0\%$ ). Our results were robust to alternative approaches for continuity correction and showed largely similar results (Appendix H).

### Inferior Vena Cava Filter Versus Inferior Vena Cava Filter

Two studies reported on the outcome of PE between Gunther Tulip vs Celect filters<sup>60</sup> and Gunther Tulip vs OPTEASE filters.<sup>61</sup> There were no statistically significant differences in the incidence of PE in the studies although the incidence of PE was higher in the Gunther Tulip arm compared with the OPTEASE arm.<sup>61</sup> Another uncontrolled study which also reported on differences between filter types found no difference in “breakthrough” PE rates between filters (Table 8).<sup>107</sup>

### Uncontrolled Studies of Inferior Vena Cava Filters

Of the 40 total studies, studies reported the occurrence of PE, with percentages ranging from 0 to 5.8 percent, with the vast majority reporting PE proportions of 2 percent or less.<sup>34,63,65-68,71,73-75,76-79,80-97, 99-106,108</sup> Figure 7 describes the proportion and 95% CI of patients with PE in uncontrolled studies of IVC filters among patients with trauma. Most of these studies had limited

follow up. The longest study reported follow up of 7 years for 97 patients, with a PE proportion of 2.1 percent.<sup>66</sup> One study reported only the total PE as the primary outcomes, with a prevalence of 3.5 percent among 226 patients (Table 9).<sup>108</sup>

## **Fatal Pulmonary Embolism**

### **Randomized Controlled Trials and Controlled Observational Studies**

We included four studies that reported on this outcome.<sup>52,55,58,59</sup> In all the included studies there were no PEs in the intervention arm. There was no VTE related deaths in the trial.<sup>52</sup> A prospective cohort study with historical controls identified a statistically significant increase in the incidence of fatal PE in patients that did not receive IVC filters (4 percent vs. zero percent. p-value < 0.03).<sup>58</sup> There were no differences in fatal PE in two prospective cohort studies that compared IVC filters with compression devices.<sup>53,54</sup>

Figure 4 shows the relative risk meta-analysis on the outcome of fatal PE (RR, 0.09 (0.01 to 0.81)). There was a precise and consistent evidence of reduction in fatal PE with IVC filters compared with no IVC filters, without any evidence of statistical heterogeneity (RR, 0.09, 95% CI 0.01 to 0.81;  $I^2=0\%$ ). However, sensitivity analysis with alternative continuity corrections were not uniformly robust for the outcome of fatal PE (Appendix H). The Peto OR approach continued to show a statistically significant reduction in fatal PE, Peto OR, 0.22 (95% CI = 0.08 to 0.58), similar to the significant reduction seen in the primary analysis. Alternative continuity corrections such as the 0.5 correction, RR 0.22 (95% CI = 0.04 to 1.16) or 0.01 correction, RR, 0.01 95% CI = 0 to 425.5) were not statistically significant. Given the fragility of these findings the significant reductions in fatal PE should be viewed with caution.

### **Uncontrolled Studies**

Among the uncontrolled studies that reported on prophylactic IVC filters in hospitalized patients with trauma, five studies reported on the outcome of fatal PE.<sup>74,80,92,95,97</sup> Four studies reported no deaths due to PE.

## **Mortality**

### **Randomized Controlled Trials and Controlled Observational Studies**

#### **Inferior Vena Cava Filters Versus No Inferior Vena Cava Filters**

We included three studies that reported on mortality in the meta-analysis.<sup>52,58,59</sup> Figure 5 shows the relative risk meta-analysis on the outcome of mortality RR, 0.70 (0.40 to 1.23;  $I^2=6.7\%$ ).

Our results were robust to alternative approaches for continuity correction and showed largely similar results (Appendix H). There were no differences observed in the trial with regards to VTE and non-VTE mortality between groups.<sup>52</sup> In another prospective cohort study, all-cause mortality was higher in the IVC filters group as compared with the compression device only group (11.4 percent vs. 5.1 percent).<sup>53</sup> Similarly, in another study, total mortality was higher in the IVC filter group than the compression device only group,<sup>54</sup> while higher mortality was reported in the control group compared with IVC filter in another study.<sup>58</sup>

## **Inferior Vena Cava Filters Versus Inferior Vena Cava Filters**

The study by Rosenthal et al. defined a secondary outcome as total mortality unrelated to VTE. In this study, the mortality was higher in the Gunther tulip group than in the Celest group (29 percent vs. 11 percent).<sup>60</sup>

## **Uncontrolled Studies**

Thirty studies reported on mortality in hospitalized patients with trauma. Figure 10 describes the proportion and 95% CI of patients with mortality in uncontrolled studies of IVC filters among patients with trauma. The mortality rates were variable and ranged from 0 percent to as high as 31 percent.<sup>82,92</sup>

## **Deep Vein Thrombosis**

### **Randomized Controlled Trials and Controlled Observational Studies**

#### **Inferior Vena Cava Filters Versus No Inferior Vena Cava Filters**

Three studies reported on DVT outcomes.<sup>52,57,59</sup> In the RCT, there were no significant differences in the incidence of DVT between the two groups. There was one DVT in the IVC filter group and none in the control group.<sup>52</sup> One retrospective cohort study reported a statistically significant increase in the incidence of DVT in the IVC filter group (20.4 percent vs. 5.2 percent,  $p$  value <0.021).<sup>57</sup> One additional study found a non-significant difference in DVT incidence, which was lower in the IVC filter group (15 percent vs. 19 percent).<sup>59</sup>

Figure 6 shows the relative risk meta-analysis on the outcome of DVT (RR 1.76, 95% CI = 0.49 to 6.18;  $p=0.38$ ). This demonstrates the substantial statistical heterogeneity among the included studies with an  $I^2=56.8\%$ . The results of sensitivity analysis to examine the influence of alternative continuity corrections were largely similar (Appendix H).

#### **Inferior Vena Cava Filters Versus Inferior Vena Cava Filters**

Two studies reported on the outcome of DVT between Gunther Tulip vs Celest filters<sup>60</sup> and Gunther Tulip vs OPTASE filters.<sup>61</sup> Although the data were sparse both studies reported a higher incidence of DVT in the Gunther Tulip arm. There were no statistically significant differences in the incidence of DVT.

## **Uncontrolled Studies**

Twenty-three studies reported the total DVT events, with proportions ranging from 0 to 23 percent, with a total sample size ranging between one to 249 patients.<sup>34,62,63,74,77,78,80,81,83,87,89-92,94,95,97-100,102,104,107</sup> Figure 9 describes the proportion and 95% CI of patients with DVT in uncontrolled studies of IVC filters among patients with trauma.

Nine studies reported lower extremity DVT events with sample sizes of one to 122 patients.<sup>64,65,69,70,72,75,79,93,107</sup> The follow up was limited to a hospital stay or up to 2 months, except for one study that had a 1-year followup.<sup>70</sup> The event rates ranged between 0 and 7.8 percent. Only two studies reported upper-extremity DVT events.<sup>68,76</sup> Those two studies had 17 and 83 patients, respectively, and one upper extremity DVT occurred in either group, corresponding to rates of 5.8 and 1.2 percent, respectively.

## Filter Complications

### Randomized Controlled Trials and Controlled Observational Studies

#### Inferior Vena Cava Filters Versus No Inferior Vena Cava Filters

Four comparative studies reported data on filter complications<sup>53,54,58,59</sup>. The majority of the adverse events were related to filter complications, such as tilting,<sup>53</sup> migration,<sup>110</sup> IVC thrombosis and insertion-site thrombosis.<sup>54</sup> Of these, insertion-site thrombosis was the most common, occurring in 5.7 percent of patients in one study.<sup>53</sup> Other filter complications such as tilting and migration occurred less frequently, occurring in 1 to 2 percent of patients in most studies (Table 10).

#### Inferior Vena Cava Filters Versus Inferior Vena Cava Filters

Two studies examined the comparative effectiveness of different kinds of filters and reported adverse events.<sup>60,61</sup> In the study by Rosenthal et al., four patients developed groin hematomas and six patients in the Gunther Tulip group had filter misplacement at insertion.<sup>60</sup> In the Celect arm, one patient developed a groin hematoma and another patient had filter migration. In the study by Keller et al., one patient developed filter migration, and 7 percent of the patients developed acute caval occlusion in the Gunther Tulip arm.<sup>61</sup> In the OPTEASE arm, 3 percent of the patients developed acute caval occlusion. No filter migrations occurred in the OPTEASE arm.

### Uncontrolled Studies

#### Strut Fracture

Seven uncontrolled studies reported on the outcome of strut fracture with IVC filters.<sup>34,65,66,70,76,79,81</sup> These rates were uniformly low and affected fewer than 1.5 percent of filter recipients (Table 11).

#### Filter Migration

Sixteen uncontrolled studies reported on the rare occurrence of filter migration (Table 11).<sup>66,71-74,82,84,86,87,90,91,99,100,102,103,111</sup>

#### Filter Tilt

Eight uncontrolled studies reported on the rare complication of filter tilt.<sup>34,71,74,81,89,97,99,102</sup> One study of 132 patients with 5-year follow up data reported substantial filter tilt (> 14 degrees) among 5.5% of participants. The same study also reported strut malposition proportions as high as 38 percent.<sup>97</sup> Another small study of 13 patients, assessing the retrievability of Bard filters at 180 days, reported a mild filter tilt (3 to 25 degrees) in eight cases (61.5%), and more severe filter tilt (greater than 10%) in two patients (15%)<sup>71</sup> (Table 11).

#### Filter Thrombosis

Seventeen uncontrolled studies reported on the complication of filter related thrombosis.<sup>65,69,71,74,75,77,79,80-82,84,87,90,96,100,103,104</sup> These included the complications of insertion-site thrombosis or occlusion.<sup>82</sup> The rates were uniformly low. The rates of insertion related thrombosis was zero in several studies<sup>71,82,96,102</sup> and 3.1 percent at 5 years in the long term study<sup>97</sup> (Table 11).

Our data on filter-related thrombosis should be interpreted with caution. In the primary studies, occurrence of thrombus within an IVC filter is variably reported as a device-related complication (i.e., the filter promoted thrombosis) or described as a successful use of the device (i.e., the filter did what it was supposed to do—it trapped a large embolus). The long-term impact of filter-related thrombosis is unclear—it can be entirely asymptomatic or cause significant symptoms in the legs and lower body.

### **Arterial-Venous Fistulas**

Two uncontrolled studies reported on the outcome of arterial-venous fistulas<sup>79,94</sup> with IVC filters. The percentage of patients developing fistulas ranged from 0<sup>79</sup> to 0.5 percent.<sup>94</sup>

### **Filter Misplacement**

Ten uncontrolled studies reported on the outcome of filter misplacement.<sup>77,79,81,84,89,92,94-96,100</sup> The percentage of patients having filter misplacement ranged from as low as 0 percent to as high as 3.2 percent.<sup>79,96</sup> The overall proportions were uniformly low to allow any meaningful analysis (Table 11).

### **Filter Penetration or Perforation**

Ten uncontrolled studies reported on the complication of filter perforation or penetration.<sup>63,65,67,77,79,82,85,89,90,96</sup> Five studies reported no filter perforation in any patients.<sup>79,81,82,90,96</sup> The overall rates were uniformly low to allow any meaningful analysis. One small study reported small (<1 cm) IVC defects without contrast extravasations in three patients among 44 patients who underwent uneventful filter retrieval<sup>77</sup> (Table 11).

### **Inferior Vena Cava Thrombosis or Occlusion**

Thirteen uncontrolled studies reported on the complication of IVC thrombosis or occlusion.<sup>70,73,80,84,89,91,95,98-100,102,103,108</sup> The overall proportions were uniformly low. Two studies reported no IVC thrombosis or occlusion<sup>80,103</sup> (Table 11).

### **Bleeding**

Thirteen uncontrolled studies reported on bleeding complications.<sup>77,79,81,84,89,90,92,94-97,100,103</sup> The type of bleeding included minor bleeding, groin hematomas, and non-serious bleeding. The percentages ranged from no episodes of bleeding in several studies to rates as high as 3 percent of filter recipients.<sup>97</sup> The overall proportions were uniformly low (Table 11).

### **Infections**

Four uncontrolled studies reported on infections.<sup>79,83,87,89</sup> Two studies reported no infections during the studies. Another study reported that 2.5 percent of patients had sepsis,<sup>83</sup> while another study reported rates as high as 3.8 percent.<sup>89</sup> None of these studies could distinguish whether these complications were filter related or due to the underlying risks of the severely injured trauma population.

### **Other Adverse Events**

Other complications reported in a single patient included technical failure to remove IVC filter in one study,<sup>62</sup> incorrect deployment of the IVC filter in a single patient in the operating room in another study,<sup>97</sup> and supraventricular tachycardia in a patient during insertion in another study.<sup>72</sup>



## **Proportion of Filters Retrieved**

### **Randomized Controlled Trials and Controlled Observational Studies**

An increasing number of temporary filters are being placed in patients with trauma to prevent PE. However there are concerns that several of these temporary filters are not retrieved in the long term placing patients at higher risk of filter related complications. Among 16 filters that were retrievable in the RCT only 2 were retrieved at 6 months.<sup>52</sup> Retrieval rates were not consistently reported in the controlled observational studies.

### **Inferior Vena Cava Filters Versus Inferior Vena Cava Filters**

In the study by Rosenthal et al., the filter retrieval rate was higher in the Celect filter arm (84 percent vs. 54 percent) compared with the Gunther Tulip filter.<sup>60</sup> The study by Keller et al. reported the filter retrieval rate as a secondary outcome. The filter retrieval rate was higher in the OPTEASE filter group than the Gunther Tulip filter (70 percent vs. 49 percent).<sup>61</sup>

### **Uncontrolled Studies**

Seventeen uncontrolled studies reported on the proportion of filters retrieved after prophylactic IVC filter placement among patients with trauma.<sup>34,62,64,65,67-71,73-79,106</sup> There was great variability in these proportions. Although, one small cohort study of 13 patients reported clinicians retrieved all of the filters they inserted, the usual recovery rates in other cohorts were lower.<sup>71</sup> These ranged from clinicians removing as few as one-third of the filters they inserted. Most other studies reported filter retrieval proportions that were higher.

### **Post-Thrombotic Syndrome**

One uncontrolled study reported on the outcome of post-thrombotic syndrome in patients having prophylactic IVC filter placement. Among 30 patients with IVC filters, post-thrombotic syndrome occurred in 14 patients.<sup>100</sup> Post-thrombotic syndrome is usually considered a long-term outcome related to DVT.

### **Length of Stay in the Hospital and Intensive Care Unit**

Only six uncontrolled studies reported on length of stay in the hospital.<sup>74,76,83,90,91,112</sup> The length of stay in the hospital ranged from a median duration of 28 days (range 11-139)<sup>74</sup> to 38.5 days (range 6-118).<sup>90</sup> Among these six studies, two studies<sup>74,90</sup> also reported on the length of stay in the intensive care unit. The median length of stay in days in the ICU was 15.4 (range 2-93) in one study<sup>90</sup> while it was 15.0 (range 1-53) in the other.<sup>74</sup>

### **Risk of Bias**

We rated the only small RCT on this question as having a high risk of bias<sup>52</sup> Among the controlled observational studies, only one was rated as having a moderate risk of bias and the remainder as having a high risk of bias.<sup>57</sup>

For the uncontrolled observational studies, we rated only four studies as having a moderate risk of bias and the remainder as having a high risk of bias.<sup>67,79,90,107</sup> (Appendix E). Two included studies had severe methodological flaws including substantial differences in injury severity score and inadequate adjustment for injury severity score and concerns for potential duplication that they were ineligible for inclusion in the meta-analysis and assessment of the strength of evidence.<sup>53,54</sup>

## Strength of Evidence

All included studies which assessed the comparative effectiveness and safety of IVC Filter vs no filters were at high risk of bias, except one study at moderate risk of bias<sup>57</sup> (Table 12).

We rated the strength of evidence as low to support reduction in PE and fatal PE in trauma with IVC filters compared with no filters. We based this rating on the high risk of bias, precision and consistency and directness of findings across studies. (Figure 3 and Figure 4). Our estimates for PE were robust to alternative statistical approaches, whereas the estimates for fatal PE were more fragile. Given the fragility of these findings the significant reductions in fatal PE should be viewed with caution

We rated the strength of evidence as insufficient to support a reduction in mortality in trauma with IVC filters. We based this rating on the high risk of bias, imprecision and inconsistency in the findings across studies (Figure 5). We rated the strength of evidence as insufficient to support an increase in DVT in trauma with IVC filters. We based this rating on the high risk of bias, imprecision and inconsistency in the findings across studies (Figure 6). We rated the strength of evidence as insufficient to support an increase in filter related thrombosis in trauma with IVC filters. We based this rating on the high risk of bias, precision, directness and unknown consistency in the findings from a single study.<sup>58</sup>

## Applicability

Most of these studies occurred in trauma centers and their findings would apply to severely injured trauma patients. Although most studies occurred at level 1 trauma centers, the findings might also apply to injured patients cared for in other settings with access to IVC filters. The patients in these studies were mostly severely injured as noted in their high mean/median ISS scores. The applicability of these findings to patients with less severe trauma is unknown. The proportion of men was typically higher than women, as expected in any trauma study, which may impact the generalizability of these results to female trauma patients. The studies are most directly applicable to the middle-aged adult patient population as that was the population most frequently studied, although most studies did not have any older age range cutoff. Information on racial composition was unavailable from several studies to comment on whether these findings are applicable to nonwhite patients. The definitions of standard therapy varied across studies making it difficult to determine applicability to settings where the standard therapy may be different.

**Table 4. Study characteristics for controlled studies (IVCF vs. control) for KQ 1**

Author, Year	Study Design	Arm	Sample Size (N)	Mean Age, Years	% Male	Mean ISS Scores
Rajasekhar A, 2011 <sup>52</sup>	RCT	IVCF	18	41.2	72.2	26.6
		Control	16	53.7	62.5	24.1
Rogers FB, 1997 <sup>53</sup>	PC	IVCF	35	58.4	NR	22.8
		Control	905	38.9	NR	9.83
Gosin JS, 1997 <sup>56</sup>	PC	IVCF	99	42.6	71.7	23.4
		Control	249	NR	NR	NR
Rogers FB, 1995 <sup>54</sup>	Historical comparison	IVCF	63	38.9	73.0	31.5
		Controls	2525	NR	NR	NR
Wilson JT, 1994 <sup>55</sup>	Historical comparison	PGF	15	31.4	NR	30.0
		Control	111	30.0	NR	29.0
Gorman PH, 2009 <sup>57</sup>	RC	IVCF	54	37.1	96.0	NR
		Control	58	48.1	69.0	NR
Rodriguez JL, 1996 <sup>59</sup>	PC	IVCF	40	44.0	58.0	31 .0
		Control	80	41.0	68.0	29.0
Khansarinia S, 1995 <sup>58</sup>	Historical comparison	PGF	108	35.9	76.0	28.0
		Control	216	38.3	75.5	25.4

IVCF = inferior vena cava filter; PGF = prophylactic Greenfield filter; RCT = randomized controlled trial; PC = prospective cohort; RC = retrospective cohort

**Table 5. Study characteristics for controlled studies of an inferior vena cava filter (IVCF) versus IVCF for KQ 1**

Author, Year	Study Design	Filter Type†	Sample Size (N)	Mean Age	% Male	Mean ISS	Filter Retrieval Rate %
Rosenthal D, 2009 <sup>60*</sup>	RC	Gunther Tulip	97	44	58.2	28.5	54
		Celect Retrievable	90	44	58.2	28.5	84
Keller IS, 2007 <sup>61</sup>	RC	Gunther Tulip	92	45.6	69.6	NR	49
		OptEase	80	47.8	58.8	NR	70

NR = not reported; RC = retrospective cohort\*Study did not report characteristics by treatment group.

†Retrievable and non-retrievable filters.

**Table 6. Study characteristics for uncontrolled studies of IVC filters in trauma**

Author, Year	Study Type	Sample Size (N)	Mean Age, Years	% Male	Filter Retrieval Rate n, (%)
O'Keefe T, 2011 <sup>62</sup>	RC	91	NR	70	(47)
Shang EK, 2011 <sup>63</sup>	Case report	1	46	0	NR
Smooth RL, 2010 <sup>108</sup>	RC	226	49	61.1	NR
Roberts A, 2010 <sup>64</sup>	RC	45	39.7	82.2	17 (37)
Doody O, 2009 <sup>65</sup>	RC	115	47.97	63.4	57 (49.6)
Phelan HA, 2009 <sup>66</sup>	Series	82	34.1	63.4	NR
Cherry RA, 2008 <sup>34</sup>	PC	244	43.8	63.5	82/140 (58.6)
Hermesen JL, 2008 <sup>67</sup>	RC	74	38.4	68	30/39 (77)
Lo CH, 2008 <sup>68</sup>	Series	17	37	70.6	13/16
Mahier A, 2008 <sup>69</sup>	RC	80	38.5	66	29 (36)
Zakhary EM, 2008 <sup>70</sup>	RC	122	38.5	70.1	47/116 (40.5)
Karmy-Jones R, 2007 <sup>107</sup>	RC	310	NR	NR	NR
Rosenthal D, 2007 <sup>106</sup>	RC	105	NR	NR	91/105 (86.7)
Binkert CA, 2006 <sup>71</sup>	RC	13	46.2	46.2	13
Gonzalez RP, 2006 <sup>72</sup>	PC	134	38.6	NR	NR
Meier C, 2006 <sup>73</sup>	Series	37	35	62	32 (86)
Meier C, 2006 <sup>74</sup>	RC	95	38	70.5	65/67 (97)
Rosenthal D, 2006 <sup>75</sup>	RC	127	42	60.6	66 (60)
Stefanidis D, 2006 <sup>76</sup>	PC	83	43	71	47 (57)
Rosenthal D, 2005 <sup>77</sup>	PC	103	40	62.1	44
Hoff WS, 2004 <sup>78</sup>	PC	35	NR	71.4	18 (51.4)
Rosenthal D, 2004 <sup>79</sup>	RC	94	38	60.6	31
Duperier T, 2003 <sup>80</sup>	RC	133	NR	NR	NR
Kurtoglu M, 2003 <sup>81</sup>	PC	11	NR	NR	NR
Offner PJ, 2003 <sup>82</sup>	PC	44	37	55	NR
Carlin AM, 2002 <sup>83</sup>	RC	NR	NR	NR	NR
Conners MS, 2002 <sup>84</sup>	RC	284	41	71	NR
Bochicchio GV, 2001 <sup>85</sup>	Case report	1	48	100	NR
Rogers F, 2001 <sup>86</sup>	Case report	1	48	100	NR
Sekharan J, 2001 <sup>87</sup>	RC	33	38.1	75.8	NR
Sing RF, 2001 <sup>88</sup>	Case report	2	54	50	NR
Sing RF, 2001 <sup>89</sup>	PC	158	42.2	71.5	NR
Greenfield LJ, 2000 <sup>90</sup>	Series	249	43	61.8	NR
Wojcik R, 2000 <sup>91</sup>	RC	105	54.8	71.4	NR
Benjamin ME, 1999 <sup>92</sup>	Series	23	46	86.95	NR
Hughes GC, 1999 <sup>93</sup>	Case report	2	32.5	100	NR
Langan EM, 1999 <sup>94</sup>	PC	NR	NR	NR	NR
McMurtry AL, 1999 <sup>95</sup>	RC	248	33.7	68.1	NR

**Table 6. Study characteristics for uncontrolled studies of IVC filters in trauma (continued)**

Author, Year	Study Type	Sample Size (N)	Mean Age, Years	% Male	Filter Retrieval Rate n, (%)
O'Keefe T, 2011 <sup>62</sup>	RC	91	NR	70	(47)
Shang EK, 2011 <sup>63</sup>	Case report	1	46	0	NR
Smooth RL, 2010 <sup>108</sup>	RC	226	49	61.1	NR
Roberts A, 2010 <sup>64</sup>	RC	45	39.7	82.2	17 (37)
Doody O, 2009 <sup>65</sup>	RC	115	47.97	63.4	57 (49.6)
Phelan HA, 2009 <sup>66</sup>	Series	82	34.1	63.4	NR
Cherry RA, 2008 <sup>34</sup>	PC	244	43.8	63.5	82/140 (58.6)
Hermesen JL, 2008 <sup>67</sup>	RC	74	38.4	68	30/39 (77)
Lo CH, 2008 <sup>68</sup>	Series	17	37	70.6	13/16
Mahier A, 2008 <sup>69</sup>	RC	80	38.5	66	29 (36)
Zakhary EM, 2008 <sup>70</sup>	RC	122	38.5	70.1	47/116 (40.5)
Karmy-Jones R, 2007 <sup>107</sup>	RC	310	NR	NR	NR
Rosenthal D, 2007 <sup>106</sup>	RC	105	NR	NR	91/105 (86.7)
Binkert CA, 2006 <sup>71</sup>	RC	13	46.2	46.2	13
Gonzalez RP, 2006 <sup>72</sup>	PC	134	38.6	NR	NR
Meier C, 2006 <sup>73</sup>	Series	37	35	62	32 (86)
Meier C, 2006 <sup>74</sup>	RC	95	38	70.5	65/67 (97)
Rosenthal D, 2006 <sup>75</sup>	RC	127	42	60.6	66 (60)
Stefanidis D, 2006 <sup>76</sup>	PC	83	43	71	47 (57)
Rosenthal D, 2005 <sup>77</sup>	PC	103	40	62.1	44
Hoff WS, 2004 <sup>78</sup>	PC	35	NR	71.4	18 (51.4)
Rosenthal D, 2004 <sup>79</sup>	RC	94	38	60.6	31
Duperier T, 2003 <sup>80</sup>	RC	133	NR	NR	NR
Kurtoglu M, 2003 <sup>81</sup>	PC	11	NR	NR	NR
Offner PJ, 2003 <sup>82</sup>	PC	44	37	55	NR
Carlin AM, 2002 <sup>83</sup>	RC	NR	NR	NR	NR
Conners MS, 2002 <sup>84</sup>	RC	284	41	71	NR
Bochicchio GV, 2001 <sup>85</sup>	Case report	1	48	100	NR
Rogers F, 2001 <sup>86</sup>	Case report	1	48	100	NR
Sekharan J, 2001 <sup>87</sup>	RC	33	38.1	75.8	NR
Sing RF, 2001 <sup>88</sup>	Case report	2	54	50	NR
Sing RF, 2001 <sup>89</sup>	PC	158	42.2	71.5	NR
Greenfield LJ, 2000 <sup>90</sup>	Series	249	43	61.8	NR
Wojcik R, 2000 <sup>91</sup>	RC	105	54.8	71.4	NR
Benjamin ME, 1999 <sup>92</sup>	Series	23	46	86.95	NR
Hughes GC, 1999 <sup>93</sup>	Case report	2	32.5	100	NR
Langan EM, 1999 <sup>94</sup>	PC	NR	NR	NR	NR
McMurtry AL, 1999 <sup>95</sup>	RC	248	33.7	68.1	NR

**Table 6. Study characteristics for uncontrolled studies of IVC filters in trauma (continued)**

Author, Year	Study Type	Sample Size (N)	Mean Age, Years	% Male	Filter Retrieval Rate n, (%)
Tola JC, 1999 <sup>96</sup>	RC	NR	NR	NR	NR
Rogers FB, 1997 <sup>97</sup>	PC	132	39.1	73	NR
Sing RF, 1997 <sup>98</sup>	Series	8	NR	87.5	NR
Nunn CR, 1997 <sup>99</sup>	PC	49	31	NR	NR
Patton JH Jr, 1996 <sup>100</sup>	RC	110	47.2	61.8	NR
Zolfaghari D, 1995 <sup>101</sup>	RC	45	NR	51.1	NR
Leach TA, 1994 <sup>102</sup>	PC	201	NR	73	NR
Millward SF, 1994 <sup>103</sup>	PC	3	36	100	NR
Rogers FB, 1993 <sup>104</sup>	PC/RC	34	41.6	NR	NR
Bach JR, 1990 <sup>105</sup>	Case report	1	NR	0	NR

ISS = Injury Severity Score; IVC = inferior vena cava; N = number; NR = not reported; PC = prospective cohort; RC = retrospective cohort

**Table 7. Outcomes data for controlled studies (inferior vena cava filter vs. control)**

Author, Year	Arm	Sample Size (N for Analysis)	Total DVT n	Total Mortality n	Fatal PE n	PE n
Rajasekhar A, 2011 <sup>52</sup>	IVCF	18	1	1*	0	0
	Control	16	0	0	0	1
Rogers FB, 1997 <sup>53</sup>	IVCF	35	NR	4	NR	1
	Control	905	NR	46	NR	1
Gosin JS, 1997 <sup>56</sup>	IVCF	99	NR	NR	NR	0
	Control	249	NR	NR	NR	12
Rogers FB, 1995 <sup>54</sup>	IVCF	63	19	3	1	1
	Historical Controls	2525	NR	28	7	25†
Wilson JT, 1994 <sup>55</sup>	IVCF	15	0	NR	0	0
	Control	111	NR	NR	3	8‡
Gorman PH, 2009 <sup>57</sup>	IVCF	54	11	NR	NR	1
	Control	58	3	NR	NR	0
Rodriguez JL, 1996 <sup>59</sup>	IVCF	40	6	2	0	1
	Control	80	15	13	8	14
Khansarinia S, 1995 <sup>58</sup>	PGF§	108	NR	18	0	0
	Control	216	NR	47	9**	13Ω

DVT = deep vein thrombosis; IVCF = inferior venous cavity filter; PE = pulmonary embolism

\*Non-VTE-related death.

†25-total PEs in historical control group, of these 7 were fatal PEs; ‡8- total PEs, of these 3 were fatal PEs; §PGF (Prophylactic Greenfield Filter).

\*\*Statistically significant difference in fatal PE, P = 0.03; Ω13-total PEs, of these 9 were fatal PEs.

**Table 8. VTE outcomes and complications for comparison of different types of IVC filters**

Source	Filter Type	Sample Size (N for Analysis)	Filter Retrieval Rate (%)	Total DVT (n)	Total Mortality (%)	PE (n)
Rosenthal D, 2009 <sup>60</sup> #	Gunther Tulip	97	54	2	29*	1
	Celect Retrievable	90	84	NR	11*	1
Keller IS, 2007 <sup>61</sup> ##	Gunther Tulip Filter	92	49	1	NR	2
	OptEase Filter	80	70	NR	NR	1

DVT = deep vein thrombosis; N = number; PE = pulmonary embolism

\*Non-VTE-related death.

#Rosenthal et al. also reported on complications for Gunther Tulip compared with Celect filters: groin hematomas 4.1 % vs. 1.1% and Filter misplacement/migration: 6.2% vs. 1.1%.

##Keller et al also reported on complications for Gunther Tulip compared with Optease: Filter migration: 1.1% vs. 0% Caval occlusion: 7 % vs. 3%.

**Table 9. Outcomes data for uncontrolled studies of inferior vena cava filters**

Author, Year	Total DVT n (%)	Total Mortality n (%)	PE n (%)
O'Keefe T, 2011 <sup>62</sup>	10 (15)	NR	NR
Smooth RL, 2010 <sup>108</sup>	NR	NR	8 (4)
Roberts A, 2010 <sup>64</sup>	0 (0)	NR	NR
Doody O, 2009 <sup>65</sup>	NR	NR	1 (0.9)
Phelan HA, 2009 <sup>66</sup>	NR	15 (15.5)	2 (2.1)
Cherry RA, 2008 <sup>34</sup>	22 (9)	NR	4 (1.6)
Hermesen JL, 2008 <sup>67</sup>	NR	4 (4.3)	3 (3.2)
Lo CH, 2008 <sup>68</sup>	NR	1 (5.9)	1 (5.9)
Mahier A, 2008 <sup>69</sup>	NR	NR	NR
Zakhary EM, 2008 <sup>70</sup>	NR	NR	NR
Karmy-Jones R, 2007 <sup>107</sup>	18 (20)	NR	NR
Gonzalez RP, 2006 <sup>72</sup>	0 (0)	NR	NR
Meier C, 2006 <sup>73</sup>	NR	1 (2.7)	1 (2.7)
Meier C, 2006 <sup>74</sup>	2 (2.1)	7 (7.4)	1 (1.1)
Rosenthal D, 2006 <sup>75</sup>	NR	39 (30.7)	1 (0.8)
Stefanidis D, 2006 <sup>76</sup>	NR	3 (4)	0 (0)
Rosenthal D, 2005 <sup>77</sup>	2 (1.9)	24 (23.3)	1 (1)
Hoff WS, 2004 <sup>78</sup>	3 (8.6)	NR	0 (0)
Rosenthal D, 2004 <sup>79</sup>	NR	19 (20.2)	1 (1.1)
Duperier T, 2003 <sup>80</sup>	31 (23.3)	0 (0)	1 (0.8)
Kurtoglu M, 2003 <sup>81</sup>	0 (0)	NR	0 (0)
Offner PJ, 2003 <sup>82</sup>	NR	0 (0)	0 (0)
Carlin AM, 2002 <sup>83</sup>	5 (6.4)	2 (4)	0 (0)
Connors MS, 2002 <sup>84</sup>	NR	36 (12.7)	1 (0.4)
Sekharan J, 2001 <sup>87</sup>	2 (6.1)	18 (17)	0 (0)
Sing RF, 2001 <sup>89</sup>	8 (5.1)	18 (11.4)	1 (0.6)
Greenfield LJ, 2000 <sup>90</sup>	16 (10.8)	39 (15.6)	3 (1.5)
Wojcik R, 2000 <sup>91</sup>	NR	13 (6.8)	0 (0)
Benjamin ME, 1999 <sup>92</sup>	0 (0)	3 (13)	0 (0)
Langan EM, 1999 <sup>94</sup>	24 (12.8)	27 (14.4)	1 (0.5)
McMurtry AL, 1999 <sup>95</sup>	6 (2.4)	31 (13)	4 (1.6)
Tola JC, 1999 <sup>96</sup>	NR	4 (0.2)	0 (0)
Rogers FB, 1997 <sup>97</sup>	12 (9.1)	6 (4.4)	3 (2.3)
Sing RF, 1997 <sup>98</sup>	1 (12.5)	1 (12.5)	NR
Nunn CR, 1997 <sup>99</sup>	1 (2.0)	NR	0 (0)
Patton JH Jr, 1996 <sup>100</sup>	7 (6.4)	22 (20)	0 (0)
Zolfaghari D, 1995 <sup>101</sup>	- NR	1 (1.2)	0 (0)
Leach TA, 1994 <sup>102</sup>	1 (0.5)	1 (0.5)	0 (0)
Millward SF, 1994 <sup>103</sup>	NR	0 (0)	0 (0)
Rogers FB 1993 <sup>104</sup>	6 (17.6)	2 (5.9)	0 (0)

DVT = deep vein thrombosis; NR = not reported; PE = pulmonary embolism

**Table 10. Adverse events for controlled studies (inferior vena cava filter vs. control)**

Author, Year	Arm	Sample Size (n)	Filter Related Complications			
			Filter Tilt (%)	Filter Migration (%)	Filter Thrombosis (%)	IVC Thrombosis/Occlusion (%)
Rogers FB, 1997 <sup>53</sup>	IVCF	35	1	NR	2	NR
	Control	905	NR	NR	NR	NR
Rogers FB, 1995 <sup>54</sup>	IVCF	63	NR	NR	2	2
	Control	3088	NR	NR	NR	NR
Rodriguez JL, 1996 <sup>59*</sup>	IVCF	40	NR	NR	NR	NR
	Control	80	NR	NR	NR	NR
Khansarinia S, 1995 <sup>58,†</sup>	PGF	108	NR	1	1†	NR
	Control	216	NR	NR	NR	NR

IVC = inferior vena cava; NR = not reported; PGF = Prophylactic Greenfield Filter

\*gastrointestinal bleeding requiring blood transfusion: 4 patients.

†Internal jugular vein thrombosis due to the PGF insertion.

‡Authors reported on infection as a complication, but none of the groups developed this complication.

None of the studies reported these filter related adverse events: strut fracture, misplacement, perforation and bleeding.



**Table 11. Adverse events for uncontrolled studies of inferior vena cava filters**

Author, Year	Filter Complications							Bleeding Events, N
	Strut Fracture, n (%)	Filter Tilt, n (%)	Filter Migration, n (%)	Filter Thrombosis, n (%)	Misplacement, n (%)	Perforation, n (%)	IVC Thrombosis/Occlusion, n (%)	
Shang EK, 2011 <sup>113</sup>	NR	NR	NR	NR	NR	1 (100%)	NR	NR
Smooth RL, 2010 <sup>108</sup>	NR	NR	NR	NR	NR	NR	15 (6.6)	NR
Doody O, 2009 <sup>65</sup>	1 (1.6)	NR	NR	15 (24.6)	NR	2 (3.3)	1 (1.6)	NR
Phelan HA, 2009 <sup>66</sup>	1 (1.5)	NR	0 (0)	NR	NR	NR	NR	NR
Cherry RA, 2008 <sup>34</sup>	2 (0.8)	1 (0.4)	NR	NR	NR	NR	3 (1.2)	NR
Hermesen JL, 2008 <sup>67</sup>	NR	NR	NR	NR	NR	1 (1.1)	NR	NR
Mahier A, 2008 <sup>69</sup>	NR	NR	NR	8 (25)	NR	NR	NR	NR
Zakhary EM, 2008 <sup>70</sup>	1 (0.6)	NR	NR	NR	NR	NR	4 (3.4)	NR
Binkert CA, 2006 <sup>71</sup>	NR	8 (61.5)*	0 (0)	0 (0)	NR	NR	NR	NR
Gonzalez RP, 2006 <sup>72</sup>	NR	NR	2 (1.5)	NR	NR	NR	NR	NR
Meier C, 2006 <sup>73</sup>	NR	NR	1 (2.7)	NR	NR	NR	5 (13.5)	NR
Meier C, 2006 <sup>74</sup>	NR	2 (3)†	1 (1.1)	5 (5.3)	NR	NR	NR	NR
Rosenthal D, 2006 <sup>75</sup>	NR	NR	NR	3 (2.4)	NR	NR	NR	NR
Stefanidis D, 2006 <sup>76</sup>	1 (1.2)	NR	NR	NR	NR	NR	NR	NR
Rosenthal D, 2005 <sup>77</sup> §	NR	NR	NR	3 (6.8)§	3 (2.9)	3 (6.8)§	NR	3 (2.9)
Rosenthal D, 2004 <sup>79</sup>	0 (0)§	NR	NR	3 (3.2)	3 (3.2)	0 (0)§	NR	2 (2.1)
Duperier T, 2003 <sup>80</sup>	NR	NR	NR	1 (0.8)	NR	NR	0 (0)	NR
Kurtoglu M, 2003 <sup>81</sup> §	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Offner PJ, 2003 <sup>82</sup> §	NR	NR	0 (0)	0 (0)	NR	0 (0)	NR	NR

**Table 11. Adverse events for uncontrolled studies of inferior vena cava filters (continued)**

Author, Year	Filter Complications							Bleeding Events, N
	Strut Fracture, n (%)	Filter Tilt, n (%)	Filter Migration, n (%)	Filter Thrombosis, n (%)	Misplacement, n (%)	Perforation, n (%)	IVC Thrombosis/Occlusion, n (%)	
Conners MS, 2002 <sup>84</sup>	NR	NR	1 (0.4)	1 (0.4)	6 (2)	NR	3 (1)	1 (0.4)
Sekharan J, 2001 <sup>87</sup>	NR	NR	0 (0)	1 (0.9)	NR	NR	NR	NR
Sing RF, 2001 <sup>89</sup>	NR	2 (1.3)	NR	NR	1 (0.63)	1 (0.6)	1 (0.6)	2 (1.3)
Greenfield LJ, 2000 <sup>90</sup> §	NR	NR	1 (1.4)	5 (3.5)	NR	0 (0)	NR	2 (0.8)‡
Wojcik R, 2000 <sup>91</sup>	NR	NR	1 (1)	NR	NR	NR	1 (0.95)	NR
Benjamin ME, 1999 <sup>92</sup>	NR	NR	NR	NR	1 (4.3)	NR	NR	0
Langan EM, 1999 <sup>94</sup>	NR	NR	NR	NR	1 (0.5)	NR	NR	2 (1.1)
McMurtry AL, 1999 <sup>95</sup>	NR	NR	NR	NR	2 (0.8)	NR	3 (1.2)	0
Tola JC, 1999 <sup>96</sup>	NR	NR	0 (0)	0 (0)	0 (0)	0 (0)	NR	0 (0)
Rogers FB, 1997 <sup>97</sup>	NR	7 (5.5)	NR	NR	NR	NR	NR	4 (3.0)
Sing RF <sup>98</sup>	NR	NR	NR	NR	NR	NR	1 (12.5)	NR
Nunn CR, 1997 <sup>99</sup>	NR	1 (2.0)	1 (2.0)	NR	NR	NR	1 (2.0)	NR
Patton JH Jr, 1996 <sup>100</sup>	NR	NR	1 (0.9)	3 (2.7)	3 (2.7)	NR	1 (0.9)	0 (0)
Leach TA, 1994 <sup>102</sup>	NR	1 (0.5)	1 (0.5)	NR	NR	NR	0 (0)	NR
Millward SF, 1994 <sup>103</sup>	NR	NR	0 (0)	1 (33.3)	NR	NR	0 (0)	0 (0)
Rogers FB, 1993 <sup>104</sup>	NR	NR	NR	1 (2.9)	NR	NR	NR	NR

IVC = Inferior vena cava; N = number; NR = not reported

\*Mild Filter tilt in eight cases (61.5%) and more severe tilt in 2 cases 15%.

‡Data for subset of patients who underwent filter retrieval.

‡Data for overall baseline population.

§These studies also reported on insertion-vein thrombosis and rates ranged from 0% in (Offner PJ, 2003), 2% in (Rosenthal D, 2005), 2% in (Greenfield LJ, 2000), 9% in (Kurtoglu M, 2003).

**Table 12. Body of evidence for placement of inferior vena cava filter versus no filter in the prevention of VTE in hospitalized patients with trauma**

Author, Year	Outcome	Risk of Bias	Directness	Precision	Consistency	Strength of Evidence and Magnitude of Effect
	PE	High	Direct	Precise	Consistent	Low that IVC filter placement is associated with a lower incidence of PE in hospitalized patients with trauma compared with no IVC filter placement RR 0.20 (95% CI = 0.06 to 0.70; $I^2=0\%$ )*
Rajeseckhar, A 2011 <sup>52</sup>		High	Direct	Imprecise	Consistent	0% vs. 6.2%
Wilson JT, 1994 <sup>55</sup>		High	Direct	Imprecise		0% vs. 7.2%
Gosin JS, 1997 <sup>56</sup>		High	Direct	Precise		0% vs. 4.8%
Gorman PH, 2009 <sup>57</sup>		Moderate	Direct	Imprecise		1.8% vs. 0%
Khansarinia, S 1995 <sup>58</sup>		High	Direct	Precise		0% vs. 6.0%
Rodriguez JL, 1996 <sup>59</sup>		High	Direct	Precise		2.5% vs. 17.5%
Author, Year	Fatal PE	High	Direct	Precise	Consistent	Low that IVC filter placement is associated with a lower incidence of fatal PE in hospitalized patients with trauma compared with no IVC filter placement RR 0.09 (0.01 to 0.81; $I^2=0\%$ )*
*Rajeseckhar, A 2011 <sup>52</sup>		High	Direct	Imprecise	Consistent	0% vs. 0%
Wilson JT, 1994 <sup>55</sup>		High	Direct	Imprecise		0% vs. 2.7%
Khansarinia, S 1995 <sup>58</sup>		High	Direct	Precise		0% vs. 5.5%
Rodriguez JL, 1996 <sup>59</sup>		High	Direct	Imprecise		0% vs. 10.0%
Author, Year	Mortality	High	Direct	Imprecise	Inconsistent	Insufficient that IVC filter placement is associated with less mortality in hospitalized patients with trauma compared with no IVC filter placement RR 0.70 (0.40 to 1.23; $I^2=6.7\%$ )
*Rajeseckhar, A 2011 <sup>52</sup>		High	Direct	Imprecise	Inconsistent	5.5% vs. 0%
Khansarinia, S 1995 <sup>58</sup>		High	Direct	Imprecise		16.6% vs. 21.7%
Rodriguez JL, 1996 <sup>59</sup>		High	Direct	Imprecise		5.0% vs. 16.2%

**Table 12. Body of evidence for placement of inferior vena cava filter versus no filter in the prevention of VTE in hospitalized patients with trauma (continued)**

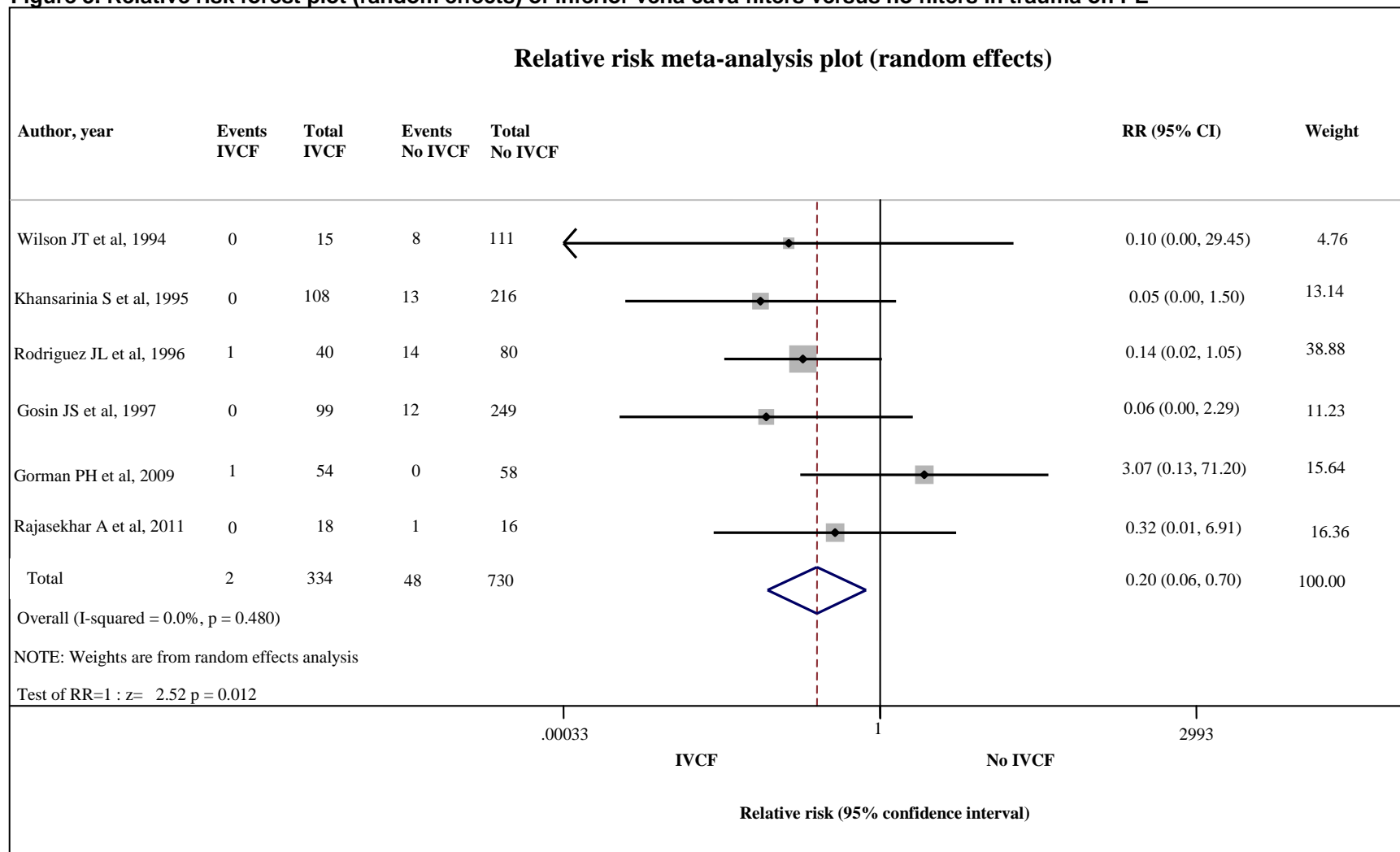
Author, Year	Outcome	Risk of Bias	Directness	Precision	Consistency	Strength of Evidence and Magnitude of Effect
	DVT	High	Direct	Imprecise	Inconsistent	Insufficient that IVC filter placement is associated with a higher incidence of DVT compared with no IVC filter placement RR 1.76 (95% CI = 0.49 to 6.18; $I^2=56.8\%$ ); $p=0.38$
Rajasekhar, A 2011 <sup>52</sup>		High	Direct	Imprecise	Inconsistent	5.5% vs. 0%
Rodriguez JL, 1996 <sup>59</sup>		High	Direct	Imprecise		15.0% vs. 18.7%
Gorman PH, 2009 <sup>57</sup>		Moderate	Direct	Precise		20.4% vs. 5.2%
Author, Year	Filter related thrombosis**	High	Direct	Imprecise	Unknown	Insufficient to support that IVC filter placement is associated with a higher incidence of filter related thrombosis compared with no IVC filter placement
Khansarinia, S 1995 <sup>58</sup>		High	Direct	Imprecise	unknown	1.8% vs. 0%

DVT = deep vein thrombosis; IVC = inferior vena cava; RCT = randomized controlled trial; VTE = venous thromboembolism

\*No VTE-related deaths in the RCT.

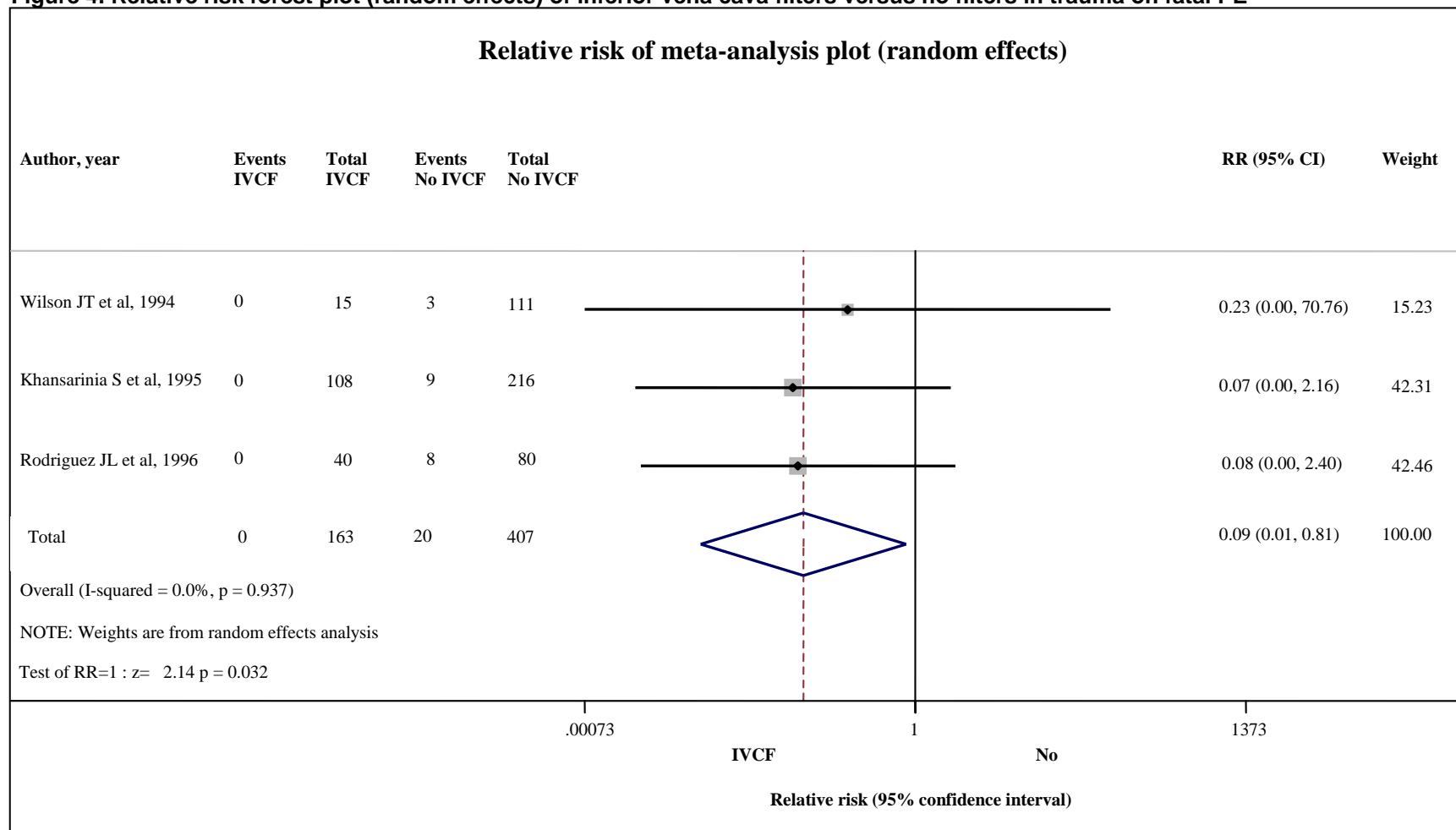
\*\*Graded on Filter related thrombosis. Data were too sparse on other complications such as filter tilt and migration to provide meaningful SOE grades on these specific complications.

**Figure 3. Relative risk forest plot (random effects) of inferior vena cava filters versus no filters in trauma on PE**



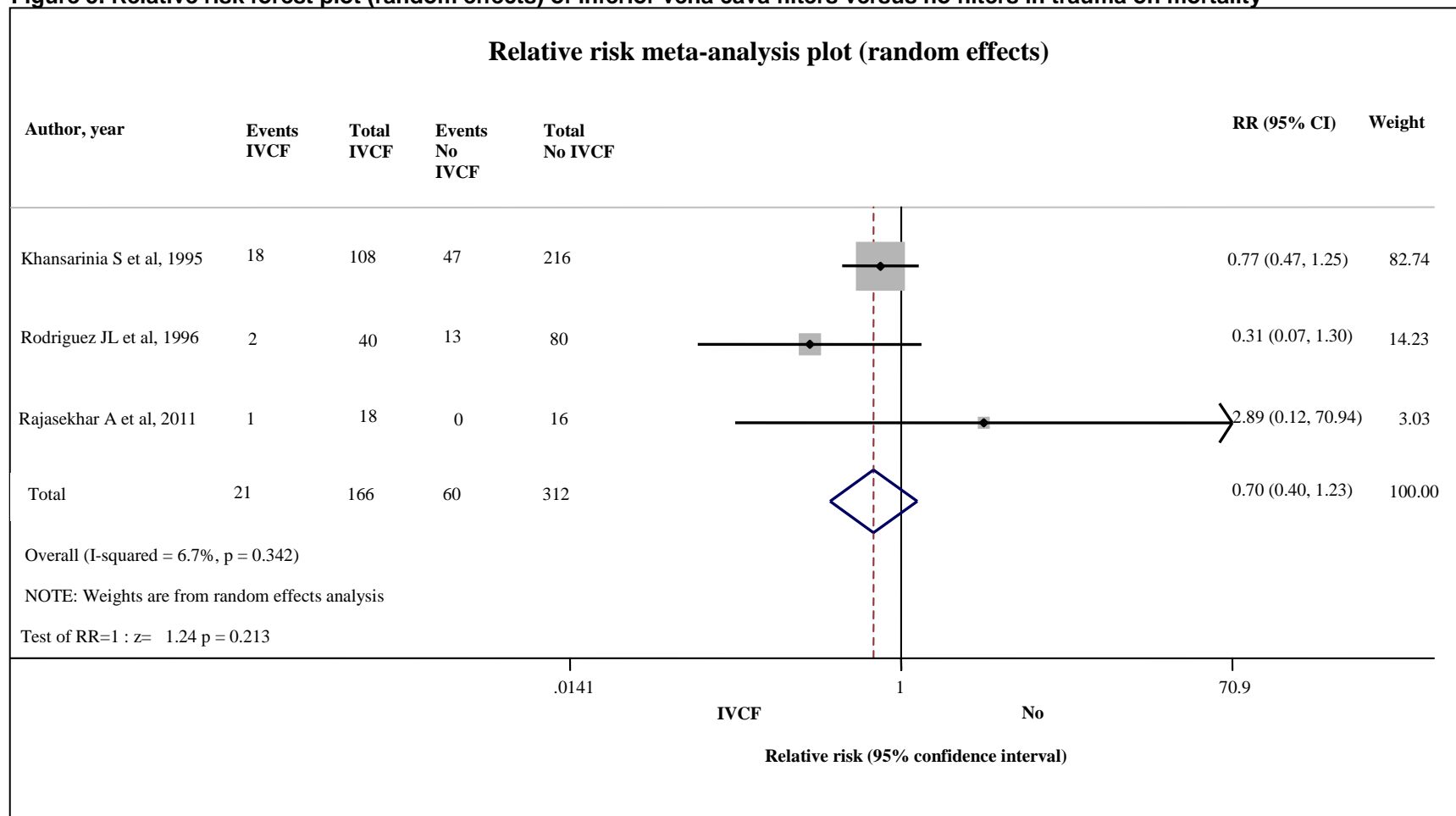
CI = confidence interval; IVCF = inferior vena cava filter; PE = pulmonary embolism; RR = relative risk

**Figure 4. Relative risk forest plot (random effects) of inferior vena cava filters versus no filters in trauma on fatal PE**



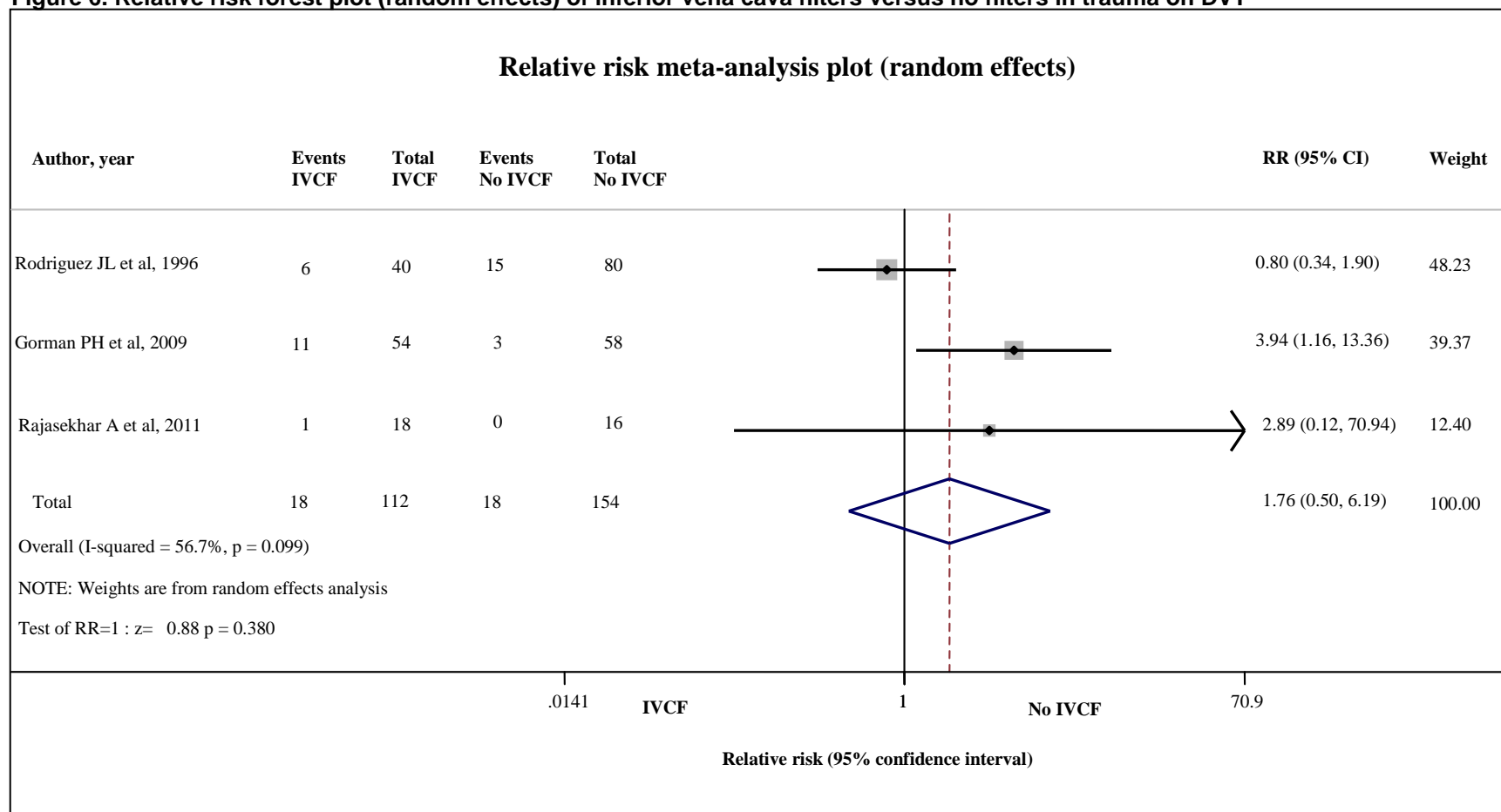
CI = confidence interval; IVCF = inferior vena cava filter; PE = pulmonary embolism; RR = relative risk

**Figure 5. Relative risk forest plot (random effects) of inferior vena cava filters versus no filters in trauma on mortality**



CI = confidence interval; IVCF = inferior vena cava filter; RR = relative risk

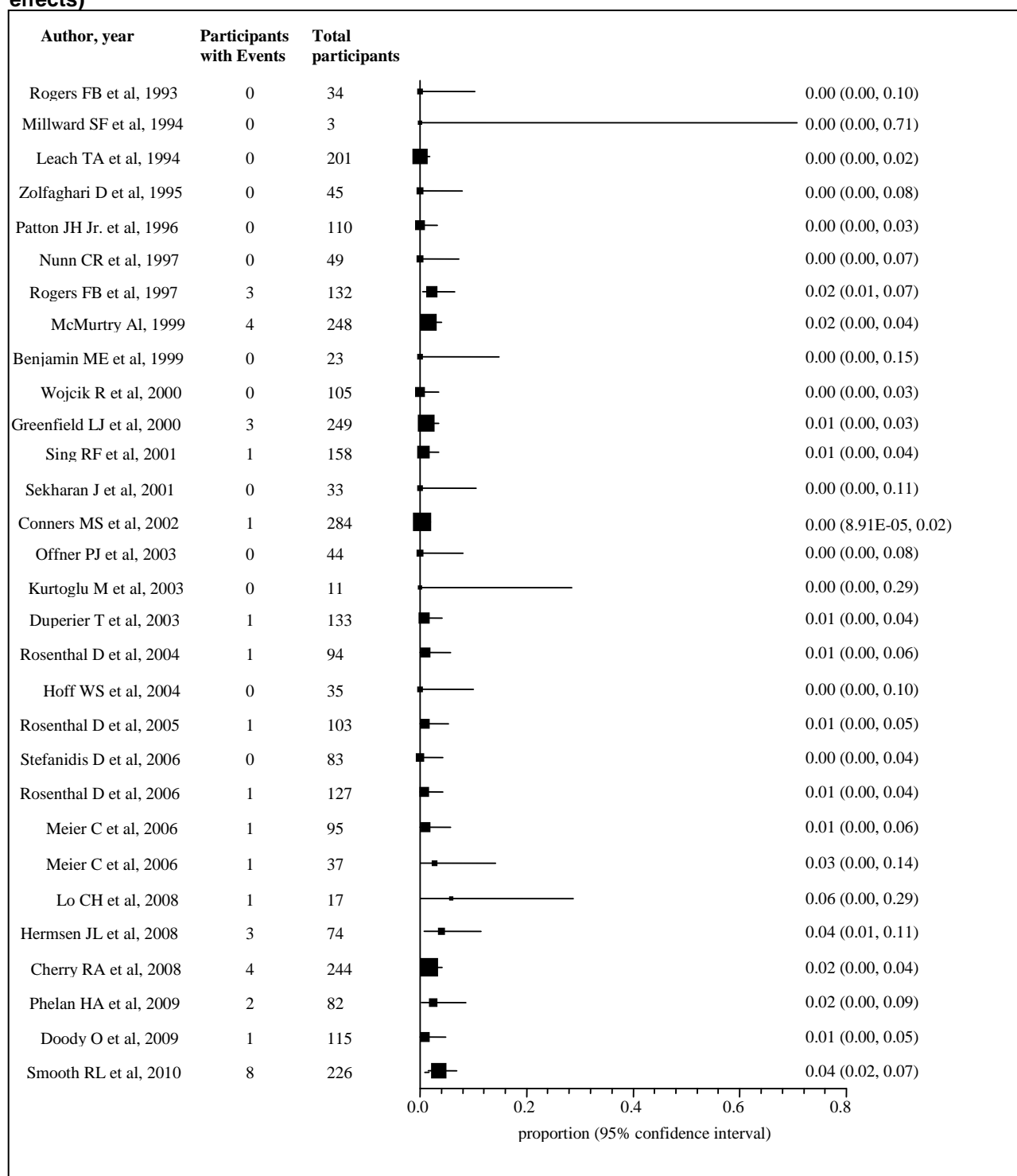
**Figure 6. Relative risk forest plot (random effects) of inferior vena cava filters versus no filters in trauma on DVT**



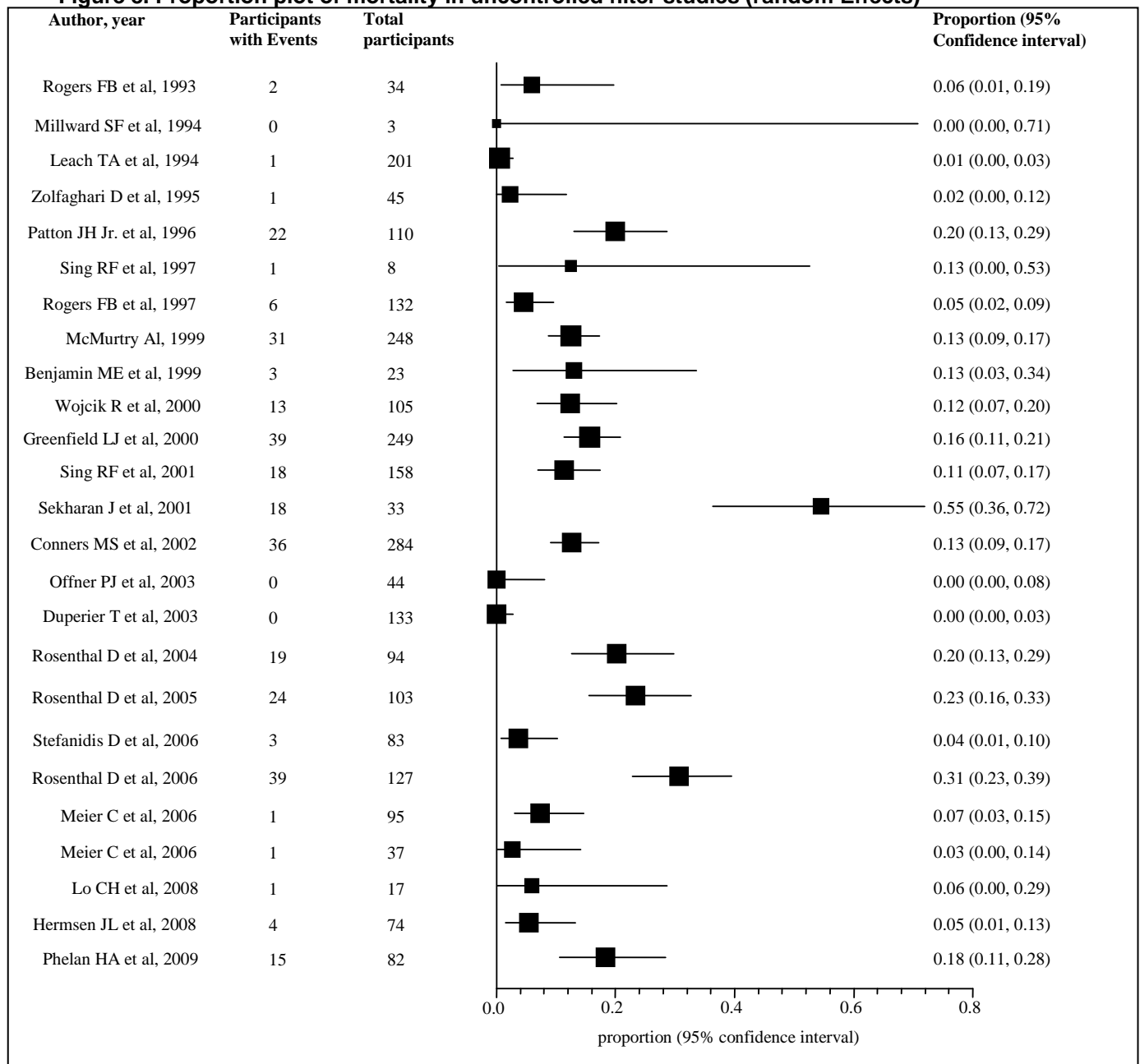
CI = confidence interval; DVT = deep vein thrombosis; IVCF = inferior vena cava filter; RR= relative risk



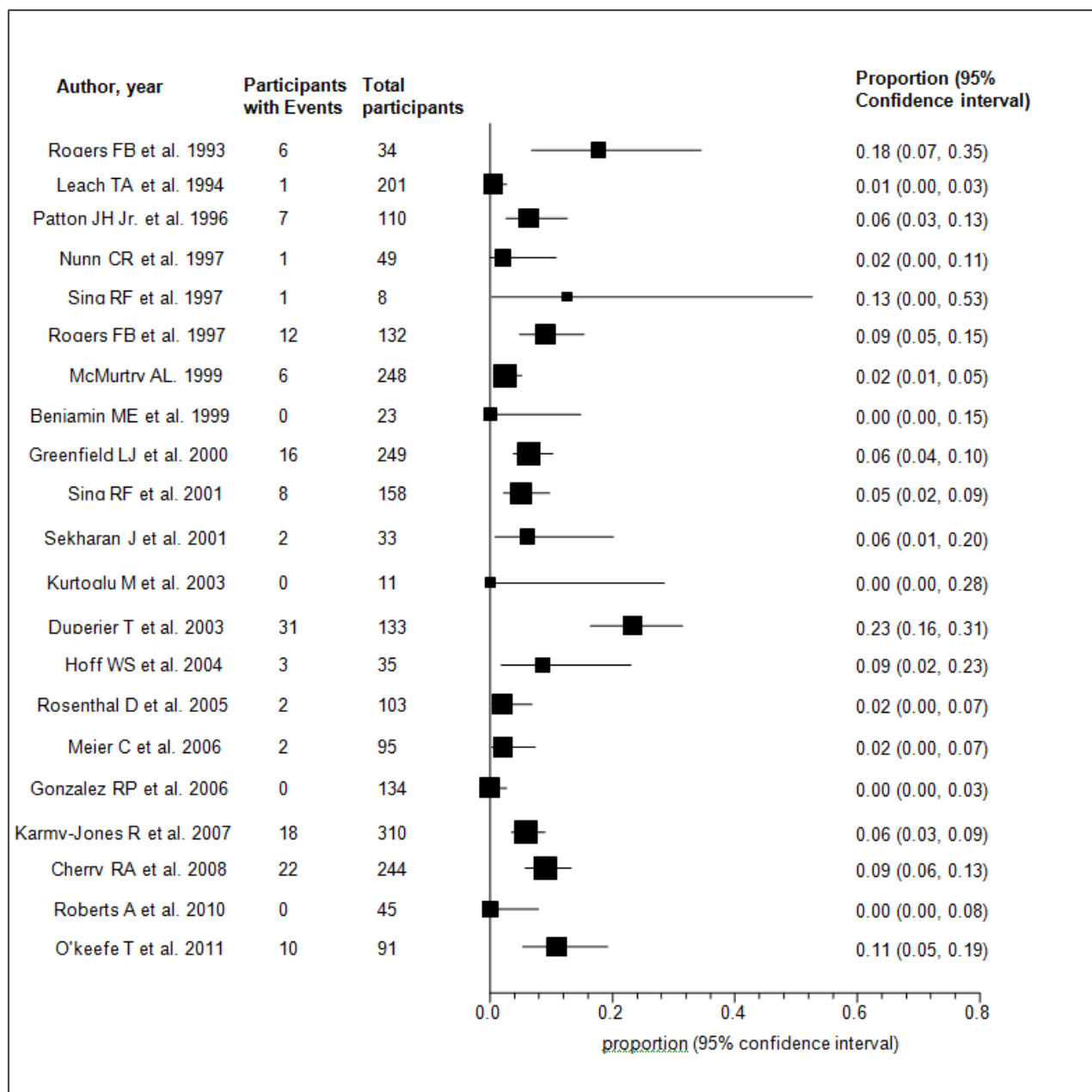
**Figure 7. Proportion plot for PE in uncontrolled studies of inferior vena cava filters (random effects)**



**Figure 8. Proportion plot of mortality in uncontrolled filter studies (random Effects)**



**Figure 9. Proportion of deep vein thrombosis in uncontrolled studies of inferior vena cava filters**



## Key Question 2a

What are the comparative effectiveness and safety of pharmacological and mechanical strategies to prevent venous thromboembolism in hospitalized patients with traumatic brain injury?

### Key Findings and Evidence Grades

- The strength of evidence is low that enoxaparin reduces the rates of DVT compared with no pharmacoprophylaxis in hospitalized patients with traumatic brain injury
- The strength of evidence is low that UFH reduces total mortality compared with no pharmacoprophylaxis in hospitalized patients with traumatic brain injury
- The strength of evidence is insufficient to comment on the comparative effectiveness and safety of any other pharmacological and mechanical strategies on VTE outcome and bleeding.

### Study Characteristics

Eight studies evaluated the effectiveness of pharmacological and mechanical strategies to prevent VTE in hospitalized patients with TBI.<sup>50,114-120</sup> Most studies took place in North America.<sup>50,114,115,117-120</sup> Two studies reported the source of funding.<sup>50,119</sup>

Of eight studies, two were a RCT<sup>50,116</sup>, five were retrospective cohort studies,<sup>114,115,117,118,120</sup> and one was a prospective cohort study.<sup>119</sup> Most studies recruited from the year 2000 onwards.<sup>50,114,115,116,117,118,120</sup>

Most studies enrolled patients admitted to Level 1 trauma centers,<sup>50,114,115,117,118,120</sup> One study included patients with a Glasgow Coma Scale score less than 8<sup>119</sup> and another included TBI patients with a head abbreviated injury score greater than 1<sup>118</sup>. One cohort excluded patients with contraindications to anticoagulants<sup>114</sup> and the trials excluded patients with history of thromboembolism, liver disease, an INR greater than 1.5, or platelets less than 100,000 or 50,000/ uL.<sup>50,116</sup> One cohort excluded patients requiring craniotomy<sup>118</sup> (Table 13).

### Participant Characteristics

The number of participants in the included studies ranged from 32 to 812. Five studies reported the mean age of the participants which ranged from 36 to 47 years<sup>50,115,117-119</sup>. The majority of included participants were men (range 57 to 78 percent, respectively).<sup>50,114,115,118,119</sup> No studies reported the race of participants. All studies but one reported the Injury Severity Score of participants on admission; the mean ranged from 15.7 to 33.8.<sup>50,114-119</sup> Three studies reported the mean Glasgow Coma Scale score of participants; it ranged from 6.8 to 13.5<sup>50,114,119</sup> (Table 13).

### Intervention Characteristics

#### Pharmacological Agent Versus Pharmacological Agent

One retrospective cohort study compared the effectiveness of different LMWHs (enoxaparin versus dalteparin) in preventing VTE in brain injury patients.<sup>114</sup> Another compared the effectiveness of enoxaparin versus UFH.<sup>115</sup> The two studies used the following doses:

enoxaparin at 30 mg every 12 hours, dalteparin at 5,000 U daily, or UFH at 5,000 units three times per day (Table 13).

### **Pharmacological Agent Versus Sequential Compression Devices**

The RCT compared the effectiveness of enoxaparin 40 mg daily with sequential compression devices in preventing VTE events in TBI patients<sup>116</sup> (Table 13).

### **Pharmacological Agent Versus Control (No Pharmacoprophylaxis)**

Three retrospective cohort studies and one RCT conducted in patients with brain injury evaluated the effectiveness of enoxaparin, UFH or dalteparin in preventing VTE events as compared to no treatment.<sup>50,117,118,120</sup> The dosing schedules were 30 mg of enoxaparin or 5,000 IU of UFH administered subcutaneously every 12 hours; the dose of dalteparin used was not specified. The three cohort studies used sequential compression devices concurrently (Table 13).

### **Mechanical Agent Versus Control**

One prospective cohort study of TBI patients examined the effectiveness of sequential compression devices compared with a control group in preventing VTE<sup>119</sup> (Table 13).

### **Ascertainment**

Most studies did not routinely screen for VTE.<sup>50,114-116,120</sup> One study performed weekly surveillance using duplex ultrasound examination or technetium venoscans and ventilation/perfusion scans.<sup>119</sup> One study only routinely screened patients at high risk for VTE.<sup>118</sup>

## **Outcomes**

### **Venous Thromboembolism**

#### **Pharmacological Agent Versus Pharmacological Agent**

Two studies evaluated the effectiveness of enoxaparin when compared with dalteparin and UFH respectively. One cohort study demonstrated that rates of venous thrombosis were similar in both patients treated with enoxaparin and dalteparin (7% vs. 7.5%, p=NS).<sup>121</sup> Similarly, the other cohort study showed that rates of deep venous thrombosis were similar in both enoxaparin and UFH groups (1% vs. 1%, p=NR)<sup>115</sup>

#### **Pharmacological Agent Versus Pharmacological Agent**

Two studies evaluated the effectiveness of enoxaparin when compared with dalteparin and UFH respectively. One cohort study demonstrated that rates of venous thrombosis were similar in both patients treated with enoxaparin and dalteparin (7% vs. 7.5%, p=NS).<sup>121</sup> Similarly, the other cohort study showed that rates of deep venous thrombosis were similar in both enoxaparin and UFH groups (1% vs. 1%, p=NR)<sup>115</sup>

#### **Pharmacological Agent Versus Intermittent Pneumatic Compression**

The single RCT demonstrated lower rates of DVT in the enoxaparin treated group as compared with the group receiving intermittent pneumatic compression (5 vs. 6.6 percent, respectively, p=0.07), whereas the rates of PE were higher in the enoxaparin group compared

with the group receiving intermittent pneumatic compression (6.6 vs. 3.3 percent, respectively,  $p=0.04$ )<sup>116</sup>(Table 14).

### **Any Pharmacologic Agent Versus Control (No Pharmacoprophylaxis)**

Three retrospective cohort studies evaluated the effectiveness of pharmacoprophylaxis in reducing total venous thromboembolic events when compared with control; the results were highly heterogeneous.<sup>117,118,120</sup> In one study<sup>117</sup> the rates of VTE were higher in patients treated with enoxaparin when compared with control (3.92 vs. 2.2%,  $p=0.29$ ) but another study demonstrated the opposite effect, rates of VTE being lower in UFH treated group (1 vs. 3%  $p=0.019$ ).<sup>118</sup> The third study demonstrated no difference in rates of VTE between dalteparin and control groups (0% vs. 0%).<sup>120</sup>

A RCT and cohort study assessed the rates of DVT in TBI patients treated with enoxaparin for pharmacoprophylaxis when compared with control and placebo respectively.<sup>50,115</sup> Both studies consistently demonstrated reduced rates of DVT in patients treated with enoxaparin (1% vs 2%,  $p=NR$ ; 0% vs 3.6%,  $p=NR$ ).<sup>50,115</sup> In addition to this, the cohort study also demonstrated reduced rates of DVT in patients treated with UFH when compared with control (1 vs. 2%,  $p=NR$ ).<sup>115</sup>

A cohort study showed that rates of PE were double in the UFH group compared with control (4 vs. 2 percent, respectively,  $p$  value not reported) but there no PE events in patients treated with enoxaparin.<sup>115</sup> However, in a RCT, patients in both enoxaparin and control groups did not experience any PE events (0 vs. 0%,  $p=NR$ )<sup>50</sup>(Table 14).

### **Intermittent Pneumatic Compression Device Versus Control (No Prophylaxis)**

One cohort study showed similar rates of total VTE in the pneumatic compression and control groups (28.6 vs. 22.2 percent, respectively,  $p=0.7$ ) but increased rates of total DVT in control groups (0 vs 11.1%,  $p=NR$ ). However, the rates of PE were increased in IPC group as opposed to control (28.6 vs. 11.11 percent, respectively,  $p$  value not reported)<sup>119</sup> (Table 14).

## **Fatal Pulmonary Embolism**

### **Enoxaparin Versus Intermittent Pneumatic Compression Devices**

The RCT showed increased rates of fatal PE in enoxaparin treated patients as opposed to patients treated with pneumatic compression (6.6 vs. 3.3 percent, respectively,  $p=0.04$ )<sup>116</sup>(Table 14).

## **Mortality**

### **Enoxaparin Versus Unfractionated Heparin**

One study showed that total mortality was lower in the enoxaparin group as opposed to the unfractionated heparin group (5 percent versus 15.8, respectively,  $p<0.05$ )<sup>115</sup> (Table 14).

### **Enoxaparin Versus Intermittent Pneumatic Compression**

Total mortality was similar in both enoxaparin and pneumatic compression group (13.3 vs. 11.6 percent, respectively,  $p=0.08$ )<sup>116</sup> (Table 14).

## **Pharmacological Agent Versus Control (No Pharmacoprophylaxis)**

One study showed lower rate of mortality in the UFH group relative to the control group (0.75 percent versus 3.6 percent, respectively),<sup>118</sup> and another study showed lower rates of mortality in the enoxaparin and heparin groups relative to the control group (5 percent versus 16 percent versus 47 percent, respectively,  $p<0.05$ )<sup>115</sup> (Table 14).

## **Adverse Outcomes**

### **Bleeding Outcomes**

#### **Enoxaparin Versus Unfractionated Heparin**

A cohort study showed that rates of progression of ICH were higher in heparin treated patients in comparison with enoxaparin treated patients (12% vs. 5%,  $p<0.05$ ).<sup>115</sup> Similarly, the rates of intracranial hemorrhage that required craniectomy in the two groups were 1 and 0 percent, respectively, ( $p<0.05$ ). Another study reported the rates of intracranial bleeding in patients treated with enoxaparin and dalteparin (0.08 vs. 0 percent, respectively)<sup>114</sup> (Table 14).

#### **Pharmacological Agent Versus Sequential Compression Devices**

A RCT showed that exacerbation of epidural hematoma occurred in 1.6 percent, respectively, in both enoxaparin and intermittent sequential compression groups.<sup>116</sup> The rates of hematuria, injection site hematoma and bleeding from tracheostomy site were 8.3, 3.3, and 1.6 percent, in the enoxaparin group and 6.6, 0, and 0 percent in the sequential compression devices group respectively (Table 14).

## **Pharmacological Agent Versus Control (No Pharmacoprophylaxis)**

A cohort study showed that rates of progression of intracranial hemorrhage were lower in the unfractionated heparin group relative to the control group (3 versus 6 percent,  $p=0.055$ )<sup>118</sup> while a RCT showed that rates of progression of intracranial bleeding were higher in enoxaparin treated patients (5.9 vs. 3.6%).<sup>50</sup> The third study however showed that there was no progression of intracranial hemorrhage in both dalteparin and control groups<sup>120</sup> (Table 14).

## **Mean Hospital Stay**

### **Pharmacological Agent Versus Control**

A cohort study showed that the median hospital stay was longer in the enoxaparin and unfractionated heparin groups than in the control group. (19 versus 17 versus 4 days, respectively,  $p<0.05$ )<sup>115</sup> while a randomized controlled trial demonstrated a marginally increased length of stay in patients treated with enoxaparin compared with placebo (4.9 vs. 4.5 days).<sup>50</sup>

### **Mean Intensive Care Unit stay**

#### **Pharmacological Agent Versus Control**

A cohort study also showed that median ICU stay was longer in the enoxaparin and unfractionated heparin groups relative to the control group (11 vs. 8 vs. 2 days respectively,  $p<0.05$ )<sup>115</sup> while the randomized controlled trial demonstrated the opposite (2.5 vs. 3.2 days).<sup>50</sup>

## **Pharmacological Agent Versus Sequential Compression Devices**

In one RCT the mean intensive care unit stay was similar in both the enoxaparin and intermittent pneumatic compression groups (10.7 vs. 10.3 days, respectively, p value not reported).<sup>116</sup>

## **Mechanical Agent Versus Control**

In one study the mean ICU stay was 21.2 days in the sequential compression group and 18.4 days in the control group (p =0.5).<sup>119</sup>

## **Infections**

### **Pharmacological Agent Versus SCDs**

The RCT evaluated the rates of infections.<sup>116</sup> The enoxaparin treated patients and patients treated with intermittent pneumatic compression had similar rates of infection (23.3 vs. 20 percent, respectively, P =0.07).

## **Risk of Bias**

We rated a cohort study as having moderate risk of bias and a randomized controlled trial to be at low risk of bias.<sup>50,114</sup> We rated the remaining studies as high risk of bias.<sup>115-120,122,123</sup> The RCT had biases arising from improper randomization and blinding.<sup>116</sup> The cohort studies generally had incomplete description of the important confounders and lack of adjustment for differences between groups. They also had incomplete accounting of losses to followup. All of these are important confounders and threaten the internal validity of these studies.

## **Strength of Evidence**

Most of the included studies that assessed the comparative effectiveness of pharmacological and mechanical prophylaxis in hospitalized patients with traumatic brain injury were at high risk of bias. We rated the strength of evidence as low to support that enoxaparin reduced the rates of DVT compared with no pharmacoprophylaxis in hospitalized patients with traumatic brain injury based on direct, consistent evidence from a cohort study and a RCT.<sup>50,115</sup> We also rated the strength of evidence as low to support that UFH reduced the rates of mortality compared with no pharmacoprophylaxis. We based this rating on consistent, direct and precise evidence from two cohort studies.<sup>115,118</sup> The remainder of comparisons on the outcomes of PE, DVT, VTE and exacerbation of intracranial hemorrhage for were all rated as insufficient. This rating was based on either inconsistencies in the body of evidence, or our inability to assess consistency (Table 15).

## **Applicability**

The participants that these studies recruited were typical of participants admitted to other trauma centers and hence findings are generalizable. We did not have details to assess the applicability of this evidence to older subgroups and other racial groups since the studies inconsistently reported race.



**Table 13. Study, participant, and intervention characteristics for KQ 2a**

Author, Year	Study Design	Intervention (Dose)	N	Mean Age Years	% Male	Mean ISS	Mean GCS	Mean AIS Head
Dudley, R.R., 2010 <sup>114</sup>	Retrospective cohort	Enoxaparin (30mg, sc, bd)	128	47.4	77.3	31.1	8	NR
		Dalteparin (5000 U, sc, od)	159	45.9	72.3	35	6.9	NR
Minshall, C.T., 2011 <sup>115</sup>	Retrospective cohort	Enoxaparin (30mg, sc, bd)	158	41.2	75	29	NR	3.8
		UFH (5000 U, sc, tid)	171	42	78	33.8	NR	4.1
		Usual care/ No Intervention	57	38.3	69	30.9	NR	4.3
Kurtoglu, M., 2004 <sup>116</sup>	Randomized controlled trial	Enoxaparin (40 mg, od)	60	NR	NR	19.5	NR	NR
		IPC	60	NR	NR	18.3	NR	NR
Salottolo, K., 2010 <sup>117</sup>	Retrospective cohort	Enoxaparin (30mg, sc, bd)	255	48	NR	NR	NR	NR
		no prophylaxis	225	59.5	NR	NR	NR	NR
Phelan, H.A., 2012 <sup>50</sup>	Randomized controlled trial	Enoxaparin (30mg, sc, bd)	34	40.7	64	17.3	13.5	3.5
		Placebo	28	42.6	57	15.7	13.0	3.1
Scudday, T., 2010 <sup>118</sup>	Retrospective cohort	UFH (NR)	402	45.2	69	23.8	NR	3.4
		no prophylaxis	410	51.5	69	16.6	NR	3.4
Sadeh, Y., 2012 <sup>120</sup>	Retrospective cohort	Dalteparin	93	NR	NR	NR	NR	NR
		No prophylaxis	29	NR	NR	NR	NR	NR
Gersin, K., 1992 <sup>119</sup>	Prospective cohort	Scd	14	38.3	71.4	30.5	7.1	NR
		no intervention	18	36.1	77.8	32.1	6.8	NR

AIS = Abbreviated Injury Scale; bd = twice daily; BMI = body mass index; IPC = intermittent pneumatic compression devices; ISS = Injury Severity Score; GCS = Glasgow coma scale; NR = Not reported; od = once daily; sc = subcutaneous; SCD = sequential compression devices; UFH = Unfractionated heparin

**Table 14. Venous thromboembolic, mortality, and major bleeding outcomes in traumatic brain injury patients receiving pharmacological/mechanical prophylaxis**

Author, Year	Intervention	Surveillance for VTE	N Patients	% VTE	% DVT	% PE	% Mortality	% Progression of ICH
Dudley, R.R., 2010 <sup>114</sup>	Enoxaparin	No	128	7*	NR	NR	NR	0.08
	Dalteparin	No	159	7.5*	NR	0.6	NR	0
Minshall, C.T., 2011 <sup>115</sup>	Enoxaparin	No	158	NR	1	0**	5	5**
	UFH	No	171	NR	1	4**	15.8	12**
	No Intervention	No	57	NR	2	2	47	NR
Kurtoglu, M., 2004 <sup>116</sup>	Enoxaparin	No	60	NR	5	6.6**†	13.3	1.6
	IPC	No	60	NR	6.6	3.3**†	11.6	1.6
Salottolo, K., 2010 <sup>117</sup>	Enoxaparin	No	255	3.92*	NR	NR	NR	NR
	no prophylaxis	No	225	2.2	NR	NR	NR	8.44
Phelan, H.A., 2012 <sup>50</sup>	Enoxaparin	No	34	NR	0	0	NR	5.9
	Placebo	No	28	NR	3.6	0	NR	3.6
Scudday, T., 2010 <sup>118</sup>	UFH	No	402	1**	NR	NR	0.75	3**
	no prophylaxis	Yes	410	3**	NR	NR	3.66	6**
Sadeh, Y., 2012 <sup>120</sup>	Dalteparin	No	93	0	NR	NR	NR	0
	No prophylaxis	No	29	0	NR	NR	NR	0
Gersin, K., 1992 <sup>119</sup>	Scd	Yes	14	28.6*	0	28.6	NR	NR
	no intervention	Yes	18	22.2*	11.1	11.11	NR	NR

DVT = deep vein thrombosis; ICH = intracranial hemorrhage; IPC = intermittent pneumatic compression devices; PE = pulmonary embolism; TBI = traumatic brain injury;

UFH = unfractionated heparin; USG = ultrasonogram; V/Q = ventilation-perfusion; VTE = venous thromboembolism

\* p value not significant.

\*\* p value significant.

† Of the total PE, 6.6% in the enoxaparin arm and 3.3% in the IPC arm were fatal.

**Table 15. Body of evidence for pharmacological prophylaxis for patients with traumatic brain injury**

Author, Year	Outcomes	Patients (N)	Risk of Bias	Directness	Precision	Consistency	Magnitude of Effect	Strength of Evidence
<b><i>Enoxaparin vs. Dalteparin</i></b>								
Dudley, R.R., 2010 <sup>114</sup>	VTE	287	Moderate	Direct	Imprecise	Unknown	7% vs. 7.5%; p=0.868	Insufficient evidence to comment on effectiveness of enoxaparin vs. dalteparin in reducing VTE in TBI patients
Dudley, R.R., 2010 <sup>114</sup>	Progression of ICH	287	Moderate	Direct	Unknown	Unknown	0.08% vs. 0%*	Insufficient evidence to comment on effectiveness of enoxaparin vs. dalteparin in reducing progression of ICH in TBI patients
<b><i>Enoxaparin vs. UFH</i></b>								
Minshall, C.T., 2011 <sup>115</sup>	DVT	329	High	Direct	Unknown	Unknown	1% vs. 1%*	Insufficient evidence to comment on effectiveness of enoxaparin vs. UFH in reducing DVT in TBI patients
Minshall, C.T., 2011 <sup>115</sup>	PE	329	High	Direct	Precise	Unknown	0% vs. 4% ; p<0.05	Insufficient evidence to comment on effectiveness of enoxaparin vs. UFH in reducing PE in TBI patients
Minshall, C.T., 2011 <sup>115</sup>	mortality	329	High	Direct	Precise	Unknown	5% vs. 15.8%; p<0.05	Insufficient evidence to comment on effectiveness of enoxaparin vs. UFH in reducing mortality in TBI patients
Minshall, C.T., 2011 <sup>115</sup>	Progression of ICH	329	High	Direct	Precise	Unknown	5% vs. 12%; p<0.05	Insufficient evidence to comment on effectiveness of enoxaparin vs. UFH in reducing progression of ICH in TBI patients
<b><i>Enoxaparin vs. Control/IPC/Placebo</i></b>								
Salottolo, K., 2010 <sup>117</sup>	VTE	480	High	Direct	Imprecise	Unknown	3.9% vs. 2.2%; p=0.29	Insufficient evidence to comment on effectiveness of enoxaparin vs. IPC/control in reducing VTE in TBI patients
	DVT	397	Moderate	Direct	Imprecise	Consistent		Low grade evidence that enoxaparin reduces DVT in TBI patients when compared with IPC/control

**Table 15. Body of evidence for pharmacological prophylaxis for patients with traumatic brain injury (continued)**

Author, Year	Outcomes	Patients (N)	Risk of Bias	Directness	Precision	Consistency	Magnitude of Effect	Strength of Evidence
<i>Enoxaparin vs. Control/IPC/Placebo (continued)</i>								
Phelan, H.A., 2012 <sup>50†</sup>	DVT	62	Low	Direct	Imprecise	Consistent	0% vs. 3.6%, p=0.45 (Fischer's exact)	
Minshall, C.T., 2011 <sup>115</sup>		215	High	Direct	Imprecise		1% vs. 2% *; P= ns	
Kurtoglu, M., 2004 <sup>116†</sup>		120	High	Direct	Imprecise		5% vs. 6.6%; p=0.07	
	PE	397	Moderate	Direct	Imprecise	Inconsistent		Insufficient evidence to comment on effectiveness of enoxaparin vs. IPC/control in reducing PE in TBI patients
Phelan, H.A., 2012 <sup>50†</sup>	PE	62	Low	Direct	Unknown	Inconsistent	0% vs. 0%, p=NR	
Kurtoglu, M., 2004 <sup>116†</sup>		120	High	Direct	Precise		6.6% vs. 3.3%;p=0.04	
Minshall, C.T., 2011 <sup>115</sup>		215	High	Direct	Imprecise		0% vs. 2%: #P=0.46	
Kurtoglu, M., 2004 <sup>116†</sup>	Fatal PE	120	High	Direct	Precise	Unknown	6.6% vs. 3.3%;p=0.04	Insufficient evidence to comment on effectiveness of enoxaparin vs. IPC/control in reducing Fatal PE in TBI patients
	mortality	182	Moderate	Direct	Imprecise	Inconsistent		Insufficient evidence to comment on effectiveness of enoxaparin vs. IPC/control in reducing mortality in TBI patients

**Table 15. Body of evidence for pharmacological prophylaxis for patients with traumatic brain injury (continued)**

Author, Year	Outcomes	Patients (N)	Risk of Bias	Directness	Precision	Consistency	Magnitude of Effect	Strength of Evidence
<b><i>Enoxaparin vs. Control/IPC/Placebo (continued)</i></b>								
Phelan, H.A., 2012 <sup>50†</sup>	mortality	62	High	Direct	Precise	Unknown	0% vs. 0%, p=NR	
Kurtoglu, M., 2004 <sup>116†</sup>		120	Moderate	Direct	Imprecise	Inconsistent	13.3% vs. 11.6%; p=0.08	
	Progression of intracranial hemorrhage	182	Moderate	Direct	Imprecise	Inconsistent		Insufficient evidence to comment on effectiveness of enoxaparin vs. IPC/control/placebo in reducing exacerbation of epidural hematoma in TBI patients
Phelan, H.A., 2012 <sup>50†</sup>	Exacerbation of epidural hematoma	62	Low	Direct	Imprecise	Inconsistent	5.9 vs. 3.6%, p=0.57 (Fischer's exact)	
Kurtoglu, M., 2004 <sup>116†</sup>	Progression of intracranial hemorrhage	120	High	Direct	Imprecise		1.6% vs. 1.6%*, p=0.75 (Fischer's exact)	
<b><i>UFH vs. Control</i></b>								
Scudday, T., 2010 <sup>118</sup>	VTE	812	High	Direct	Precise	Unknown	1% vs. 3%; p=0.019	Insufficient evidence to comment on effectiveness of UFH vs. control in reducing VTE in TBI patients
Minshall, C.T., 2011 <sup>115</sup>	DVT	228	High	Direct	Unknown	Unknown	1% vs. 2% *	Insufficient evidence to comment on effectiveness of UFH vs. control in reducing DVT in TBI patients
Minshall, C.T., 2011 <sup>115</sup>	PE	228	High	Direct	Unknown	Unknown	4% vs. 2%*	Insufficient evidence to comment on effectiveness of UFH vs. control in reducing PE in TBI patients
	mortality	1040	High	Direct	Precise	Consistent		Low-grade evidence that UFH reduces mortality in TBI compared with controls

**Table 15. Body of evidence for pharmacological prophylaxis for patients with traumatic brain injury (continued)**

Author, Year	Outcomes	Patients (N)	Risk of Bias	Directness	Precision	Consistency	Magnitude of Effect	Strength of Evidence
Scudday, T., 2010 <sup>118</sup>	mortality	812	High	Direct	Precise	Consistent	0.75% vs. 3.66%; P=0.007 #	
Minshall, C.T., 2011 <sup>115</sup>	mortality	228	High	Direct	Precise		15.8% vs. 47%; p<0.05	
<b><i>Dalteparin vs. Control</i></b>								
Sadeh, Y., 2012 <sup>120</sup>	VTE	122	High	Direct	Unknown	Unknown	0% vs. 0%	Insufficient evidence to comment on effectiveness of dalteparin vs. control in reducing total VTE in TBI patients
Sadeh, Y., 2012 <sup>120</sup>	Progression of ICH	122	High	Direct	Unknown	Unknown	0% vs. 0%	Insufficient evidence to comment on effectiveness of dalteparin vs. control in reducing progression of ICH in TBI patients
<b><i>IPC vs. Control</i></b>								
Gersin, K., 1992 <sup>119</sup>	VTE	32	High	Direct	Imprecise	Unknown	28.6% vs. 22.2%: p=0.7	Insufficient evidence to comment on effectiveness of IPC vs. control in reducing VTE in TBI patients
Gersin, K., 1992 <sup>119</sup>	PE	32	High	Direct	Unknown	Unknown	28.6% vs. 11.1%*	Insufficient evidence to comment on effectiveness of IPC vs. control in reducing PE in TBI patients

DVT = deep venous thrombosis; ICH = intracranial hemorrhage; IPC = intermittent pneumatic compression; PE = pulmonary embolism; SCD = sequential compression device; UFH = unfractionated heparin; VTE = venous thromboembolism

\*Randomized controlled trial.

\*P-values or tests of statistical significance not reported

#Two sided P-estimated using Fishers exact test.

## Key Question 2b

What is the optimal timing of initiation and duration of pharmacologic prophylaxis to prevent venous thromboembolism in hospitalized patients with traumatic brain injury?

### Key Findings and Evidence Grades

- The strength of evidence was insufficient to comment on the effectiveness of early (< 72 hours) versus late (> 72 hours) pharmacoprophylaxis with enoxaparin, UFH or any heparin on the outcomes of VTE, DVT, PE, fatal PE, total mortality, major and minor bleeding.

### Study Characteristics

Five retrospective cohort studies assessed the optimal timing of initiation of pharmacologic prophylaxis to prevent venous thromboembolism in patients with traumatic brain injury.<sup>36,117,122-124</sup> All studies were conducted in North America. None of the studies reported their sources of funding. All studies had recruitment dates from the year 2000 onwards. All studies included patients over 18 years of age with traumatic brain injury admitted to trauma centers. One study excluded pregnant women and patients with histories of venous thromboembolism.<sup>36</sup> Two studies excluded patients with low platelet counts<sup>36,125</sup> and one study excluded patients with penetrating head injuries<sup>123</sup> (Table 16).

### Participant Characteristics

The numbers of participants in these studies ranged from 64 to 669. The mean age of participants was reported in three studies and ranged from 37 to 44 years.<sup>36,122,124</sup> Only two studies reported on sex and the majority of participants were men.<sup>36,122</sup> The mean Injury Severity Score was reported in two studies at 28.6<sup>36</sup> and 33.2 respectively.<sup>124</sup> One study reported a mean Glasgow Coma Scale score of 9.25<sup>124</sup> (Table 16).

### Intervention Characteristics

All five studies evaluated the effectiveness of pharmacoprophylaxis, initiated at different times, to prevent venous thromboembolic events in hospitalized patients with traumatic brain injury.<sup>36,117,122-124</sup> In two studies, patients were treated with only enoxaparin<sup>36,117</sup> and in one only with UFH.<sup>124</sup> In the remaining two studies patients were treated with either enoxaparin or UFH; the percentages of each are unknown and this treatment has been termed “any heparin.” Four studies reported the effectiveness of pharmacoprophylaxis in preventing venous thromboembolic events when initiated before 72 hours of hospitalization (early) compared with after 72 hours of hospitalization (late).<sup>36,117,123,124</sup> Another retrospective cohort study with three arms evaluated the effectiveness of initiating pharmacologic prophylaxis before 24 hours, 24 to 48 hours, and after more than 48 hours of hospitalization.<sup>122</sup> In three studies, sequential compression devices were placed concurrently on all patients;<sup>117,122,123</sup> in one, pneumatic compression devices were used.<sup>124</sup> The doses of enoxaparin and UFH used in all studies were 30 mg every 12 hours and 5000 IU daily, respectively (Table 16).

## **Ascertainment**

One study did weekly ultrasound examination in all patients,<sup>124</sup> while in another only high risk patients were screened routinely with weekly duplex ultrasound examinations.<sup>123</sup> Three studies did not screen patients for venous thromboembolic events.<sup>36,117,122</sup>

## **Outcomes**

### **Total venous thromboembolic events**

#### **Early (<72 hrs) Versus Late (>72 hrs) Pharmacoprophylaxis**

A single study showed that rate of all venous thromboembolism was greater in patients who were started on enoxaparin before than 72 hrs of hospitalization (early) compared with patients in whom enoxaparin was started after 72 hours (5.56 percent versus 2.72 percent, OR 2.10, p value=0.26).<sup>117</sup>

### **Deep Vein Thrombosis**

#### **Early (<72 hrs) Versus Late (72 hrs) Pharmacoprophylaxis**

In a different study, two out of 47 patients in an early UFH prophylaxis (<72 hours) group developed DVT compared with one out of 17 patients a late UFH prophylaxis (>72 hours) group.<sup>124</sup> The difference was not statistically significant (p=1.00) The effectiveness of prophylaxis with any heparin initiated within 72 hours of admission as compared with later than 72 hours was reported in another cohort study, where the percentage of patients developing DVTs in the two groups were 10.4 percent and 14.6 percent respectively (p value not reported).<sup>123</sup> In one cohort study, of the 268 patients receiving enoxaparin within 72 hours of hospitalization, one patient developed upper extremity proximal DVT and three developed lower extremity DVT.<sup>36</sup> Of the 401 patients beginning prophylaxis after 72 hours, five patients developed upper extremity DVT and nine patients developed DVT of the lower extremity. The difference in rates of upper and lower extremity deep venous thromboses between the two groups was not statistically significant (p=0.24 and 0.28 respectively) (Table 17).

#### **Other Timings of Initiation of Prophylaxis**

Another cohort study assessed the DVT risk per 100 patients in the 3 arms. The proportion of DVT in patients with any heparin initiated before 24 hours, 24 to 48 hours and after 48 hours were 3.6/100 patients, 4.5/100 patients, 15.4/100 patients respectively. The p values are not reported<sup>122</sup> (Table 17).

### **Pulmonary Embolism**

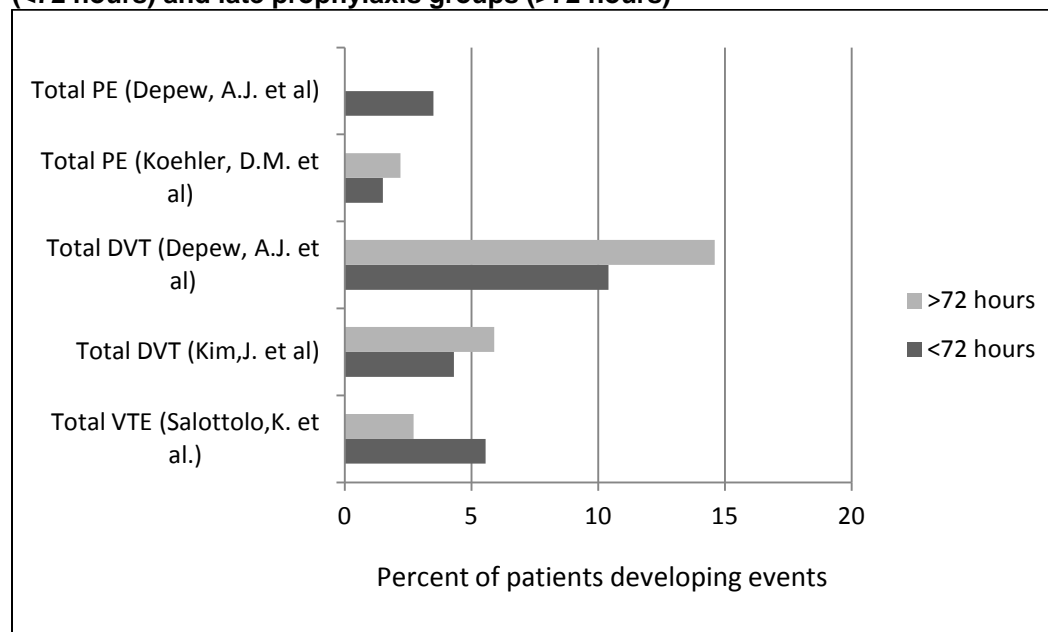
#### **Early (<72 hrs) Versus Late (72 hrs) Pharmacoprophylaxis**

In one cohort, 4.3 percent of patients receiving UFH as prophylaxis within 72 hours of hospitalization developed PE as compared with none in the group that received the same prophylaxis after 72 hrs of admission (p=0.96).<sup>124</sup> Similarly, in another cohort, 3.5% of patients receiving any heparin within 72 hours of hospital admission developed PEs while no PEs occurred in the group that received prophylaxis after 72 hours (p value not reported).<sup>123</sup> In a third



cohort, there was a higher rate of pulmonary embolism in the group receiving enoxaparin as prophylaxis within 72 hours of hospital admission compared with after 72 hours (1.5 percent versus 2.2 percent, respectively,  $p=0.49$ )<sup>36</sup> (Table 17).

**Figure 10. Studies reporting percentage of patients developing thromboembolic outcomes in early (<72 hours) and late prophylaxis groups (>72 hours)**



DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism

## Other Outcomes

### Fatal PE

Of the 401 patients in one study receiving prophylaxis with enoxaparin later than 72 hours after hospitalization, 1 patient died due to pulmonary embolism.<sup>36</sup> There were no fatal pulmonary embolic events in the group receiving the same prophylaxis within 72 hours (p value not reported).

### Mortality

One cohort reported four deaths in a group of 47 patients receiving UFH within 72 hours of admission and one in the group of 17 patients receiving prophylaxis after 72 hours ( $p=1.0$ ).<sup>124</sup> Another cohort reported that there were no deaths due to bleeding in either the early and late prophylaxis groups.<sup>36</sup>

### Major Bleeding

The rates of radiographic progression of intracranial hemorrhage were reported in three studies.<sup>36,117,123</sup> In one study, the rates were similar in patients treated with enoxaparin within 72 hours of hospital admission and after 72 hours (1.46% vs. 1.54%, respectively ( $p=0.912$ )).<sup>36</sup> Similar findings were observed in another study (3.5% vs. 3.8%, p value not reported).<sup>123</sup> Only one study showed that rates of progression of intracranial hemorrhage were lower in the group receiving enoxaparin prophylaxis earlier rather than later (6.48 percent versus 14.3 percent,  $p=0.92$ )<sup>117</sup> (Table 17).

## **Minor Bleeding**

Two studies reported rates of minor bleeding events. According to one study, the rates of hematuria in patients treated with UFH within 72 hours of hospital admission and after 72 hours were six percent (p=1.00).<sup>124</sup> Another study reported that none of the patients developed any non-cranial bleeding complications from enoxaparin prophylaxis.<sup>36</sup>

## **Risk of Bias**

All five included studies were at high risk of bias. The studies had biases arising from incomplete description of principal confounders and their adjustment and improper accounting of losses to follow-up.

## **Strength of Evidence**

All of the included studies that assessed the comparative effectiveness of early versus late pharmacoprophylaxis in hospitalized patients with traumatic brain injury were at high risk of bias. We rated the strength of evidence as insufficient for all comparisons and outcomes. We based this rating on either inconsistencies in the body of evidence, or our inability to assess consistency (consistency unknown) in a single study (Table 18).

## **Applicability**

The studies were generally representative of patients with traumatic brain injury in the United States. Gender was inconsistently reported thus we could not assess the applicability of these findings to females. Some studies excluded patients with previous VTE as well as those at higher risk of bleeding such as those with low platelet counts limiting generalizability to these high risk subgroups.

**Table 16. Study, participants, and intervention characteristics for KQ 2b**

Author, Year	Study Design	Intervention (Dose)	Timing of First Dose	N Patients	Mean Age Years	% Male	Mean ISS/GCS/AIS Head
Koehler D.M., 2011, <sup>36</sup>	Retrospective cohort	Enoxaparin (30mg, sc, bd)	<=72 hrs	268	39.8	69	27.8/NR/4
		Enoxaparin (30mg, sc, bd)	>72 hrs	401	40.2	75	29.4/NR/NR
Kim J., 2002, <sup>124</sup>	Retrospective cohort	UFH (5000 U, sc, bd)	<72 hrs	47	37.7	NR	30.7/9.1/NR
		UFH (5000 U, sc, bd)	>72 hrs	17	44	NR	35.7/9.4/NR
Salotto K., 2011, <sup>117</sup>	Retrospective cohort	Enoxaparin (30mg)	<=72 hrs	108	NR	NR	NR
		Enoxaparin (30mg)	>72 hrs	147	NR	NR	NR
Reiff D.A., 2009, <sup>122</sup>	Retrospective cohort	Any heparin	<24 hrs	84	37.2	71.4	NR
		Any heparin (NR)	24 to <48 hrs	177	39.8	62.7	NR
		Any heparin (NR)	>48 hrs	293	43	63.8	NR
Depew A.J., 2008, <sup>123</sup>	Retrospective cohort	Any heparin (30 mg/5000 U, sc, bd)	<72 hrs	29	NR	NR	NR
		Any heparin (30 mg/5000 U, sc, bd)	>72 hrs	41	NR	NR	NR

AIS = Abbreviated Injury Scale; bd = twice daily; BMI = Body mass index; GCS = Glasgow Coma Scale; ISS = Injury Severity Score; NR = not reported; sc = subcutaneous; UFH = unfractionated heparin

**Table 17. Venous thromboembolic, mortality, and major bleeding outcomes in traumatic brain injury patients receiving early and late pharmacological prophylaxis**

Author, Year	Intervention	Surveillance for VTE	N Patients	% DVT	% PE	% Mortality	% Progression of ICH
Koehler D.M., 2011, <sup>36</sup>	Enoxaparin < 72hrs	No	268	NR	1.5*	NR	1.46*
	Enoxaparin >72 hrs	No	401	NR	2.2*	NR	1.54*
Kim J., 2002, <sup>124</sup>	UFH < 72 hrs	Yes	47	4.3*	4.3*	8.5*	NR
	UFH >72 hrs	Yes	17	5.9*	0*	5.9*	NR
Salotto K., 2011, <sup>117</sup>	Enoxaparin < 72hrs	No	108	NR	NR	NR	6.48*
	Enoxaparin >72 hrs	No	147	NR	NR	NR	14.29*
Reiff D.A., 2009, <sup>122</sup>	Any heparin <24 hrs	No	84	NR	NR	NR	NR
	Any heparin 24-48 hrs	No	177	NR	NR	NR	NR
	Any heparin >48 hrs	No	293	NR	NR	NR	NR
Depew A.J., 2008, <sup>123</sup>	Any heparin <72 hrs	No	29	10.4	3.5	NR	3.5
	Any heparin >72 hrs	No	41	14.6	0	NR	3.8

DVT = deep vein thrombosis; ICH = intracranial hemorrhage; NR = not reported; PE = pulmonary embolism; TBI = traumatic brain injury; UFH = unfractionated heparin; VTE = venous thromboembolism \*p value not significant

**Table 18. Body of evidence for timing of pharmacological prophylaxis for patients with traumatic brain injury**

Author, Year	Outcomes	Risk of Bias	Directness	Precision	Consistency	Magnitude of Effect
Enoxaparin <72 hrs vs. >72 hrs						
	VTE	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin started <72 hrs vs. >72 hrs in reducing VTE in TBI patients
Salotto K., 2011 <sup>117</sup>		High	Direct	Imprecise	Unknown	5.6% vs. 2.7%;p=0.26
	DVT	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin started <72 hrs vs. >72 hrs in reducing DVT in TBI patients
Koehler D.M., 2011 <sup>36</sup>		High	Direct	Imprecise	Unknown	1.5% vs. 3.5%;p= 0.12
	PE	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin started <72 hrs vs. >72 hrs in reducing PE in TBI patients
Koehler D.M., 2011 <sup>36</sup>		High	Direct	Imprecise	Unknown	1.5% vs. 2.2%; p=0.49
	Fatal PE	High	Direct	Unknown	Unknown	Insufficient evidence to comment on effectiveness of enoxaparin started <72 hrs vs. >72 hrs in reducing fatal PE in TBI patients
Koehler D.M., 2011 <sup>36</sup>		High	Direct	Unknown	Unknown	0% vs. 0.3%*
	Progression of ICH	High	Direct	Imprecise	Inconsistent	Insufficient evidence to comment on effectiveness of enoxaparin started <72 hrs vs. >72 hrs in reducing progression of ICH in TBI patients
Koehler D.M., 2011 <sup>36</sup>		High	Direct	Imprecise	Inconsistent	1.5% vs. 1.5%; p=0.912
Salotto K.,2011 <sup>117</sup>		High	Direct	Imprecise		6.5% vs. 14.3%; p=0.92
UFH <72 hrs vs. >72 hrs						
	DVT	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of UFH started <72 hrs vs. >72 hrs in reducing DVT in TBI patients
Kim J., 2002 <sup>124</sup>		High	Direct	Imprecise	Unknown	4.3% vs. 5.9%;p=1.00
	PE	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of UFH started <72 hrs vs. >72 hrs in reducing PE in TBI patients
Kim J., 2002 <sup>124</sup>		High	Direct	Imprecise	Unknown	4.3% vs. 0%; p=0.96

**Table 18. Body of evidence for timing of pharmacological prophylaxis for patients with traumatic brain injury (continued)**

Author, Year	Outcomes	Risk of Bias	Directness	Precision	Consistency	Magnitude of Effect
<b>UFH &lt;72 hrs vs. &gt;72 hrs (continued)</b>						
	<b>Mortality</b>	<b>High</b>	<b>Direct</b>	<b>Imprecise</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of UFH started &lt;72 hrs vs. &gt;72 hrs in reducing total mortality in TBI patients</b>
Kim J., 2002 <sup>124</sup>		High	Direct	Imprecise	Unknown	8.5% vs. 5.9%; p=1.00
<b>Any Heparin &lt;72 hrs vs. &gt;72 hrs</b>						
	<b>DVT</b>	<b>High</b>	<b>Direct</b>	<b>unknown</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of any heparin started &lt;72 hrs vs. &gt;72 hrs in reducing DVT in TBI patients</b>
Depew A.J., 2008 <sup>123</sup>		High	Direct	Unknown	Unknown	10.4% vs. 14.6%*
	<b>PE</b>	<b>High</b>	<b>Direct</b>	<b>unknown</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of any heparin started &lt;72 hrs vs. &gt;72 hrs in reducing PE in TBI patients</b>
Depew A.J., 2008 <sup>123</sup>		High	Direct	Unknown	Unknown	3.5% vs. 0%*
	<b>Progression of ICH</b>	<b>High</b>	<b>Direct</b>	<b>Unknown</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of any heparin started &lt;72 hrs vs. &gt;72 hrs in reducing progression of ICH in TBI patients</b>
Depew A.J., 2008 <sup>123</sup>		High	Direct	Unknown	Unknown	3.5% vs. 3.8%

DVT = deep venous thrombosis; ICH = intracranial hemorrhage; PE = pulmonary embolism; TBI = traumatic brain injury; UFH = unfractionated heparin

#There were no randomized controlled trials.

\*Tests of statistical significance between groups or P values unavailable.

## **Key Question 3**

What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent venous thromboembolism in hospitalized patients with burns?

### **Key Points and Evidence Grades**

- The strength of evidence was insufficient to comment on the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns.

### **Study Characteristics**

We identified only one small cohort study of 20 patients that reported on PE prophylaxis with IVC filters for patients with burns.<sup>126</sup> This was a single center study in an academic medical center's burn unit conducted over a period of 2 years. The study follow up was up to 1 year after hospital discharge.

### **Participant Characteristics**

The investigators placed IVC filters in 20 patients with acute burns at high risk for PE. These risk factors included prolonged immobilization due to ventilator dependence, old age, size of burn, site of burns, previous history of VTE, and contraindications against use of anticoagulants. The investigators placed five filters due to preexisting VTE and the remaining 15 filters for PE prophylaxis. The study required Doppler imaging prior to filter placement to exclude DVT. Among the 15 patients who underwent insertion of filters strictly for prophylaxis there were nine men and six women. Of these, the mean age was 38.9 years, with a range of 22 to 69 years. Burn size ranged from 15 to 79 percent total body surface area (mean, 37.8 percent).

### **Intervention Characteristics**

Vascular surgeons placed Venatech titanium bird's nest filters; 18 were placed with femoral access and two with right jugular percutaneous access. Filter insertions happened from 1 to 75 days after the burn incident. The patients received no other VTE preventative therapies.

### **Outcomes**

#### **Deep Vein Thrombosis/Pulmonary Embolism**

There were no PEs in any patient after filter insertion.

#### **Mortality**

Data on mortality among the 15 who received filters for prophylaxis were unavailable. However, nine of the 20 enrolled patients died.

#### **Adverse Events**

The study reported no significant bleeding, IVC thromboses, or filter related complications.

## **Risk of Bias**

The study received a high risk of bias rating due to methodologic limitations in design and reporting, sample size, and the absence of a control group to allow any meaningful conclusions.

## **Strength of Evidence**

The strength of evidence was insufficient to comment on the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns. We based this rating on the high risk of bias and unknown consistency from a single study.

## **Applicability**

This was a single center study at an academic burn center and the participants were similar to those at other academic burn centers. The study did not report racial composition of participants. However the overall small sample size of the study limits generalizability.

## **Key Question 4**

What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with liver disease?

We found no studies that directly address the comparative effectiveness and safety of pharmacologic strategies among patients with liver disease.

## **Key Question 5**

What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients receiving antiplatelet therapy?

## **Key Points and Evidence Grades**

- The strength of evidence is insufficient to comment on differences in rates of major bleeding comparing prophylactic rivaroxaban with enoxaparin in patients concomitantly treated with antiplatelet agents.
- The strength of evidence is insufficient to comment on differences in rates of major bleeding comparing prophylactic dabigatran with enoxaparin in patients concomitantly treated with aspirin.

## **Study Characteristics**

We found two studies, with very similar research methods using pooled data from large phase III trials that report on the safety of pharmacologic VTE prophylaxis on patients who are concomitantly on anti-platelet agents. The study by Eriksson performed a pre-specified analysis of pooled data from four major phase III trials of the RECORD program<sup>127</sup> and reported on the safety of concomitant use of non-steroidal anti-inflammatory drugs and platelet function



inhibitors including aspirin in patients receiving pharmacologic VTE prophylaxis. The RECORD trial was a double-dummy design where over 12,000 patients undergoing elective total knee replacement or total hip replacement were randomized to receive either oral Rivaroxaban or subcutaneous enoxaparin.

Friedman et al performed a post hoc analysis of the bleeding risk in patients who received pharmacologic prophylaxis while concomitantly on NSAIDs and ASA using pooled data from three pivotal trials: RE-MODEL, RE-NOVATE, and RE-MOBILIZE.<sup>128</sup> All trials were prospective, double-blind, double dummy, randomized and multicenter and used a non-inferiority design; they compared 220mg and 150mg dabigatran etexilate once daily with 40 mg enoxaparin subcutaneously in patients undergoing knee arthroplasty and total hip arthroplasty (Table 19).

## **Participant Characteristics**

In the Eriksson study there were 6,093 patients in the Rivaroxaban arm and 6,107 patients in the enoxaparin or placebo arm. In both arms the mean age was 68 years and 47 percent of the participants were male. The mean weight was 82 kg in the Rivaroxaban arm and 83 kg in the enoxaparin arm. Nine percent of patients from each arm (563 in rivaroxaban; 526 in enoxaparin) concomitantly used PFIs or ASA at least once during the at-risk period (defined as starting at day 1 of surgery and ending up to 2 days after the last intake of the study medication).

In the Friedman study out of the total 8,135 patients, 4,405 (54.1%) were on concomitant NSAIDs and 386 (4.7%) were on concomitant ASA. The baseline characteristics of those on ASA as compared with the rest of the groups were similar. The percentage of females in all groups ranged 57.8%-60.9%, the mean age ranged between 65.1±10.3 to 66.1±10.0 years and the average BMI ranged 29.2±5.7 to 29.6±5.5.

## **Intervention Characteristics**

In the Eriksson study, in a double-dummy design, patients were randomized to receive either oral Rivaroxaban 10mg once daily starting 6 to 8 hours after surgery or subcutaneous enoxaparin 40 mg daily starting 12 hours before surgery (RECORD 1-3) or enoxaparin 30mg twice daily starting 12 to 24 hours after wound closure or adequate hemostasis was achieved (RECORD 4). Patients undergoing total hip arthroplasty received oral Rivaroxaban for 31–39 days or subcutaneous enoxaparin for 31–39 days or enoxaparin (RECORD 1) or enoxaparin for 10–14 days with placebo tablets for 31–39 days (RECORD 2); patients undergoing total knee arthroplasty (RECORD 3 and 4) received Rivaroxaban or enoxaparin for 10–14 days. The co-medications investigated in this pre-specified analysis were NSAIDs and PFIs or ASA. There was no limitation on the choice of a specific drug or dose of NSAIDs, PFIs or ASA in the study protocol.

In the Friedman study, the RE-MODEL and RENOVATE trials were performed in Europe and compared 220 mg and 150 mg dabigatran etexilate once daily with 40 mg enoxaparin (in patients undergoing knee arthroplasty-RE-MODEL; total hip arthroplasty-RE-NOVATE). The RE-MOBILIZE trial compared 220 mg or 150 mg once daily dabigatran etexilate with 30 mg enoxaparin twice daily in patients undergoing knee arthroplasty (Table 20).

## Outcomes

### Rivaroxaban Versus Enoxaparin

The only endpoints evaluated in the Eriksson study were the composite major and minor clinically relevant bleeding and any bleeding occurring after first post-operative oral study drug intake (rivaroxaban or matching placebo tablet). These events were recorded during the at-risk period (from day of surgery, which is day 1, to the last intake of study drug or until the onset of event, whichever came first). The authors looked at three time periods: day 1–3; day 4–7 and after day 7 based on the consideration that the use of co-medications may vary over time and the relative risk of bleeding decreases over time after surgery. The relative bleeding rates were calculated for each time period as well as for the entire at-risk period and expressed as rates per 100 patient-weeks.

The relative bleeding rates for use versus non-use of PFIs or ASA with rivaroxaban and enoxaparin remained relatively constant and were similar between rivaroxaban and enoxaparin groups over the three at-risk time intervals. Over the total at-risk period, the number of patients concomitantly on PFIs or ASA who had any bleeding events were 3.6% for the rivaroxaban group (20/563) and 3.25% for the enoxaparin group (17/526) with a corresponding relative rate ratios of 1.32 in the rivaroxaban group (95% CI 0.85-2.05) and 1.40 in the enoxaparin/placebo group (95% CI 0.87-2.25). The number of patients who had the composite of major and non-major clinically relevant bleeding were 1.4% for the rivaroxaban group (98/563) and 1.0% for the enoxaparin group (5/526) with a relative rate ratio of 1.11 (95% CI 0.55-2.55) and 1.13 (95% CI 0.47-2.75) for rivaroxaban and enoxaparin respectively (Tables 21 and 22).

### Dabigatran Versus Enoxaparin

In the Friedman study, the reported outcome was major bleeding events defined as clinically overt bleeds associated with transfusion of 2 or more units of packed red cells, symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding or bleeding that leads to surgery. The percentage of major bleeding events for dabigatran 220mg, with and without concomitant ASA (<160mg/day) were 1.6% and 1.4% (OR 1.14; CI 0.26-5.03),  $P=0.862$  respectively. The percentage of bleeding events for enoxaparin with and without concomitant ASA were 3.0% and 1.2% (OR 2.57; CI 0.83-7.94),  $P=0.101$  as compared with concomitant ASA of 1.6% for both 220mg and 150mg of dabigatran. For both NSAIDs and ASA the authors did not find a significant difference in bleeding between patients with and without concomitant therapy in any treatment arm and there was no significant difference in major bleeding events between dabigatran and enoxaparin within co-medication subgroups (Table 22).

### Risk of Bias

Both the Eriksson and Friedman studies were rated as low risk of bias because both were pre-specified explorative subgroup analyses of large randomized trials.

### Strength of Evidence

The strength of evidence is insufficient to comment on differences in rates of major bleeding comparing prophylactic rivaroxaban with enoxaparin in patients concomitantly treated with

antiplatelet agents. We based this rating on a single trial with low risk of bias, imprecise findings and unknown consistency.

The strength of evidence is insufficient to comment on differences in rates of major bleeding comparing prophylactic dabigatran with enoxaparin in patients concomitantly treated with aspirin. This rating was based on results from a RCT with low risk of bias, imprecise findings and unknown consistency (Table 23).

## Applicability

The findings of this study might be applicable to patients who are undergoing total hip arthroplasty or total knee arthroplasty who will need VTE prophylaxis while continuing to be on ASA.

**Table 19. Study and participant characteristics for KQ 5**

Author, Year	Study Design	Arm, n	Age (Years) Mean	Male (%)	Weight (kg) Mean
Eriksson B.I, 2012 <sup>127</sup>	Pooled data from 4 trials (RECORD 1-4).	Arm 1 (Rivaroxaban), 563	68	47	82
		Arm 2 (Enoxaparin/placebo), 526	68	47	83
Friedman,R.J, 2012 <sup>128</sup>	Pooled data from 3 trials (RE-MODEL, RE-NOVATE, RE-MOBILIZE)	Arm 1 (220 mg Dabigatran, no ASA), 1149	66.1	NR	NR
		Arm 2 (150 mg Dabigatran, no ASA), 1149	65.4	NR	NR
		Arm 3 (Enoxaparin, no ASA), 1167	66.1	NR	NR
		Arm 4 (220 mg Dabigatran + ASA), 126	65.5	NR	NR
		Arm 5 (150 mg Dabigatran + ASA), 128	65.1	NR	NR
		Arm 6 (Enoxaparin+ ASA), 132	65.6	NR	NR

Kg = kilograms; n = number; NR = not reported; VTE = venous thromboembolism

**Table 20. Intervention characteristics for KQ 5**

Author, Year	Arm Name	Drug Name	Dose, Route, Frequency of Anticoagulant	Timing of First Dose	Concurrent Therapy
Eriksson B.I, 2012 <sup>127</sup>	Rivaroxaban	Rivaroxaban	10mg, Oral, od	6-8 hours after surgery	PFI or ASA
	Enoxaparin/placebo	Enoxaparin/placebo	40mg, SC, od	12 hours before surgery	PFI or ASA
		Enoxaparin/placebo	30mg, SC, bid	12-24 hours after wound closure or after adequate hemostasis was obtained	PFI or ASA
		Enoxaparin/placebo	40mg, SC, od	12 hours before surgery	PFI or ASA
		Enoxaparin/placebo	30mg, SC, bid	12-24 hours after wound closure or after adequate hemostasis was obtained	PFI or ASA
Friedman,R.J, 2012 <sup>128</sup>	Arm 1 (220 mg Dabigatran, no ASA), 1149	Dabigatran	220mg, Oral, Daily	1-4/6-12 hours after surgery	None
	Arm 2 (150 mg Dabigatran, no ASA), 1149	Dabigatran	150mg, Oral, Daily	1-4/6-12 hours after surgery	None
	Arm 3 (Enoxaparin, no ASA), 1167	Enoxaparin	40mg, SC, od 30mg, SC, bid	6-12 hours after surgery	None
	Arm 4 (220 mg Dabigatran + ASA), 126	Dabigatran	220mg, Oral, Daily	1-4/6-12 hours after surgery	ASA
	Arm 5 (150 mg Dabigatran + ASA), 128	Dabigatran	150mg, Oral, Daily	1-4/6-12 hours after surgery	ASA
	Arm 6 (Enoxaparin+ ASA), 132	Enoxaparin	40mg, SC, od 30mg, SC, bid	6-12 hours after surgery	ASA

ASA = acetylsalicylic acid; NR = not reported; PFI = platelet function inhibitors; SC = subcutaneous; VTE = venous thromboembolism

**Table 21. Outcomes (any bleeding) for KQ 5 over the total at-risk period**

Author, Year	Arm, n	Number of Patients With Co-Medications	Outcome	n (%) of Patients With Outcomes	Rate per 100 Patient-Weeks With Co-Medication	Rate per 100 Patient-Weeks Without Co-Medication	Measures of Association, Rate Ratio* for Use vs. Non-use (95% CI)
Eriksson B.I, 2012 <sup>127</sup>	Rivaroxaban, 6093	563	Any Bleeding	20 (3.6)	2.04 (1.25-3.15)	1.76 (1.58-1.95)	1.32 (0.85-2.05)
	Enoxaparin/placebo, 6107	526	Any Bleeding	17 (3.2)	2.06 (1.20-3.29)	1.63 (1.46-1.81)	1.40 (0.87-2.25)

CI = confidence interval

**Table 22. Outcomes (major bleeding) for KQ 5 over the total at-risk period**

Author, Year	Arm Name, n	N for Analysis	Outcome	Patients With Outcome, n (%)
Eriksson B.I, 2012 <sup>127</sup>	Rivaroxaban, 6093	563 (with co-medication-PFI/ASA)	Major and non-major clinically relevant bleeding	8 (1.4)
	Enoxaparin/placebo, 6107	526 (with co-medication-PFI/ASA)	Major and non-major clinically relevant bleeding	5 (1.0)
Friedman,R.J, 2012 <sup>128</sup>	Arm 1 (220 mg Dabigatran, no ASA), 1149	1149	Major bleeding	16 (1.4)
	Arm 2 (150 mg Dabigatran, no ASA), 1149	1149	Major bleeding	11 (1.0)
	Arm 3 (Enoxaparin, no ASA), 1167	1167	Major bleeding	14 (1.2)
	Arm 4 (220 mg Dabigatran + ASA), 126	126	Major bleeding	2 (1.6)
	Arm 5 (150 mg Dabigatran + ASA), 128	128	Major bleeding	2 (1.6)
	Arm 6 (Enoxaparin+ ASA), 132	132	Major bleeding	4 (3.0)

ASA = acetylsalicylic acid; NR = not reported; PFI=platelet function inhibitors; SC = subcutaneous; VTE = venous thromboembolism

**Table 23. Body of evidence for pharmacologic prophylaxis for venous thromboembolism among patients on antiplatelet agents**

Author, Year	Outcomes	Risk of Bias	Directness	Precision	Consistency	Magnitude of Effect
<b>Rivaroxaban vs. enoxaparin</b>						Insufficient evidence to comment on difference in rates of major bleeding with prophylactic rivaroxaban or enoxaparin in patients concomitantly treated with antiplatelet agents
Eriksson B.I, 2012 <sup>127</sup>	Major bleeding	Low	Direct	Imprecise	unknown	3.6% vs. 3.25%*
<b>Dabigatran vs. enoxaparin *</b>						Insufficient evidence to comment on difference in rates of major bleeding with prophylactic dabigatran or enoxaparin in patients concomitantly treated with aspirin
Friedman,R.J, 2012 <sup>128</sup>	Major bleeding <sup>‡</sup>	Low	Direct	Imprecise	unknown	1.6% vs. 3.0%, Risk ratio 0.68 (95% C.I. 0.22 to 2.1) *

\*Data presented for 150 mg dose of dabigatran.

‡The major bleeding events are defined as fatal bleeds; clinically overt bleeds in excess of what was expected and either associated with a  $\geq 20$ g/l reduction in hemoglobin or leading to transfusion of two or more units of packed cells or whole blood; symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding requiring treatment cessation; bleeding leading to reoperation; and surgical site bleeds.

## Key Question 6

What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent venous thromboembolism in hospitalized patients undergoing bariatric surgery?

### Key Points and Evidence Grades

In hospitalized patients having bariatric surgery:

- The strength of evidence is low that prophylactic inferior vena cava filters do not decrease the risk of PE relative to no filter use, in patients also receiving non-invasive mechanical measures.
- The strength of evidence is low that prophylactic inferior vena cava filters increase the risk of all-cause death relative to no filter use, in patients also receiving non-invasive mechanical measures.
- The strength of evidence is insufficient that prophylactic inferior vena cava filters increase the risk of post-operative DVT relative to no filter use, in patients also receiving non-invasive mechanical measures and pharmacological prophylaxis.
- The strength of evidence is insufficient that prophylactic inferior vena cava filters decrease the risk of fatal PE relative to no filter use, in patients also receiving non-invasive mechanical measures.
- The strength of evidence is insufficient to support the comparative effectiveness and safety of any pharmacological strategies

### Study Characteristics

We identified 21 articles that reported on VTE prevention strategies in hospitalized patients undergoing bariatric surgery. There were no RCTs addressing this KQ; all included studies were observational cohort studies. We also identified two case reports (1 patient each) that described filter complications in bariatric surgery patients. Six studies reported prospective data collection,<sup>129-134</sup> and one other reported that a portion of the data were collected prospectively.<sup>135</sup> The remaining studies were retrospective cohorts,<sup>131,135,136-146,149</sup> or case reports of filter complications.<sup>147,148</sup> All studies took place in the United States; only three enrolled patients from multiple centers<sup>136,143,149</sup> (Table 24 and Table 25).

### Participant Characteristics

Patients underwent a variety of surgical procedures including: Roux-en-Y gastric bypass (both open and laparoscopic, but predominantly laparoscopic), sleeve gastrectomy, adjustable laparoscopic gastric banding, and biliary-pancreatic diversion. Patient characteristics were generally consistent across studies. All studies included both men and women, and the mean age of participants, when reported, ranged from 39.5 to 49.8 years. Most studies reported mean Body Mass Index (BMI) which ranged from 45 to 71 kg/m<sup>2</sup>. Most studies did not explicitly describe the prevalence of a prior history of VTE. The duration of followup was generally 2 to 6 weeks, however one study reported a mean follow-up of 262 days<sup>137</sup> and another study reported follow-up of greater than 2 years.<sup>146</sup>

Among the 12 studies that reported on filters,<sup>134-142,147-149</sup> five included control groups of patients undergoing bariatric surgery who did not receive filters.<sup>135,136,138,139,149</sup> Two of these were multicenter, observational studies of patients included in large clinical registries.<sup>136,149</sup> Five studies reported on uncontrolled cohorts of patients who underwent filter placement.<sup>134,137,140,141,142</sup> Studies size ranged from one patient (case reports of filter complications) to 97,128 patients (registry study).<sup>136</sup> The uncontrolled cohorts ranged in size from nine patients<sup>142</sup> to 59 patients.<sup>134</sup> The smallest of these cohorts focused on patients undergoing bilateral common iliac vein filter placement (rather than IVC filter placement) in patients with unusually large inferior vena cava diameters.<sup>142</sup> Two studies were case reports of single bariatric surgical patients who had filter-related complications.<sup>147,148</sup> The studies on pharmacologic prophylaxis ranged in size from 40 patients<sup>133</sup> to 668 patients.<sup>143</sup>

Patient and hospitalization characteristics varied by treatment allocation in studies that compared interventions. For the more intensive prophylaxis, the studies appeared to target patients at higher risk of thrombosis. In the registry studies by Birkmeyer et al.<sup>149</sup> and Li et al.,<sup>136</sup> patients with filters tended to have lower baseline mobility, be male, and have a prior history of VTE. Li et al.<sup>136</sup> also noted that patients receiving filters more frequently had sleep disordered breathing and pulmonary hypertension. In the study by Kardys et al.,<sup>137</sup> clinicians preferentially placed filters in patients with a history of prior VTE, a known hypercoagulable state or a history of profound immobility, or who were morbidly obese (having a mean BMI of 71.2 kg/m<sup>2</sup>). Overby et al. offered filters to patients with elevated levels of coagulation markers, impaired mobility, severe sleep apnea or hypoventilation, prior VTE, and more severe obesity.<sup>139</sup> Obeid et al. also preferentially placed filters in the most obese patients, and those with prior VTE; they also placed significantly more filters in men than in women.<sup>138</sup> In the study by Gargiulo et al.,<sup>135</sup> investigators preferentially placed filters in patients with BMI greater than 55 kg/m<sup>2</sup>.

Similarly, clinicians appeared to use different pharmacological regimens depending on the severity of obesity, or according to practice patterns at the study center that related to patient risk for thrombosis. Consequently, different prophylactic regimens tended to be associated with the type of surgery (laparoscopic vs. open), the duration of surgery, or the length of hospital stay. Of the four studies of pharmacological prophylaxis that used enoxaparin doses of 60 mg twice daily,<sup>129,133,144,146</sup> two did so only in the most obese patients (with BMIs of >59 kg/m<sup>2</sup>, average BMI of 65<sup>146</sup> or >50 kg/m<sup>2</sup>, average BMI of 57.4<sup>129</sup>). In the one study that compared unfractionated heparin with enoxaparin,<sup>130</sup> BMI was slightly but significantly higher in enoxaparin-treated patients (48.7 vs. 47 kg/m<sup>2</sup>,  $p = 0.04$ ), and mean operative time was more than 30 minutes longer in the unfractionated heparin-treated patients (130 vs. 160 minutes,  $p < 0.001$ ). In the single study of prolonged pharmacological prophylaxis versus inpatient prophylaxis alone, the 132 patients who underwent surgery between 2003 and 2005 received 30 mg twice daily of enoxaparin subcutaneously starting 1 hour prior to surgery and continued through hospitalization, which averaged 3.0 days in duration. A second group of 176 patients who underwent surgery in 2006 and 2007, received enoxaparin starting 12 hours postoperatively, and continued throughout hospitalization (averaging 2.2 days in duration) and for a 10-day period following discharge. In addition to the significantly shorter length-of-stay in the second group, patients in this group had fewer open procedures (0 versus 4 patients) and fewer conversions to open procedures after failed laparoscopic interventions (0 versus 5 patients).<sup>131</sup>



## Intervention Characteristics

### Inferior Vena Cava Filters

Of the 12 studies of filters, 11 studies evaluated IVC filters,<sup>134-141,147,148,149</sup> and one studied bilateral common iliac vein filters.<sup>142</sup> The types of filters varied according to physician practice and preference. Filters included the retrievable Gunther Tulip<sup>®</sup>, Bard Recovery<sup>®</sup>, OptEase<sup>®</sup>, Cook Celest<sup>®</sup>, Bard G2<sup>®</sup>; as well as filters that are not generally intended for retrieval including Greenfield stainless steel, Simon Nitinol<sup>®</sup>, and Cordis TRAPEASE<sup>®</sup> filters. The large registry studies by Birkmeyer et al. and Li et al did not report on the specific filter types.<sup>136,149</sup> Six studies of filter prophylaxis described concurrent use of both mechanical prophylaxis with sequential compression devices and pharmacotherapy (enoxaparin, heparin, or warfarin).<sup>134,135,137-139,147</sup> Two described the use of filters with concurrent heparin or low molecular weight heparin prophylaxis only.<sup>141,148</sup> Only one of the controlled studies reported filter retrieval rates,<sup>139</sup> however all four of the uncontrolled cohort studies that used retrievable filters reported filter retrieval rates,<sup>134,140-142</sup> which ranged from 68 to 100 percent. There were no studies comparing different types of IVC filters head-to-head.

### Pharmacologic Prophylaxis

Studies of pharmacologic prophylaxis involved patients receiving at least two different regimens based on our inclusion criteria. All studies used active drug therapy in all patients, rather than comparisons with placebo or no prophylaxis. Enoxaparin and unfractionated heparin were the only specific drugs studied. Seven studies employed varying doses of enoxaparin,<sup>129,132,133,143-146</sup> two of which used weight-based dosing.<sup>129,146</sup> In the one study that included patients receiving either enoxaparin or unfractionated heparin,<sup>130</sup> one group of patients received enoxaparin 40 mg subcutaneously twice daily and group received unfractionated heparin 5,000 units subcutaneously every 8 hours. In one study, all patients received enoxaparin 30 mg subcutaneously twice daily, but the timing of initiation and duration of prophylaxis differed between the two comparison groups.<sup>131</sup> The dosing regimens of enoxaparin were: 30 mg once daily<sup>143</sup> or twice daily,<sup>131,132,145,146</sup> 40 mg once daily<sup>143</sup> or twice daily,<sup>129,130,133,143-146</sup> 50 mg twice daily,<sup>146</sup> and 60 mg twice daily.<sup>129,133,144,146</sup>

### Dose of Pharmacotherapy

We categorized doses as “standard” prophylactic dosing (enoxaparin 30 mg twice daily or 40 mg once daily and heparin 5,000 units every 8 hours) or “augmented” dosing, including enoxaparin 40 mg, 50 mg, and 60 mg twice daily. According to this classification, four studies included groups of patients receiving standard versus augmented dosing,<sup>132,143,145,146</sup> and three studies compared two or more augmented dosing regimens.<sup>129,144,146</sup> One of these studies also included patients who received reduced dosing (30 mg once daily).<sup>143</sup> Each of the four studies that included two or more augmented dosing regimens included a group receiving 40 mg twice daily and a group receiving 60 mg twice daily.<sup>129,133,144,146</sup>

### Timing of Pharmacotherapy

Four studies initiated pharmacotherapy prior to surgery,<sup>130,131,145,146</sup> and four studies initiated pharmacotherapy after surgery;<sup>129,132,133,144</sup> the timing was variable in the five-center study by Hamad et al.<sup>143</sup> The planned duration of pharmacotherapy was for the hospital stay in three studies;<sup>130,131,133</sup> until “fully ambulatory” or hospital discharge in one study;<sup>145</sup> for 2 weeks

postoperatively in one study;<sup>144</sup> for 10 days following discharge in one study;<sup>129</sup> was not clearly specified in one study;<sup>146</sup> and varied by center in the multicenter study by Hamad et al., ranging from 2 to 10 days.<sup>143</sup> In the pharmacokinetic study by Rowan et al. that compared two different doses of enoxaparin, the study assessed anti-Xa level after the first and third doses of the drug, so the total duration of prophylaxis was neither relevant to the results, nor reported.<sup>132</sup> Some studies described concurrent mechanical prophylactic interventions, including pneumatic compression devices in six studies<sup>129-132,145,146</sup> and early ambulation in four.<sup>129,132,145,146</sup> None of the included studies indicated that other non-pharmacologic prophylactic measures were delivered to only one treatment arm and not the other.

## **Ascertainment of Thrombotic Outcomes**

Most studies relied on clinically diagnosed (symptomatic) thrombosis, and did not employ routine surveillance for VTE prior to hospital discharge. However, three studies reported using ultrasound and/or computed tomographic venography prior to filter removal.<sup>134,139,142</sup> and one study reported performing bilateral lower extremity ultrasound prior to hospital discharge.<sup>131</sup>

## **Outcomes**

### **Pulmonary Embolism**

#### **Inferior Vena Cava Filter Versus No Inferior Vena Cava Filter**

In the study by Gargiulo et al.,<sup>135</sup> no perioperative PEs occurred in the 58 patients with filters (0 percent), whereas the nine of the 351 patients without filters suffered from PE (2.6 percent), of whom five died (1.4 percent). There were no multivariable adjustments for differences between groups. Obeid et al. compared 1,847 patients who did not get filters with 246 patients who did.<sup>138</sup> Perioperative PE occurred in 11 of those who did not get filters (0.59 percent) and two of those with filter (0.8 percent). In the study by Overby et al.,<sup>139</sup> there were five PEs identified in the 170 patients who did not receive filters (2.9 percent), and one in the 160 patients who did (0.63 percent). Li et al. found a higher rate of PE among the 322 patients with filters (0.31%) than in 96,806 without filters (0.12%),  $P = 0.33$ .<sup>136</sup> No authors adjusted for potential confounders in their analyses.

#### **Uncontrolled Studies of Inferior Vena Cava Filters**

In the uncontrolled cohort studies, perioperative PE rates ranged from 0 to 6.5 percent.<sup>137</sup>

### **VTE Outcomes (Pulmonary Embolism and/or Deep Vein Thrombosis)**

#### **Low-Molecular Weight Heparin Versus Unfractionated Heparin**

In the study by Kothari et al. that compared enoxaparin 40 mg subcutaneously twice daily with unfractionated heparin 5,000 units every 8 hours, a single PE occurred in the heparin-treated patients (0.42 percent), with no thrombotic events in the enoxaparin-treated patients within 30 days of surgery<sup>130</sup> (Table 28).

#### **Enoxaparin Versus Extended-duration Enoxaparin**

In the study by Raftopoulos et al, thrombotic events occurred in six of the 132 patients in the short-term prophylaxis group (4.5 percent) and none of the 176 in the extended-prophylaxis

group ( $p = 0.006$ ).<sup>131</sup> Three of the thrombotic events were DVTs and three were PEs. This difference remained statistically significant after excluding from the analysis patients who required conversion to open procedures ( $p = 0.03$ ) (Table 28-see footnote).

### **Enoxaparin at Standard Versus Augmented Dosing**

Three studies reported on VTE outcomes in patients receiving standard versus augmented enoxaparin dosing.<sup>143,145,146</sup> In the study by Scholten et al., among 92 patients receiving enoxaparin 30 mg twice daily (standard dosing) there were five thrombotic events (5.4 percent), including four PEs (4.3 percent) and one DVT (1.1 percent).<sup>145</sup> In this same study, among 389 patients who received 40 mg twice daily (augmented) there were two thrombotic events (0.5 percent), both DVTs. In the study by Singh et al.,<sup>146</sup> none of the 11 patients receiving standard dose enoxaparin (30 mg twice daily) had thrombotic events. Similarly, none of the 159 patients who received augmented dosing (ranging from 40 mg to 60 mg every 12 hours according to weight) had thrombotic events. Hamad et al. found one patient of 264 (0.4 percent) with a PE with standard dosing of 40 mg once daily, and one patient of 180 (0.6 percent) with a PE in the augmented treatment group dosed with 40 mg twice daily.<sup>143</sup> There were no DVTs described in either arm (Table 28).

### **Enoxaparin at Standard Versus Reduced Dosing**

In the five-center study by Hamad et al., two of the centers used enoxaparin at 30 mg once daily (reduced dosing, 224 patients), and two other centers used 40 mg once daily (standard dosing, 264 patients).<sup>143</sup> The study reported thrombotic events in five patients (2.2 percent) receiving 30 mg once daily (4 PEs [1.8 percent] and 1 DVT [0.4 percent]). There was one PE in a patient receiving 40 mg once daily (0.4 percent) (Table 28).

### **Differing Augmented Enoxaparin Dosing Regimens, 40 mg Twice Daily Versus 50 or 60 mg Twice Daily**

In the study by Borkgren-Okonen et al., among the 124 patients receiving 40 mg twice daily, there were two thrombotic events (1.6 percent) (1 PE [0.8 percent] and 1 DVT [0.8 percent]).<sup>129</sup> Among the 99 patients receiving 60 mg twice daily, there were no thrombotic events. Singh et al. reported no thrombotic events among the 145 patients receiving 40 mg twice daily and no events among the five patients receiving 60 mg twice daily.<sup>146</sup> Additionally, no patients of the nine receiving 50 mg twice daily developed thrombosis. Ojo et al.<sup>144</sup> and Simone et al.<sup>133</sup> did not report on thrombotic outcomes (Table 28).

## **Deep Vein Thrombosis**

### **Inferior Vena Cava Filter Versus No Inferior Vena Cava Filter**

Obeid et al. reported perioperative DVT in 12 (0.65 percent) patients not receiving filters and three (1.2 percent) of those who did.<sup>138</sup> Overby et al. reported DVT in four patients without filters (2.4 percent) and five patients with filters (3.1 percent).<sup>139</sup> In the registry study by Li et al., DVT occurred in 0.93% of patients with filters compared with 0.12% of those without ( $P < 0.001$ ).<sup>136</sup>

## **Uncontrolled Studies of Inferior Vena Cava Filters**

In the uncontrolled cohort studies of IVC filters, perioperative DVT rates ranged from 0 percent<sup>134,141,142</sup> to 21 percent (5 of 24 patients)<sup>140</sup> (Table 26).

## **Composite Outcomes**

### **Inferior Vena Cava Filter Versus No Inferior Vena Cava Filter**

Birkmeyer et al.,<sup>149</sup> found that patients treated at hospitals that used filters in over 10 percent of their bariatric surgery patients had a significantly higher risk of perioperative VTE (PE and DVT combined) than patients treated at hospitals with less liberal use of filters [OR 1.6 (95 % C.I. 1.2 to 2.0).] The data did not allow for assessment of individual endpoints such as PE or mortality (Table 26). The odds ratio for death or permanent disability associated with filter placement was 2.4 (95% C.I. 0.99 to 6.3) after adjustment for the likelihood of receiving a filter. In the same study, after adjustment for differences between groups, IVC filter use was not statistically significantly associated with VTE or major complications.<sup>149</sup> However there was a trend toward more “serious complications” (including reoperation, renal failure, and other complications associated with risk of death or disability) in patients receiving filters [OR: 1.4 (95% confidence interval, 0.91 to 2.2)].

## **Mortality**

### **Inferior Vena Cava Filter Versus No Inferior Vena Cava Filter**

Obeid et al. reported two patients with filters died (0.81 percent) and four patients who did not receive filters died (0.22 percent).<sup>138</sup> In the study by Gargiulo et al. there were no fatalities in the 58 patients with filters and five fatal PEs among the 351 patients who did not receive filters (1.4 percent)<sup>135</sup> (Table 26). Death from PE or indeterminate causes occurred in 0.31% of those with filters and in 0.03% of those without filters (P = 0.003) in the registry study by Li et al.<sup>136</sup> As noted above (in Composite Outcomes) in the study by Birkmeyer et al.,<sup>149</sup> the odds ratio for death or permanent disability associated with filter placement was 2.4 (95% C.I. 0.99 to 6.3) after adjustment for the likelihood of receiving a filter.

## **Uncontrolled Studies of Inferior Vena Cava Filters**

Three of these uncontrolled cohorts reported all-cause perioperative mortality rates of 0 percent,<sup>134</sup> 2.4 percent,<sup>141</sup> and 6.5 percent<sup>137</sup> (Table 26).

## **Low-Molecular Weight Heparin Versus Unfractionated Heparin**

There were no deaths in either group in the study by Kothari et al. that compared unfractionated heparin with enoxaparin<sup>130</sup> (Table 29).

## **Enoxaparin Versus Extended-Duration Enoxaparin**

There were no perioperative deaths in this study<sup>130</sup> (Table 29).

## **Enoxaparin at Standard Versus Augmented Dosing**

None of the three studies reported any perioperative deaths among patients receiving standard or augmented enoxaparin dosing<sup>143,145,146</sup> (Table 29).

## **Enoxaparin at Standard Versus Reduced Dosing**

Two of the patients receiving reduced dosing of enoxaparin died (0.9 percent) compared with none of those receiving standard dosing in a single study<sup>143</sup> (Table 29).

## **Differing Augmented Enoxaparin Dosing Regimens, 40 mg Twice Daily Versus 50 or 60 mg Twice Daily**

Only one study reported on mortality. Borkgren-Okonek et al. reported one death in a patient receiving 60 mg twice daily (0.4 percent) and no deaths among the patients receiving 40 mg twice daily. The study attributed the fatality to respiratory failure and prolonged post-operative mechanical ventilation in a patient with a BMI of 82 and did not attribute it to VTE or bleeding<sup>129</sup> (Table 29).

## **Filter Complications**

The cohort studies (both controlled and uncontrolled) reported adverse events including: filter migration to the heart (one patient),<sup>149</sup> nonfatal IVC thrombosis (one patient),<sup>140</sup> fatal IVC thrombosis (one patient),<sup>149</sup> errant placement of the filter into the common iliac vein (one patient),<sup>141</sup> wrong positioning of the filter (two patients),<sup>137</sup> pneumothorax (one patient),<sup>139</sup> hemopericardium (one patient),<sup>139</sup> and the inability to perform a transvenous ablation of a cardiac accessory pathway due to the filter (one patient).<sup>139</sup>

Among the case reports of unexpected filter complications, in one case the filter migrated to the right ventricle and was successfully removed percutaneously via a transjugular approach.<sup>148</sup> The second report attributed a patient death to an occlusive thrombus at the site of the IVC filter occurring 2 weeks postoperatively.<sup>147</sup> Additional autopsy findings included a small rent in the IVC with a small retroperitoneal hematoma, thought to be not large enough to have caused the patient's death. The authors postulated that an acute decrease in cardiac filling due to acute IVC occlusion was responsible for this patient's hemodynamic collapse (Table 27).

## **Bleeding**

### **Low-Molecular-Weight Heparin Versus Unfractionated Heparin**

In the study by Kothari et al, bleeding events requiring transfusion occurred in 14 patients (5.9 percent) treated with enoxaparin and three patients (1.3 percent) receiving heparin ( $p=0.01$ ).<sup>130</sup> Reoperation for bleeding was required in four patients in the enoxaparin group (1.7 percent) and none in the heparin group (Table 29).

### **Enoxaparin Versus Extended-Duration Enoxaparin**

Bleeding events requiring reoperation occurred in one patient in the short-term prophylaxis group (0.75 percent) and one patient in the extended prophylaxis group (0.56 percent).<sup>131</sup> There was no significant difference between the two groups in the mean drop in hemoglobin during surgery (Table 29).

### **Enoxaparin at Standard Versus Augmented Dosing**

In the study by Scholten et al.,<sup>145</sup> among 92 patients receiving enoxaparin 30 mg twice daily (standard dosing), there was one bleeding event that required transfusion (1.1 percent). Among the 389 patients who received 40 mg twice daily (augmented), there was a single bleeding event requiring re-operation. Singh et al. reported no bleeding events reported among the 11 patients

receiving standard dose enoxaparin (30 mg twice daily), while among the 159 patients who received augmented dosing, there were five bleeding episodes requiring transfusion (3.1 percent), one of which required reoperation (0.6 percent).<sup>146</sup> Hamad et al. reported three bleeding events requiring transfusion among the 264 patients receiving standard dosing (1.1 percent), and three bleeding events requiring transfusion in 180 patients receiving augmented dosing (1.7 percent)<sup>143</sup> (Table 29).

### **Enoxaparin at Standard Versus Reduced Dosing**

Bleeding requiring transfusion was reported in one patient receiving reduced dosing enoxaparin (0.4 percent) and in three patients receiving standard dosing (1.1 percent)<sup>143</sup> (Table 29).

### **Differing Augmented Enoxaparin Dosing Regimens, 40 mg Twice Daily Versus 50 or 60 mg Twice Daily**

Borkgren-Okonek et al. reported major bleeding events in five (4.03 percent) of the 124 patients receiving 40 mg twice daily, one of whom required reoperation (0.8 percent). One patient who received 60 mg twice daily developed major bleeding (1.0 percent), but did not require reoperation.<sup>129</sup> Singh et al. reported four bleeding events (2.8 percent) among the 145 patients receiving 40 mg twice daily, one of which one required reoperation (0.7 percent). There was one major bleeding event (20.0 percent) among the five patients receiving 60 mg twice daily; the patient did not require reoperation.<sup>146</sup> Ojo et al. reported no bleeding events in either group.<sup>144</sup> Simone et al. reported one bleeding episode (4.2 percent), which required transfusion among the 24 patients receiving 40 mg twice daily, and no bleeding events among the 16 patients receiving 60 mg twice daily<sup>147</sup> (Table 29).

### **Anti-Xa levels**

Two studies reported on this outcome.<sup>132,133</sup>

### **Enoxaparin at Standard Versus Augmented Dosing**

One of the studies that included patients receiving either standard dose enoxaparin (30 mg twice daily) or augmented dosing (40 mg twice daily), and studied only pharmacokinetic endpoints, specifically anti-Xa levels drawn after the first and third doses of the drug, measured 4 hours after the dose.<sup>132</sup> The study defined appropriate prophylactic levels as 0.18-0.44 units/mL. Nineteen patients (mean weight 141.6 kg) received the 30 mg twice-daily dose, and 33 patients (mean weight 135.6 kg) received the 40 mg twice-daily dose. Patients receiving 30 mg twice daily had mean anti-Xa levels of 0.06 units/mL after the first dose, and 0.8 units/mL after the third dose. Levels were 0.14 and 0.15 units/mL, respectively, in patients receiving 40 mg doses. None of the patients receiving 30 mg doses had therapeutic levels after the first dose, and only 9 percent had therapeutic levels after the third dose. In those receiving 40 mg, 31 and 42 percent were therapeutic after the first and third doses, respectively.

### **Differing Augmented Enoxaparin Dosing Regimens, 40 mg Twice Daily Versus 50 or 60 mg Twice Daily**

In the study by Simone et al., 24 patients (mean weight 135 kg) received 40 mg twice daily and 16 patients (mean weight 127 kg) received 60 mg twice daily.<sup>147</sup> The study measured anti-Xa levels 4 hours after the first and third doses of drug and defined appropriate prophylactic levels

as 0.18-0.44 units/mL. Mean anti-Xa levels were 0.173 units/mL in the 40 mg group and 0.261 units/mL in the 60-mg group, after the first dose. After the third dose, levels were 0.21 and 0.43 units/mL respectively. None of the patients receiving the 60 mg dose remained subtherapeutic after three doses, in contrast to 44 percent of those receiving 40 mg. However, there were no supratherapeutic levels in the patients receiving 40 mg, in contrast to 57 percent of the levels in patients receiving 60 mg doses.

## **Risk of Bias**

All of the observational studies, except one which was rated as moderate risk of bias<sup>149</sup> were rated to have a high risk of bias due to severe methodological limitations in design and analysis. The preference of the surgical team or the protocol employed at the center during a particular timeframe usually defined the prophylactic strategy. Some authors described allocating interventions based on real or perceived risk factors for postoperative VTE, such as prior history of VTE, age, degree of immobility, or severity of obesity; or varied the dose of pharmacotherapy based on patient weight in an effort to ensure that patients received an adequate prophylactic blood level of the drug. This targeted prophylactic approach would tend to bias these studies toward poorer efficacy of more aggressive prophylactic strategies employed in riskier patients. In keeping with the low numbers of patients and events, none of the studies performed multivariable adjustments to account for patient differences according to intervention allocation, except one that sought to define the efficacy of IVC filters by comparing those who got filters with those who did not by propensity score methods.<sup>149</sup> None of the studies focusing on differing intensity, timing, or duration of pharmacologic prophylaxis used multivariate adjustment to account for differences between patients who received different prophylactic strategies.

## **Strength of Evidence**

Among studies that evaluated IVC filters, we rated the overall risk of bias as high for all outcomes. We considered the evidence direct for all outcomes other than anti-Xa levels. The random effects meta-analysis forest plot for IVC filter vs no filter on the outcomes of PE, mortality and DVT are shown in Figures 11–13. We rated the strength of evidence as low to support that prophylactic filters do not decrease the risk of PE relative to no use. We based this rating on consistent and direct evidence from high risk of bias studies (Table 30). There was low statistical heterogeneity in the risk of PE associated with IVC filters ( $I^2 = 16.3\%$ ); all studies had confidence intervals that overlapped unity. We rated the strength of evidence as insufficient to support that prophylactic filters increase the risk of postoperative DVT. We based this rating on consistent and direct evidence from high risk of bias studies with a confidence interval spanning unity (Table 30). The estimate of an increased risk of DVT with IVC filters was precise in the registry study by Li,<sup>136</sup> with point estimates suggesting increased risk of DVT with IVC filters in all studies. Statistical heterogeneity was high ( $I^2 = 62.6\%$ ). We rated the strength of evidence as low to support that prophylactic filters are associated with an increased risk of mortality. We based this rating on consistent, precise and direct evidence from moderate and high risk of bias studies (Table 30). There was no statistical heterogeneity in the risk of mortality associated with IVC filters ( $I^2 = 0.0\%$ ). Although one small study reported an effect that was opposite to the direction of effect in other studies, the width of the confidence interval overlapped with other studies showing an increased risk.

We rated the strength of evidence as insufficient for all outcomes and comparisons for the pharmacologic interventions. We based this rating on the overall risk of bias as high for all

comparisons and outcomes. We considered most of the evidence direct except for the surrogate outcome of anti-Xa levels. We rated the strength of evidence as insufficient for all outcomes and comparisons because of the inconsistencies and imprecision in the body of evidence from such high risk of bias studies.

## **Applicability**

Patient characteristics were consistent with those expected in the bariatric surgery population, including obese middle-aged patients of both sexes. Types of surgeries included the main types of bariatric procedures currently employed in the United States. (including Roux-en-Y gastric bypass and adjustable gastric banding); most surgeries were laparoscopic, consistent with current practice. Most studies did not report race, so we cannot make firm conclusions related to potential interactions between race and prophylactic strategy. Although many studies reported single center experiences, patient characteristics and surgery types appear relatively consistent across study centers. The single-center nature of these studies, by itself, is not a major factor limiting generalizability since the characteristics of patients recruited were similar to those in other centers. However, several of these studies targeted specific pharmacologic strategies and IVC filters for patients with more severe obesity such as BMI > 55 kg/m<sup>2</sup>. Thus the applicability of these findings to those with lower levels of BMI is uncertain.



**Table 24. Characteristics of studies of IVC filters among patients undergoing bariatric surgery**

Author, Year	Design	Arm	N	Mean Age, Years	Male,%	Body Mass Index, kg/m <sup>2</sup>
Controlled Observational Studies						
Birkmeyer, N. J., 2010 <sup>149</sup>	Retrospective Cohort	Filter	542	NR	30	>50 in 72%
		No filter	5834	NR	19	>50 in 34%
Gargiulo, N.J., 2006 <sup>135</sup>	Retrospective-Prospective	Filter	58	NR	41.3	>55 in 100%
		No filter	351	NR		>55 in 12%
Li, W., 2012 <sup>136</sup>	Retrospective Cohort	Filter	322	47	31.4	45.3
		No Filter	96806	46	21.1	44.5
Obeid, F. N., 2007 <sup>138</sup>	Retrospective Cohort	Filter	246	46.6	23.6	60
		No filter	1847	44.7	14	48.8
Overby, D. W., 2009 <sup>139</sup>	Retrospective Cohort	Filter	160	NR	14.55	51.42
		No filter	170	NR		
Uncontrolled Observational Studies						
Kardys, C. M. 2008 <sup>137</sup>	Retrospective Cohort	Filter	31	42	NR	71.2
Piano, G., 2007 <sup>134</sup>	Prospective Cohort	Filter	59	43	17	61
Schuster, R., 2007 <sup>140</sup>	Retrospective Cohort	Filter	24	49.8	58.3	>50 in 88%
Van Ha, T. G., 2011 <sup>142</sup>	Retrospective Cohort	Filter	9	45	60	>50
Vaziri, K., 2010 <sup>141</sup>	Retrospective Cohort	Filter	41	48	29	58.4
Case Reports of Filter Complications						
Schweitzer, M., 2006 <sup>147</sup>	Case report	Filter	1	63	Female	45
Veerapong J., 2008 <sup>148</sup>	Case report	Filter	1	31	Male	74

BMI = body mass index; N = number; NR = not reported

**Table 25. Characteristics of studies of pharmacologic comparisons among patients undergoing bariatric surgery**

Author, Year	Design	Intervention and Comparator	N Patients	Mean Age Years	%Male	BMI(kg/m <sup>2</sup> )
Borkgren-Okonek, M. 2008 <sup>129</sup>	Prospective Cohort	Enoxaparin 40mg sq q12, SCD, ambulation and preop heparin sq, BMI ≤50 and qd for 10 days post discharge (A)	124	44.7	22.6	44.9
		Enoxaparin 60mg sq q12, SCD, ambulation and preop heparin sq, BMI >50 and qd for 10 days post discharge (A)	99	44.3	27.3	57.4
Hamad, G.G., 2005 <sup>143</sup>	Retrospective Cohort	Enoxaparin 40mg sq q12 (A)	180	39.7	3	46
		Enoxaparin 40mg sq qd (S)- post op for 12-120 hours	84	47.5	29	56.8
		Enoxaparin 40mg sq qd (S)-post op for 12-24 hours	180	41.9	10	49.9
		Enoxaparin 30mg sq qd (R)-pre op	100	39.5	25	47
		Enoxaparin 30mg sq qd (R)-post discharge	124	42.1	18	51.5
Kothari, S. 2007 <sup>130</sup>	Prospective Cohort	Enoxaparin 40mg sq q12 and SCD, ambulation (A)	238	42	NR	48.7
		Heparin sq 5000iu q8hrs and SCD, ambulation (S)	238	44	NR	47
Ojo, P., 2008 <sup>144</sup>	Retrospective Cohort	Enoxaparin 40mg sq q12 (S)	59	48	33.9	57
		Enoxaparin 60mg sq q12 (A)	68	46	61.8	58
Raftopoulos, I., 2008 <sup>131</sup>	Prospective Cohort	Enoxaparin 30mg sq q12 extended for 10days post d/c (S)	176	44.1	18.75	46.1
		Enoxaparin 30mg sq q12 during hospital stay, SCD (S)	132	42.6	15.2	47.8
Rowan, BO., 2008 <sup>132</sup>	Prospective Cohort	Enoxaparin 40mg sq q12, SCD and ambulation (A)	33	40.8	18	48.5
		Enoxaparin 30mg sq q12, SCD and ambulation (S)	19	41.7	26	48.4
Scholten, D. J., 2002 <sup>145</sup>	Retrospective Cohort	Enoxaparin 40mg sq q12, SCD and ambulation (A)	389	44.3	15.8	50.4
		Enoxaparin 30mg sq q12 and SCD, ambulation (S)	92	43.7	20.2	51.7
Simone, E. 2008 <sup>133</sup>	Prospective Cohort	Enoxaparin 40mg sq q12 (A)	24	40	12.5	48.8
Singh, K., 2011 <sup>146</sup>	Retrospective Cohort	Enoxaparin 40mg sq q12, ambulation for BMI 41-49 (A)	145	43	53	48
		Enoxaparin 50mg sq q12, ambulation for BMI 50-59 (A)	9			51
		Enoxaparin 60mg sq q12, ambulation for BMI > 60 (A)	5			65
		Enoxaparin 30mg sq q12, ambulation for BMI < 40 (S)	11			39

A = Augmented dose; BMI = body mass index; iu = International Units; NR = not reported; qd = once daily; q12 = once every 12 hours; R = reduced dose, S = Standard dose given for VTE prophylaxis; SCD = sequential compression devices; sq = subcutaneous

#Studies measured Serum Factor Xa- levels.

**Table 26. VTE outcomes among patients undergoing bariatric surgery who received inferior vena cava filters**

Study	Design	Arm	N Patients	Device Type	VTE Diagnosis	Pulmonary Embolism, n (%)	DVT (Including Device-Related DVT), n (%)	Total Mortality, n (%)
IVC Filter vs. No IVC Filter								
Birkmeyer, N. J., 2010 <sup>149</sup> †	Retrospective Cohort	Filter	542	Filter	A physician diagnosis of DVT or PE	NR	NR	10(1.85)
		No filter	5834	No filter	A physician diagnosis of DVT or PE	NR	NR	30(0.51)
Gargiulo, N.J., 2006 <sup>135</sup>	Retrospective-Pro prospective	Filter	58	Trapease, Simon-Nitinol, Greenfield, Bard Recovery	NR	0(0)	2(3)	0(0)#
		No filter,	351	No filter	NR	9(2.56)	NR	5(1.42)#
Li, W., 2012 <sup>136</sup>	Retrospective Cohort	Filter	322	NR	NR	1(0.31)	3(0.93)	1(0.31)
		No Filter	96806	No Filter	NR	116(0.12)	116(0.12)	29(0.03)
Obeid, F. N., 2007 <sup>138</sup>	Retrospective Cohort	Filter	246	NR	NR	2 (0.8)	3(1.2)	2(0.81)
		No filter	1847	No filter	NR	11 (0.59)	12 (0.65)	4(0.22)
Overby, D. W., 2009 <sup>139</sup>	Retrospective Cohort	Filter	160	Celect, Gunther Tulip, Bard Recovery, Optease, Venatech, Bard G2	CT Venography or Doppler US	1(0.63)	5(3.13)	3(0.9)
		No filter	170	No filter	CT Venography or Doppler US	5(2.94)	4(2.35)	
Uncontrolled Studies of IVC Filter								
Kardys, C. M. 2008 <sup>137</sup>	Retrospective Cohort	Filter	31	Greenfield Stainless Steel®	NR	2 (6.4)	1(3.1)	2(6.4)
Piano, G., 2007 <sup>134</sup>	Prospective Cohort	Filter	59	Gunther Tulip®	Doppler US	1 (1.69)	0 (0)	0(0)
Schuster, R., 2007 <sup>140</sup>	Retrospective Cohort	Filter	24	Gunther Tulip®	NR	1(4.2)	5 (21.0)	0(0)
Van H, T. G., 2011 <sup>142</sup>	Retrospective Cohort	Filter (Iliac vein)	10	Gunther Tulip, Celect	Doppler US, Venogram	0(0)	0(0)	0(0)
Vaziri, K., 2010 <sup>141</sup>	Retrospective Cohort	Filter	41	Gunther Tulip®, G2® filters	NR	0(0)	2 (4.9)	1(2.4)

DVT = deep vein thrombosis; N = number; NR= not reported; PE = pulmonary embolism; VTE = venous thromboembolism

#Authors reported PE related mortality. †Authors reported composite VTE outcomes only: Filter group: 11(2.03); No Filter group: 31(0.53).

**Table 27. Filter retrieval rates and device complications in bariatric surgery patients who received inferior vena cava filters**

Author, Year	Arm	N Patients	Device Type	Filter Retrieval Rate n ( %)	Device Complications, Other n (%)
<b>Controlled Observational Studies</b>					
Birkmeyer, N. J., 2010 <sup>149</sup>	Filter	542	NR	NR	2†
	No filter	5834	no filter	NR	NA
Gargiulo, N.J., 2006 <sup>135</sup>	Filter	58	Multiple	NR	3(5.17)Ω
	No filter	351	no filter	NA	NA
Li, W., 2012 <sup>136</sup>	Filter	322	NR	NR	NR
	No filter	96806	No filter	NR	NA
Obeid, F. N., 2007 <sup>138</sup>	Filter	246	NR	NR	NR
	No filter	1847	no filter	NR	NA
Overby, D. W., 2009 <sup>139</sup>	Filter	160	Multiple	147(92%)	4(2.5)§
	No filter	170	no filter	NR	NA
<b>Uncontrolled Observational Studies</b>					
Kardys, C. M. 2008 <sup>137</sup>	Filter	31	Greenfield Stainless Steel®	NR	2(6.4)β
Piano, G., 2007 <sup>134</sup>	Filter	59	Gunther Tulip®	52(88)	NR
Schuster, R., 2007 <sup>140</sup>	Filter	24	Gunther Tulip®	20(83)	NR
Van H, T. G., 2011 <sup>142</sup>	Filter (Iliac vein)	10	Gunther Tulip, Celect	10(100)	NR
Vaziri, K., 2010 <sup>141</sup>	Filter	41	Gunther Tulip®, G2® filters	28(68)	2(4.87)α
<b>Case Reports</b>					
Schweitzer, M., 2006 <sup>147</sup>	Case report	1	Optease	NA	1(100)#
Veerapong J., 2008 <sup>148</sup>	Case report	1	Gunther-Tulip	1(100)	1(100)δ

IVC = inferior vena cava; n = number; NA = not applicable; NR = not reported

†The complications included fatal IVC thrombosis and IVC filter migration to the heart.

§The complications were due to insertion (pneumothorax), early removal (hemopericardium, pulmonary embolism) and delayed removal (unable to perform transvenous accessory pathway ablation) of the IVC filter.

Ω1 postoperative IVC thrombosis occurred 4 months after Trapease IVC filter placement while 2 postoperative localized, insertion-site DVTs occurred 3 months after filter placement.

α1 patient had self-limiting pain at the insertion site of the IVC filter for 5 days while the other patient had a filter deployed in the right common iliac vein.

βThe complication was malposition of the IVC filter in the 2 patients.

#The IVC filter was completely occluded by a thrombus in this patient.

δThe IVC filter migrated to the right ventricle in this patient.

**Table 28. VTE outcomes among bariatric surgery patients undergoing pharmacological prophylaxis**

Author, Year	Design	Arm	N Patients	VTE Diagnosis	Perioperative Pulmonary Embolism, n(%)	Perioperative DVT, n(%)
Borkgren-Okonek, M. 2008 <sup>129</sup>	Prospective Cohort	Enoxaparin 40mg sq q12, SCD, ambulation and preop Heparin sq, BMI ≤50 and qd for 10 days post discharge	124	US, CTA, VQ scan	1(0.8)	1(0.8)
		Enoxaparin 60mg sq q12, SCD, ambulation and preop Heparin sq, BMI >50 and qd for 10 days post discharge	99	US, CTA, VQ scan	NR	NR
Hamad, G.G., 2005 <sup>143</sup>	Retrospective Cohort	Enoxaparin 40mg sq q12(A)	180	NR	1(0.6)	0(0)
		Enoxaparin 40mg sq qd (S) post op for 12-120 hours	84	NR	1(1)	0(0)
		Enoxaparin 40mg sq qd(S) post op for 12-24 hours	180	NR	0(0)	0(0)
		Enoxaparin 30mg sq qd(R)pre op	100	NR	2(2)	0(0)
		Enoxaparin 30mg sq qd(R)post discharge	124	NR	2(1.6)	1(0.8)
Kothari, S. 2007 <sup>130</sup>	Prospective Cohort	Enoxaparin 40mg sq q12 and SCD, ambulation	238	NR	0(0)	0(0)
		Heparin sq 5000u q8hrs and SCD, ambulation	238	NR	1(0.42)	0 (0)
Ojo, P., 2008 <sup>144</sup>	Retrospective Cohort	Enoxaparin 40mg sq q12	59	NR	NR	NR
		Enoxaparin 60mg sq q12	68	NR	NR	NR
Raftopoulos, I., 2008 <sup>131†</sup>	Prospective Cohort	Enoxaparin 30mg sq q12, SCD extended for 10days post d/c	176	Doppler US prior to d/c, chest CT	0(0)	0(0)
		Enoxaparin 30mg sq q12, SCD during hospital stay, SCD	132	Doppler US prior to d/c, chest CT	3(2.3)	3(2.3)
Scholten, D. J., 2002 <sup>145‡</sup>	Retrospective Cohort	Enoxaparin 40mg sq q12, SCD and ambulation (A)	389	NR	0(0)	2(0.5)
		Enoxaparin 30mg sq q12 and SCD, ambulation (S)	92	NR	4 (4.3)	1 (1.1)

**Table 28. VTE outcomes among bariatric surgery patients undergoing pharmacological prophylaxis (continued)**

Author, Year	Design	Arm	N Patients	VTE Diagnosis	Perioperative Pulmonary Embolism, n(%)	Perioperative DVT, n(%)
Simone, E. 2008 <sup>133</sup>	Prospective Cohort	Enoxaparin 40mg sq q12	24	NR	NR	NR
		Enoxaparin 60mg sq q12	16	NR	NR	NR
Singh, K., 2011 <sup>146</sup>	Retrospective Cohort	Enoxaparin 40mg sq q12, SCD, ambulation for BMI 41-49(A)	145	Doppler US, CT Angio	0 (0)	0 (0)
		Enoxaparin 50mg sq q12, SCD, ambulation for BMI 50-59 (A)	9	Doppler US, CT Angio	0 (0)	0 (0)
		Enoxaparin 60mg sq q12, SCD, ambulation for BMI > 60 (A)	5	Doppler US, CT Angio	0 (0)	0 (0)
		Enoxaparin 30mg sq q12, SCD, ambulation for BMI < 40 (S)	11	Doppler US, CT Angio	0 (0)	0 (0)

A = Augmented dose; LMWH = low molecular weight heparin; NR = not reported; q12 = once every 12 hours; qd = once daily; R = reduced dose; S = standard dose given for VTE prophylaxis sq = subcutaneous; UF = unfractionated heparin

†Raftopoulos, I., 2008<sup>131</sup> also reported statistically significant difference on VTE outcomes between extended duration vs enoxaparin group, 6 vs 0 or 4.5% vs 0%; P=0.006.

‡Scholten, D. J., 2002<sup>145</sup> also reported on statistically significant difference on VTE outcomes between Standard dose and Augment dose, 5 vs 2 or 5.4% vs 0.5%, P<0.01.

**Table 29. Safety profile of pharmacological interventions to prevent VTE in bariatric surgical patients**

Author, Year	Arm	N Patients	Bleeding Requiring PRBC, n (%)	Bleeding Requiring Surgery, n (%)	Minor Bleeding, n (%)	Total Peri Operative Mortality, n (%)
<b><i>Enoxaparin vs. Unfractionated Heparin</i></b>						
Kothari, S. 2007 <sup>130</sup>	Enoxaparin 40mg sq q12 and SCD, ambulation	238	14(5.9)	4(1.7)	NR	0(0)
	Heparin sq 5000u q8hrs and SCD, ambulation	238	3(1.3)	0(0)	NR	0(0)
<b><i>Enoxaparin vs. Extended-Duration Enoxaparin</i></b>						
Raftopoulos, I., 2008 <sup>131</sup>	Enoxaparin 30mg sq q12 extended for 10days post d/c	176	0(0)	1(0.56)	NR	0(0)
	Enoxaparin 30mg sq q12 during hospital stay, SCD	132	6(4.5)	1(0.75)	NR	0(0)
<b><i>Enoxaparin at Standard vs. Augmented Dosing</i></b>						
Hamad, G.G., 2005 <sup>143</sup>	Enoxaparin 40mg sq q12(A)	180	3(1.7)	NR	NR	NR
	Enoxaparin 40mg sq qd(S) post op for 12-120 hours	84	0(0)	NR	NR	NR
	Enoxaparin 40mg sq qd(S) post op for 12-24 hours	180	3(1.7)	NR	NR	NR
	Enoxaparin 30mg sq qd(R) pre op	100	0(0)	NR	NR	NR
	Enoxaparin 30mg sq qd(R) post discharge	124	1(0.8)	NR	NR	2(1.6)
Scholten, D. J., 2002 <sup>145</sup>	Enoxaparin 40mg sq q12, SCD and ambulation(A)	389	NR	1(0.26)	NR	NR
	Enoxaparin 30mg sq q12 and SCD, ambulation(S)	92	1(1.1)	NR	NR	NR
Singh, K., 2011 <sup>146</sup>	Enoxaparin 40mg sq q12, ambulation for BMI 41-49(A)	145	4(2.8)	1(0.7)	NR	NR
	Enoxaparin 50mg sq q12, ambulation for BMI 50-59(A)	9	0(0)	0(0)	NR	NR
	Enoxaparin 60mg sq q12, ambulation for BMI > 60(A)	5	1(20)	0(0)	NR	NR
	Enoxaparin 30mg sq q12, ambulation for BMI < 40(S)	11	0(0)	0(0)	NR	NR

**Table 29. Safety profile of pharmacological interventions to prevent VTE in bariatric surgical patients (continued)**

Author, Year	Arm	N Patients	Bleeding Requiring PRBC, n (%)	Bleeding Requiring Surgery, n (%)	Minor Bleeding, n (%)	Total Peri-operative Mortality, n (%)
<i>Differing Augmented Enoxaparin Dosing Regimens</i>						
Borkgren-Okonek, M. 2008 <sup>129</sup>	Enoxaparin 40mg sq q12, SCD, ambulation and preop heparin sq, BMI ≤50 and qd for 10 days post discharge	124	4(3.2)	1(0.8)	NR	0(0)
	Enoxaparin 60mg sq q12, SCD, ambulation and preop heparin sq, BMI >50 and qd for 10 days post discharge	99	1(1)	0(0)	NR	1(1)
Ojo, P., 2008 <sup>144</sup>	Enoxaparin 40mg sq q12	59	0(0)	NR	NR	NR
	Enoxaparin 60mg sq q12	68	0(0)	NR	NR	NR
Simone, E. 2008 <sup>133</sup>	Enoxaparin 40mg sq q12	24	1(4.2)	NR	NR	NR
	Enoxaparin 60mg sq q12	16	0(0)	NR	NR	NR
Singh, K., 2011 <sup>146</sup>	Enoxaparin 40mg sq q12, ambulation for BMI 41-49(A)	145	4(2.8)	1(0.7)	NR	NR
	Enoxaparin 50mg sq q12, ambulation for BMI 50-59(A)	9	0(0)	0(0)	NR	NR
	Enoxaparin 60mg sq q12, ambulation for BMI > 60(A)	5	1(20)	0(0)	NR	NR
	Enoxaparin 30mg sq q12, ambulation for BMI < 40(S)	11	0(0)	0(0)	NR	NR

A = augmented dose; n = number; NR = not reported; PRBC = PPI plus bismuth subsalicylate, rifabutin, and ciprofloxacin; R = reduced dose; S = standard dose given for VTE prophylaxis

# Authors describe serious hemorrhage as that occurring within 30 days of surgery and requiring >4 units blood products or reoperation.



**Table 30. Body of evidence for inferior vena cava filter versus controls for the prevention of pulmonary embolism in patients undergoing bariatric surgery**

Author, Year	Outcomes	Risk of Bias	Directness	Precision #	Consistency	Magnitude of Effect
<i>Filter vs. No Filter</i>						
	PE	High	Direct	Precise	Consistent	Low grade evidence to support that prophylactic IVCFs do not reduce PE in patients undergoing bariatric surgery compared with controls RR = 0.91 (95% CI = 0.32 to 2.57; p=0.858 ; $I^2=16.3\%$ )
Gargiulo, N.J., 2006 <sup>135</sup>		High	Direct	Precise		0% vs 2.6%
Li, W., 2012 <sup>136</sup>		High	Direct	Precise		0.31% vs 0.12%; p=0.33
Obeid, F. N., 2007 <sup>138</sup>		High	Direct	Imprecise		0.8 vs 0.6%; p=0.69
Overby, D. W., 2009 <sup>139</sup>		High	Direct	Imprecise		0.6% vs 2.9%; p=0.22
	Fatal PE	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of IVCF vs. controls in reducing fatal PE in patients undergoing bariatric surgery
Gargiulo, N.J., 2006 <sup>135</sup>		High	Direct	Imprecise		0% vs 11.1%
	DVT	High	Direct	Imprecise	Consistent	Insufficient evidence to support that IVCFs increase DVT in patients undergoing bariatric surgery compared with controls RR = 2.77 ( 95% CI=0.87 to 8.85; p=0.086 ; $I^2=62.6\%$ )
Gargiulo, N.J., 2006 <sup>135</sup>		High	Direct	Precise		3.4% vs NR
Li, W., 2012 <sup>136</sup>		High	Direct	Precise		0.93% vs 0.12%; p<0.001
Obeid, F. N., 2007 <sup>138</sup>		High	Direct	Imprecise		1.2% vs 0.65%; p=0.56
Overby, D. W., 2009 <sup>139</sup>		High	Direct	Imprecise		3.1% vs 2.4% p=0.74
	VTE	Moderate	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of IVCF vs controls in reducing VTE in patients undergoing bariatric surgery
Birkmeyer, N. J., 2010 <sup>149</sup>		Moderate	Direct	Precise	Unknown	2.0% vs 0.5%; p<0.0001

**Table 30. Body of evidence for inferior vena cava filter versus controls for the prevention of pulmonary embolism in patients undergoing bariatric surgery (continued)**

Author, Year	Outcomes	Risk of Bias	Directness	Precision #	Consistency	Magnitude of Effect
<i>Filter vs. No Filter (continued)</i>						
	<b>Mortality**</b>	<b>High</b>	<b>Direct</b>	<b>Precise</b>	<b>Consistent</b>	<b>Low grade evidence to support that IVCs are associated with increased mortality in patients undergoing bariatric surgery RR =3.63 (95% CI=1.99 to 6.61;p&lt;0.05; I<sup>2</sup>=0.0%)</b>
Birkmeyer, N. J., 2010 <sup>149</sup> †		Moderate	Direct	Precise		1.9% vs 0.5% p<0.0001
Gargiulo, N.J., 2006 <sup>135</sup>		High	Direct	Imprecise		0% vs. 1.4%
Li W., 2012 <sup>136</sup>		High	Direct	Precise		0.31% vs. 0.03%; p=0.003
Obeid, F. N., 2007 <sup>138</sup>		High	Direct	Imprecise		0.8% vs. 0.2%; P=0.37

CI = confidence interval; DVT = deep venous thrombosis; PE = pulmonary embolism; RR = relative risk ; VTE = venous thromboembolism†There were no randomized controlled trials; Reported on mortality and permanent disability.

\*\*Mortality rated as insufficient despite the absence of statistical heterogeneity (I<sup>2</sup>=0%) because of clinical heterogeneity with filters being channeled to high risk patients.

#See Figure 12- 14 for ratings on precision.

**Table 31. Body of evidence for pharmacological prophylaxis for the prevention of venous thromboembolism in patients undergoing bariatric surgery**

Author, Year	Outcomes	Risk of Bias	Directness	Precision	Consistency	Magnitude of Effect
<b><i>Enoxaparin vs. Unfractionated Heparin</i></b>						
	<b>PE</b>	<b>High</b>	<b>Direct</b>	<b>Imprecise</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of enoxaparin vs. unfractionated heparin in reducing PE in patients undergoing bariatric surgery</b>
Kothari, S. 2007 <sup>130</sup>		High	Direct	Imprecise		0% vs 0.4%; p=0.99
	<b>DVT</b>	<b>High</b>	<b>Direct</b>	<b>Unknown</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of enoxaparin vs. unfractionated heparin in reducing DVT in patients undergoing bariatric surgery</b>
Kothari, S. 2007 <sup>130</sup>		High	Direct	Unknown		0% vs 0%
	<b>Major bleeding#</b>	<b>High</b>	<b>Direct</b>	<b>Precise</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of enoxaparin vs. unfractionated heparin in reducing major bleeding in patients undergoing bariatric surgery</b>
Kothari, S. 2007 <sup>130</sup>		High	Direct	Precise		5.9% vs 1.3%; p=0.011
	<b>Mortality</b>	<b>High</b>	<b>Direct</b>	<b>Unknown</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of enoxaparin vs. unfractionated heparin in reducing mortality in patients undergoing bariatric surgery</b>
Kothari, S. 2007 <sup>130</sup>		High	Direct	Unknown		0% vs 0%
<b><i>Enoxaparin vs. Extended Duration of Enoxaparin</i></b>						
	<b>PE</b>	<b>High</b>	<b>Direct</b>	<b>Unknown</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of enoxaparin vs. extended-duration enoxaparin in reducing PE in patients undergoing bariatric surgery</b>
Raftopoulos, I., 2008 <sup>131</sup>		High	Direct	Unknown		2.3% vs 0%

**Table 31. Body of evidence for pharmacological prophylaxis for the prevention of venous thromboembolism in patients undergoing bariatric surgery (continued)**

Author, Year	Outcomes	Risk of Bias	Directness	Precision	Consistency	Magnitude of Effect
<i>Enoxaparin vs. Extended Duration of Enoxaparin (continued)</i>						
	<b>VTE</b>	<b>High</b>	<b>Direct</b>	<b>Precise</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of enoxaparin vs. extended-duration enoxaparin in reducing VTE in patients undergoing bariatric surgery</b>
Raftopoulos, I., 2008 <sup>131</sup>		High	Direct	Precise		4.6% vs 0% ;P=0.006
	<b>DVT</b>	<b>High</b>	<b>Direct</b>	<b>Unknown</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of enoxaparin vs. extended-duration enoxaparin in reducing DVT in patients undergoing bariatric surgery</b>
Raftopoulos, I., 2008 <sup>131</sup>		High	Direct	Unknown		2.3% vs 0%
	<b>Major bleeding#</b>	<b>High</b>	<b>Direct</b>	<b>Imprecise</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of enoxaparin vs. extended-duration enoxaparin in reducing major bleeding in patients undergoing bariatric surgery</b>
Raftopoulos, I., 2008 <sup>131</sup>		High	Direct	Imprecise		4.5% vs 0% ;p= 0.06
	<b>Mortality</b>	<b>High</b>	<b>Direct</b>	<b>Imprecise</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of enoxaparin vs. extended-duration enoxaparin in reducing mortality in patients undergoing bariatric</b>
Raftopoulos, I., 2008 <sup>131</sup>		High	Direct	Imprecise		0% vs 0%; p = NS

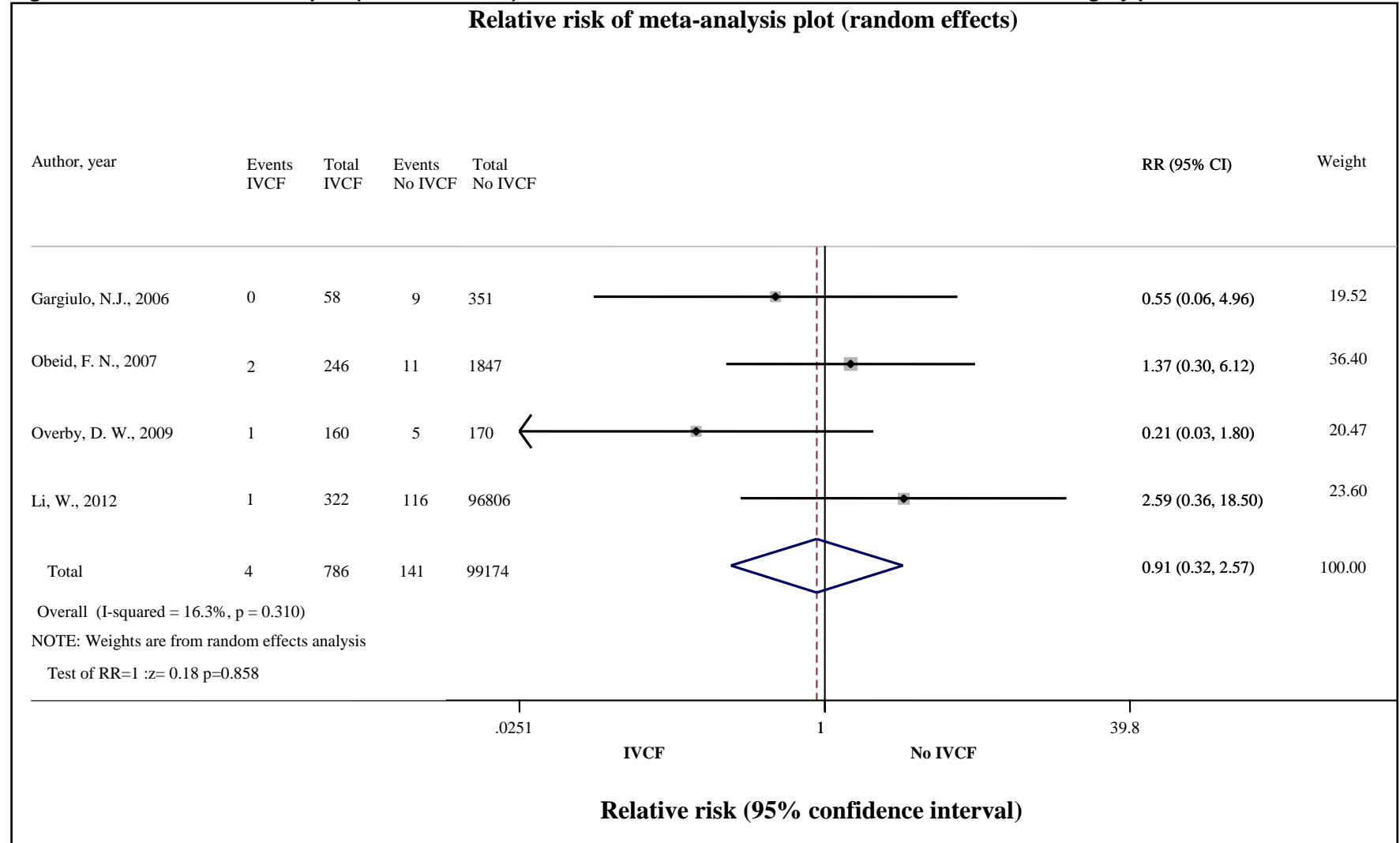
**Table 31. Body of evidence for pharmacological prophylaxis for the prevention of venous thromboembolism in patients undergoing bariatric surgery (continued)**

Author, Year	Outcomes	Risk of Bias	Directness	Precision	Consistency	Magnitude of Effect
<b><i>Enoxaparin at Standard Dosing vs. Augmented Dosing</i></b>						
	<b>PE</b>	<b>High</b>	<b>Direct</b>	<b>Unknown</b>	<b>Inconsistent</b>	<b>Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs. augmented dosing in reducing PE in patients undergoing bariatric surgery</b>
Hamad, G.G., 2005 <sup>143</sup>		High	Direct	Unknown		0.4% vs 0.6%
Scholten, D. J., 2002 <sup>145</sup>		High	Direct	Unknown		4.4% vs 0%
Singh, K., 2011 <sup>146</sup>		High	Direct	Unknown		0% vs 0%
	<b>DVT</b>	<b>High</b>	<b>Direct</b>	<b>Unknown</b>	<b>Inconsistent</b>	<b>Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs. augmented dosing in reducing DVT in patients undergoing bariatric surgery</b>
Hamad, G.G., 2005 <sup>143</sup>		High	Direct	Unknown		0% vs 0%
Scholten, D. J., 2002 <sup>145</sup>		High	Direct	Unknown		1.1% vs 0.6%
Singh, K., 2011 <sup>146</sup>		High	Direct	Unknown		0% vs 0%
	<b>VTE</b>	<b>High</b>	<b>Direct</b>	<b>Precise</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs. augmented dosing in reducing VTE in patients undergoing bariatric surgery</b>
Scholten, D. J., 2002 <sup>145</sup>		High	Direct	Precise		5.4% vs 0.6% ; p <0.01
	<b>Bleeding</b>	<b>High</b>	<b>Direct</b>	<b>Unknown</b>	<b>Consistent</b>	<b>Insufficient evidence to comment on effectiveness of enoxaparin at standard dosing vs. augmented dosing in reducing bleeding in patients undergoing bariatric surgery</b>
Hamad, G.G., 2005 <sup>143</sup>		High	Direct	Unknown		0% vs 1.7%
Singh, K., 2011 <sup>146</sup>		High	Direct	Unknown		0% vs 2.8%
Scholten, D. J., 2002 <sup>145</sup>		High	Direct	Imprecise		1.1% vs 0.26%; p=NS

DVT = deep venous thrombosis; NR = not reported; NS = not significant; PE = pulmonary embolism; VTE = venous thromboembolism

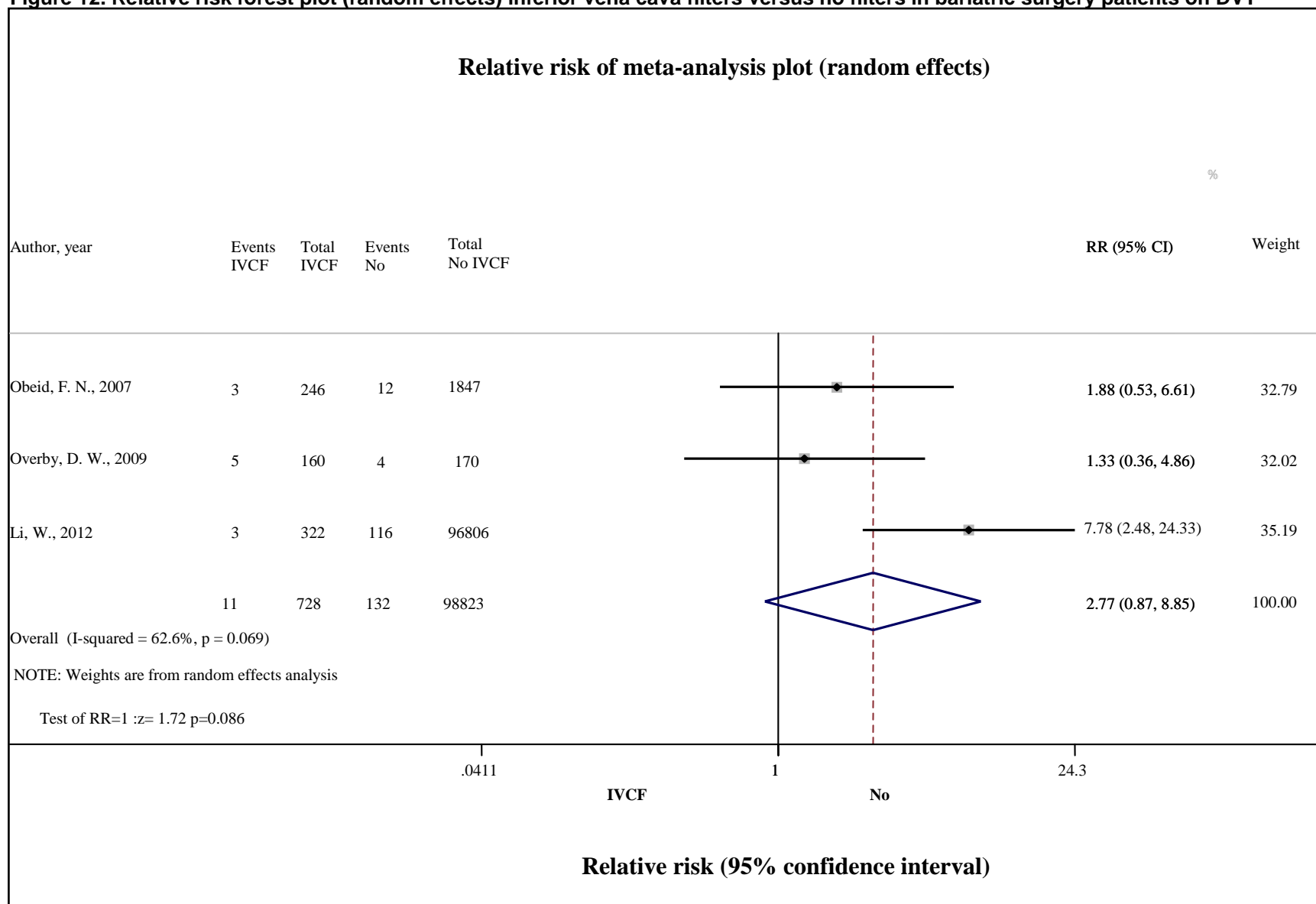
# Requiring transfusion.

**Figure 11. Relative risk forest plot (random effects) inferior vena cava filters versus no filters in bariatric surgery patients on PE**



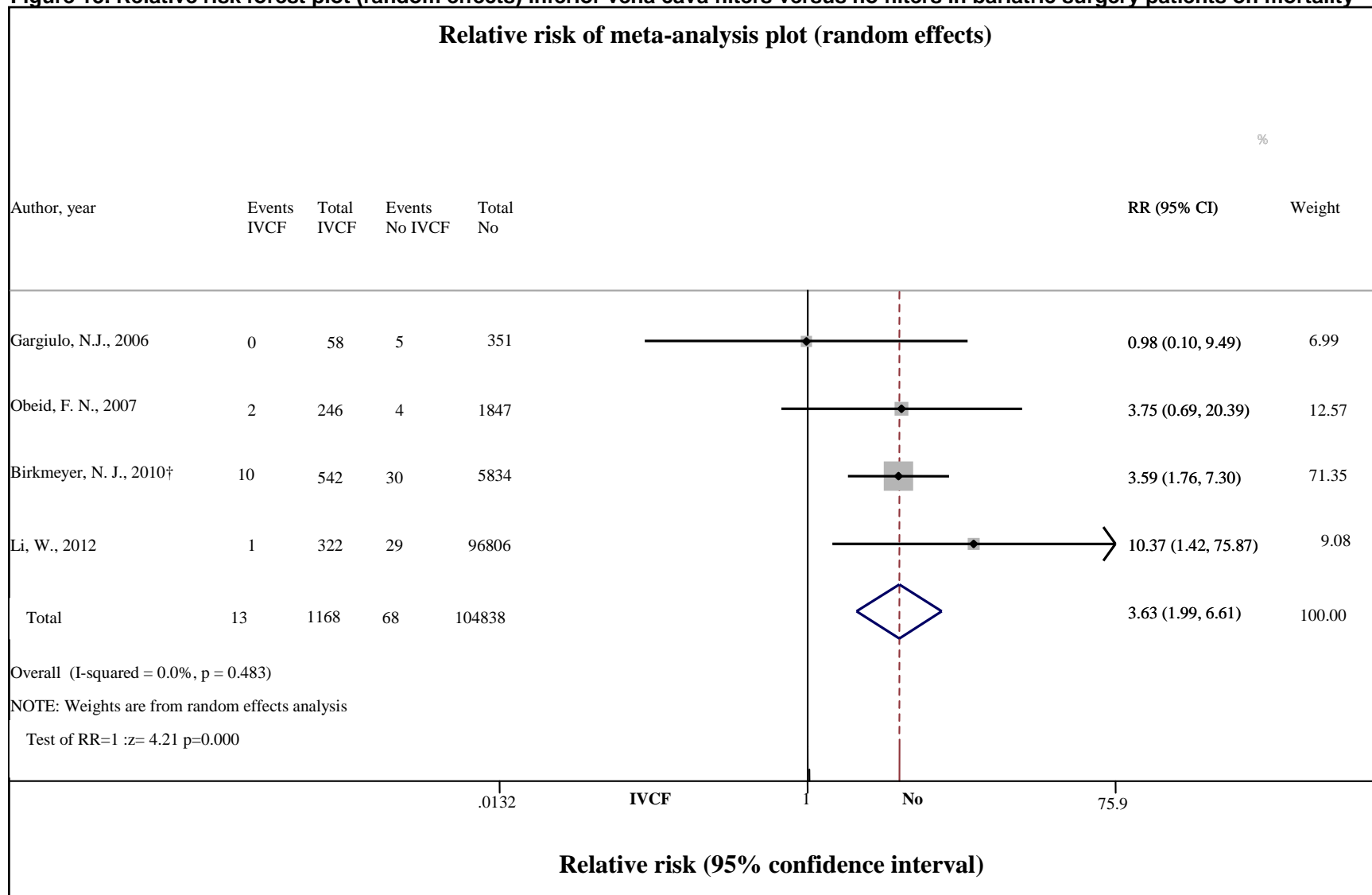
CI = confidence interval; IVCF = inferior vena cava filter; RR = relative risk

**Figure 12. Relative risk forest plot (random effects) inferior vena cava filters versus no filters in bariatric surgery patients on DVT**



CI = confidence interval; IVCF = inferior vena cava filter; RR = relative risk

**Figure 13. Relative risk forest plot (random effects) inferior vena cava filters versus no filters in bariatric surgery patients on mortality**



CI = confidence interval; IVCF = inferior vena cava filter; RR = relative risk

†Composite endpoint of mortality or permanent disability.



## Key Question 7

What are the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of venous thromboembolism during hospitalization of obese and underweight patients?

### Key Points and Evidence Grades

- The strength of evidence is insufficient to comment on the effectiveness of prophylaxis with fixed dose dalteparin over placebo in reducing VTE in hospitalized obese patients
- The strength of evidence is insufficient to comment on the effectiveness of prophylaxis with fixed dose dalteparin over placebo in reducing major bleeding and mortality in hospitalized obese patients
- The strength of evidence is insufficient to comment on whether fixed dose enoxaparin at 40 mg dose compared with various weight based dosing regimens (0.4 mg/kg or 0.5 mg/kg of enoxaparin) differ in achieving target anti-factor Xa level in obese hospitalized patients
- There were no studies that specifically evaluated underweight patients.

### Study Characteristics

Two studies reported on this Key Question. A single retrospective subgroup analysis of obese patients (BMI>30 in men, and BMI>28.6 in women) from the Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT) reported on the comparative effectiveness and safety of medications for the prevention of VTE in obese patients.<sup>150</sup> The PREVENT trial was a multicenter RCT conducted in multiple hospitals in North America and Europe that enrolled 3,706 medically ill patients and randomized them to receive either a daily dose of 5,000 U of dalteparin or placebo. The inclusion criteria were acute congestive heart failure (New York Heart Association III and IV), acute respiratory failure, infectious disease, acute rheumatic disease, or inflammatory bowel disease. In patients with infectious, rheumatic, or inflammatory bowel diseases, at least one additional VTE risk factor had to be present: chronic congestive heart failure, age of 75 years or above, obesity, varicose veins, chronic oxygen requirement, cancer, history of VTE, hormone therapy, or a myeloproliferative syndrome. The exclusion criteria included coagulopathies, advanced liver and kidney disease, as well as recent major surgery.

Freeman and colleagues sequentially assigned 31 medically ill patients with extreme obesity (defined by BMI $\geq$ 40kg/m<sup>2</sup>) to a fixed dose of enoxaparin at 40 mg daily (control group, n=11); weight based lower dose enoxaparin 0.4mg/kg (n=9); and weight based higher dose enoxaparin 0.5mg/kg (n=11). The inclusion criteria was >18 years of age, BMI $\geq$ 40kg/m<sup>2</sup> and having at least one additional major VTE risk factor (age>70 years, heart failure, respiratory failure, previous VTE, cancer, stroke, sepsis and immobility). Patients on anticoagulation, or other risk of bleeding, estimated creatinine clearance<30mL/min, or surgery or trauma within 14 days were excluded (Table 32).

## Participant Characteristics

In the PREVENT trial, of the 1,118 obese patients, 396 were men and 722 were women; 91 percent were Caucasians, and the median BMI was 32.9 kg/m<sup>2</sup>. The top three primary medical diagnoses were New York Heart Association class III or IV heart failure, acute respiratory failure, and acute infectious diseases. In the Freeman study the average BMI was 62.1kg/m<sup>2</sup> and did not differ between the 3 groups. The average age was 45.5, 43.8, and 42.7 years for fixed dose, lower dose, and higher dose respectively. The percentage of males in each group was 18.2 percent, 66.7 percent, and 27.3 percent, respectively, for fixed, lower and higher dose groups (Table 32).

## Intervention Characteristics

In the PREVENT trial, the study randomized patients to the dalteparin arm or placebo. The patients in dalteparin arm received 5,000 U subcutaneously daily or a placebo. Neither group received any additional concurrent prophylactic therapy. In the Freeman study patients were sequentially assigned to a fixed dose of enoxaparin at 40mg daily (control group, n=11); weight based lower dose enoxaparin 0.4mg/kg (n=9); and weight based higher dose enoxaparin 0.5mg/kg (n=11). All patients had anti-factor Xa level drawn upon study enrollment and then daily during their hospital stay (average 3 days) (Table 32).

## Outcomes

In the dalteparin vs placebo study the primary endpoint was a composite of symptomatic VTE, fatal PE, sudden death, and asymptomatic proximal DVT detected by compression ultrasound administered to all patients by day 21, the results of which were adjudicated by a core ultrasound laboratory blinded to group assignment. Secondary endpoints were proximal symptomatic and asymptomatic DVT, major and minor bleeding, and thrombocytopenia by day 21; as well as all-cause mortality by days 21 and 90.

In the Freeman study the primary outcome was the achievement of a peak anti-factor Xa level between 0.2-0.5IU/mL measured 4-6 hours after enoxaparin administration.

Total VTE among obese patients in the PREVENT trial, the composite primary end point, i.e., total VTE occurred in 2.8 percent of the dalteparin group (95% C.I. 1.3 to 4.3 percent), and in 4.3 percent of the placebo group (95% C.I. 2.5 to 6.2 percent), (RR, 0.64; 95% C.I. 0.32-1.28). Logistic regression analysis, modeling the probability of the primary endpoint, identified no statistical interaction between dalteparin efficacy and the presence or absence of obesity (P = 0.63). The efficacy of dalteparin in the prevention of total VTE was attenuated in obese patients with a BMI of 40 or greater. In addition to the above outcomes, the Kucher study also reported on the difference in outcomes between obese and non obese patients treated with dalteparin. There was no difference in rates of total VTE between non-obese and obese patients (2.8 vs 2.8%, p=0.5) but rates of mortality (14.3 vs 9.9%, p=0.0005) and major bleeding (1.6 vs 0%, p=0.005) were higher in non-obese patients treated with dalteparin compared with obese patients.

There were no symptomatic DVT or PE events with enoxaparin treatment in all three arms of Freeman study.

## Fatal Pulmonary Embolisms

There were no fatal PEs in the obese patients in either study.

## **Mortality**

In the PREVENT trial, among obese patients, dalteparin was associated with a statistically non-significant increase in mortality by day 21 (4.6 vs. 2.7 percent,  $P=0.14$ ) and day 90 (9.9 vs. 8.6 percent  $P=0.36$ ) compared with placebo.<sup>150</sup>

## **Major Bleeding**

Dalteparin in obese patients was not associated with an increase in major hemorrhage by day 21 (0 vs. 0.7 percent placebo;  $P>0.99$ ) compared with placebo in the PREVENT trial.<sup>150</sup> No major bleeding was reported in the Freeman study.

## **Other Adverse Events**

The PREVENT trial demonstrated that minor hemorrhage by day 21 and thrombocytopenia were not statistically significantly different between the patients with obesity randomized to dalteparin and to placebo. No adverse events are reported in the Freeman study.

## **Anti- Factor Xa levels**

In the Freeman study, the anti-factor Xa level between 0.2 and 0.5IU/mL was achieved significantly more often (86% of the time) in the higher dose group than in the lower dose group (32%) and fixed dose group (19%) ( $P<0.001$ ) and their peak anti-factor Xa level were also found to be significantly higher than the other two groups. Age, weight, BMI or creatinine clearance did not correlate with the peak anti-factor Xa level achieved and there were no adverse events reported. Additionally, 82% of patients in the fixed dose group had anti-Xa levels  $<0.2$ IU/mL while only 36% and 13% of patients in the lower dose and higher dose groups respectively had anti-factor Xa levels  $<0.2$ IU/mL ( $P<0.001$ ). This finding suggests that weight based enoxaparin dosing at 0.5mg/kg achieves target anti-Xa levels more frequently in the extremely obese, medically ill patients compared with weight based lower dose enoxaparin 0.4mg/kg or fixed dose regimens of enoxaparin 40 mg. However these findings are imprecise, and need to be replicated in other studies.

## **Risk of Bias**

We rated the Kucher study to be at moderate risk of bias since this subgroup analysis among obese patients was not prespecified. It was unclear if the comparisons reported reflected the original randomized assignments. The Freeman study was also rated to be at moderate risk of bias due to limitations in study designs, lack of adequate randomization, blinding of subjects and adjustment for confounding.

## **Strength of Evidence**

We rated the strength of evidence as insufficient for all outcomes and comparisons. We based this rating on paucity of data available, moderate risk of bias studies with imprecision and unknown consistency in outcomes reported (Table 33).

## **Applicability**

The findings of this the subgroup analysis from the PREVENT trial might be generalized to obese elderly hospitalized patients. These findings should not be generalized to patients with

coagulopathies, advanced liver and kidney disease as well as recent major surgery. The majority of participants (92%) were white limiting generalizability to other ethnic groups. Based on the finding from the Freeman study, weight based high dose enoxaparin may be expected to yield similar results in medically ill patients who are extremely obese, although the study is not adequately powered to determine clinical efficacy or safety in this patient population.

**Table 32. Study, participant, and intervention characteristics for KQ 7**

Author, Year	Study Design	Arm, n	Drug Name, Dose	Age (Years) Mean±SD	Male, n (%)	BMI Mean±SD	Weight Mean±SD	Prior History of VTE, n (%)
Freeman A, 2012 <sup>151</sup>	Prospective cohort study	Fixed-dose Enoxaparin, 11	Enoxaparin, 40 mg daily	45.5 ± 7.2	2 (18.2)	63.4 ± 11.6	175.0 ± 39.9	NR
		Lower-dose Enoxaparin, 9	Enoxaparin, 0.4 mg/kg daily	43.8 ± 15.7	6 (66.7)	60.7 ± 12.4	171.2 ± 42.8	NR
		Higher-dose Enoxaparin, 11	Enoxaparin 0.5 mg/kg daily	42.7 ± 12.3	3 (27.3)	61.3 ± 12.2	179.6 ± 30.3	NR
Kucher, N., 2005 <sup>150</sup>	Randomized Controlled Trial	Dalteparin, 558	Dalteparin	NR	NR	NR	NR	NR
		Placebo, 560	Placebo	NR	NR	NR	NR	NR

BMI = body mass index; NR = not reported; VTE = venous thromboembolism

\* Median reported.

**Table 33. Body of evidence for pharmacological prophylaxis in obese patients**

Author, Year	Outcomes	Patients (N)	Risk of Bias	Directness	Precision	Consistency	Magnitude of Effect	Strength of Evidence
<b><i>Dalteparin vs. Placebo (In Obese Patients)</i></b>								
Kucher, N., 2005 <sup>150</sup>	VTE	1118	Moderate	Direct	Imprecise	Unknown	2.8% vs 4.3%; (RR, 0.64; 95% CI 0.32-1.28)	Insufficient evidence to comment on effectiveness of dalteparin vs placebo in reducing Total VTE in obese patients
Kucher, N., 2005 <sup>150</sup>	Mortality	1118	Moderate	Direct	Imprecise	Unknown	9.9% vs 8.6%, p=0.36	Insufficient evidence to comment on effectiveness of Dalteparin vs placebo in reducing mortality in obese patients
Kucher, N., 2005 <sup>150</sup>	Major bleeding	1118	Moderate	Direct	Imprecise	Unknown	0% vs 0.7%, p>0.99	Insufficient evidence to comment on safety of Dalteparin vs placebo in reducing major bleeding in obese patients
<b><i>Enoxaparin 40 mg Daily vs. 0.4 mg/kg In Obese Patients</i></b>								
Freeman A, 2012 <sup>151</sup>	Percentage of patients achieving target anti-Factor Xa level	20	Moderate	Indirect	Imprecise	Unknown	19% vs 32%, p=NR	Insufficient evidence to comment on effectiveness of enoxaparin 40 mg daily versus 0.4 mg/kg in achieving peak anti- Factor Xa level in obese patients
<b><i>Enoxaparin 40 mg Daily vs. 0.5 mg/kg In Obese Patients</i></b>								
Freeman A, 2012 <sup>151</sup>	Percentage of patients achieving target anti-Factor Xa level	22	Moderate	Indirect	Precise	Unknown	19% vs 86%, p<0.001	Insufficient evidence to comment on effectiveness of enoxaparin 40 mg daily versus 0.5 mg/kg in achieving peak anti- Factor Xa level in obese patients
<b><i>Enoxaparin 0.4 mg/kg vs. 0.5 mg/kg In Obese Patients</i></b>								
Freeman A, 2012 <sup>151</sup>	Percentage of patients achieving target anti-Factor Xa level	20	Moderate	Indirect	Imprecise	Unknown	32% vs 86%, p=NR	Insufficient evidence to comment on effectiveness of enoxaparin 0.4 mg/kg versus 0.5 mg/kg in achieving peak anti- Factor Xa level in obese patients

VTE = venous thromboembolism

## Key Question 8

What are the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of venous thromboembolism during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis?

### Key Points and Evidence Grades

- The strength of evidence is insufficient to assess the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis. We found no studies that directly assessed our KQ.
- The strength of evidence is insufficient that UFH at 5,000 U three times daily increases the risk of major and minor bleeding events in patients with severely compromised renal function (i.e., glomerular filtration rate (GFR)  $\leq 30$  ml/min) compared with this dose in patients without severely compromised renal function.
- The strength of evidence is insufficient that enoxaparin significantly increases the risk of a major bleeding event compared with unfractionated heparin in patients with severe renal impairment (i.e., creatinine clearance  $< 30$  mL/min).

### Study Characteristics

Five studies evaluated the effectiveness and safety of pharmacologic prophylaxis for prevention of VTE in patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis or patients receiving dialysis.<sup>30,51,152-154</sup> Four studies used a randomized, controlled, parallel arm design<sup>30,51,155,156</sup> and one was a cohort design assessing separate cohorts before and after a quality improvement intervention.<sup>157</sup>

### Participant Characteristics

The reported average age of the enrolled patients ranged from 61 to 88 years. The study populations were between 17 to 100 percent male. Data regarding the race/ethnicity of study participants were not provided.

The studies used slightly different definitions of renal impairment. Two studies used a GFR or creatinine clearance of less than 30 ml/min to designate severe renal impairment and 30-60 ml/min to signify moderate renal impairment.<sup>51,157</sup> Other definitions of renal impairment were a creatinine clearance (CrCl) between 20-50 ml/min,<sup>30</sup> patients with a creatinine clearance between 30 and 50 mL/min<sup>156</sup>, and an estimated glomerular filtration rate less than 60 mL/min.<sup>155</sup>

### Intervention Characteristics

The studies included diverse regimens with virtually no overlap. Therefore, we summarize the pharmacologic regimens for each study below.

## **Randomized, Controlled Trials**

Participants in the study by Bauersachs et al. received UFH at 5,000 IU three times daily. This trial also used certoparin, which is not approved in the U.S., therefore, we limited our summary to the UFH arm.<sup>51</sup>

In a study by Mahé et al., participants with a GFR of 20 to 50 mL/min received tinzaparin at 4,500 IU once daily or enoxaparin at 4,000 IU once daily.<sup>30</sup>

The trial by Dahl and colleagues randomly assigned patients who were over 75 years of age and/or had moderate renal dysfunction (defined as creatinine clearance between 30 and 49 mL/min) to receive enoxaparin 40 mg daily and dabigatran 150 mg daily.<sup>156</sup>

Shorr and colleagues published a post hoc subgroup analysis of a multicenter trial in which orthopedic patients were randomly assigned to receive desirudin 15 mg twice daily or enoxaparin 40 mg once daily.<sup>155</sup>

## **Prospective Cohort Studies**

Elsaid, et al. assessed VTE and bleeding events associated with the use of unfractionated heparin 5,000 units either two or three times daily and enoxaparin 30 mg once or twice daily across patients stratified by renal function (creatinine clearance <30, 30-59, and  $\geq 60$  mL/min). They made assessments before and after an intervention that was designed to eliminate use of enoxaparin in patients whose creatinine clearance was less than 30 mL/min.<sup>157</sup>

## **Outcomes**

### **DVT/PE Outcomes**

#### **Randomized, Controlled Trial: Tinzaparin Versus Enoxaparin**

The trial which had a main endpoint of anti-Xa of drug did not record any VTE events in patients who received tinzaparin or enoxaparin.<sup>30</sup>

#### **Randomized, Controlled Trial: Certoparin Versus Unfractionated Heparin**

As stated, one RCT compared the effectiveness of certoparin with unfractionated heparin.<sup>51</sup> Since certoparin is not approved in the U.S., we could not use this trial to assess our KQ. However, the study stratified the results by renal function (GFR $\leq$ 30 mL/min versus GFR>30 mL/min), allowing us to assess a question related to our KQ. The rate of DVT among patients treated with unfractionated heparin in patients with GFR greater than 30 mL/min was marginally lower than those with severe renal dysfunction (10.3 vs. 11.1 percent).

#### **Randomized, Controlled Trial: Dabigatran Versus Enoxaparin**

There was no significant difference detected in the rate of major venous thromboembolic event between patients receiving dabigatran (4.3%) and enoxaparin (9%, OR: 0.48, 95% CI: 0.13-1.73, p=0.271).<sup>156</sup>

#### **Randomized, Controlled Trial: Desirudin Versus Enoxaparin**

Patients receiving desirudin experienced a significantly lower rate of major VTE compared with patients receiving enoxaparin, 4.9% vs. 7.6%, p=0.019).<sup>155</sup> This relationship was particularly pronounced for patients whose creatinine clearance was between 30-44 mL/min. In



patients with this level of renal dysfunction, 11.1% of patients taking enoxaparin vs. 3.4% of those taking desirudin experienced a major VTE (OR:3.52; 95% CI: 1.48-8.4; p=0.004).

## **Prospective Cohort Studies: Enoxaparin Versus Unfractionated Heparin**

The prospective cohort study did not report the rates of VTE.

### **Serum Anti-Xa Levels**

In one RCT, enoxaparin accumulated to a greater extent from day one to day eight in elderly patients with renal impairment than did tinzaparin.<sup>30</sup> The ratio of maximum concentration on day eight to day one was 1.22 for enoxaparin and 1.05 for tinzaparin (p=0.016). The ratio of drug concentration area under the curve from day eight to day one yielded similar inferences, 1.26 for enoxaparin and 1.12 for tinzaparin.

### **Bleeding**

In the RCT that assessed tinzaparin and enoxaparin, five bleeding events occurred in patients receiving tinzaparin versus four such events in patients receiving enoxaparin (p=0.67).<sup>30</sup> Three of these were major bleeds, two in the tinzaparin group and one in the enoxaparin group (p=0.61).

The rate of major bleeding was significantly higher among patients randomly assigned to receive enoxaparin (4.7%) versus dabigatran (0%, p=0.039).<sup>156</sup>

There was no difference detected in the rate of major bleeding between patients who received desirudin (0.8%) versus enoxaparin (0.2%).<sup>155</sup>

Patients with severe renal dysfunction who received 5,000 IU of UFH three times a day had an increased risk for all bleeds (relative risk (RR): 3.4, 95% CI: 2.0-5.9), major bleeds (RR: 7.3, 95% CI: 3.3-16), and minor bleeds (RR: 2.6 (95% CI: 1.4-4.9) compared with patients treated with UFH without severe renal dysfunction.<sup>51</sup>

In the prospective cohort study, patients receiving enoxaparin were significantly more likely to experience a major bleeding episode compared with patients receiving unfractionated heparin (13.5% vs. 4.2%, RR: 3.2, 95% CI: 1.4-7.3). This result was largely driven by the subgroup of patients with a creatinine clearance less than 30 mL/min. For this subgroup with severe renal impairment, patients receiving enoxaparin were significantly more likely to have a bleed compared with patients receiving unfractionated heparin (18.9% vs. 4.1%, RR: 4.68, 95% CI: 1.1-20.6). There was no difference in the bleeding rates for patients whose creatinine clearances were greater than 60 mL/min.<sup>157</sup>

### **Risk of Bias**

We rated the prospective cohort study to have a high risk of bias because of limitations in the study design.<sup>157</sup> We are unable to rule out differences between the groups confounding the relationship between the treatments of interest and outcomes. Additionally, we were unable to assess the level of surveillance for VTE or bleeding events. Of the four RCTs, three were assessed to be at moderate risk of bias and one at high risk of bias. The three moderate risk of bias RCTs were post hoc subgroup analyses of larger RCTs.<sup>51,155,156</sup> We could not determine if these comparisons preserved the original randomization.<sup>51,155,156</sup> The high risk of bias RCT carried out open randomization of study participants and failed to blind subjects and investigators<sup>30</sup> (Appendix E).

## **Strength of Evidence**

We rated the strength of evidence as insufficient to assess the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis. We based this rating on the risk of bias associated with published studies and unknown consistency of evidence regarding associations that were reported.

We rated the strength of evidence as insufficient that 5,000 U of unfractionated heparin three times daily increases the risk of major and minor bleeding events in patients with severely compromised renal function (i.e., GFR  $\leq$  30 ml/min) compared with this dose in patients without severely compromised renal function. We based this rating on a high risk of bias of included studies and inconsistent evidence (Table 27).

Likewise, we rated the strength of evidence as insufficient that enoxaparin significantly increases the risk of a major bleeding event compared with unfractionated heparin in patients with severe renal impairment (i.e., creatinine clearance  $<$  30 mL/min). We based this rating on a high risk of bias and inconsistent published evidence (Table 34).

## **Applicability**

The design, analytic goals, patient populations and studied regimens were very diverse among these studies. The results could generally be applied to patients with varying degrees of renal dysfunction.

**Table 34. Body of evidence for pharmacological prophylaxis of venous thromboembolism in patients with renal insufficiency**

Author, Year	Outcomes	Risk of Bias	Directness	Precision	Consistency	Strength of Evidence and Magnitude of Effect
<b><i>Tinzaparin vs. Enoxaparin</i></b>						
	VTE	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of tinzaparin vs. enoxaparin in reducing VTE in patients with renal insufficiency
Mahe, 2007 <sup>30</sup>		High	Direct	Imprecise	Unknown	0 events in 27 patients (tinzaparin) vs 0 events in 28 patients (enoxaparin)
	Bleeding	High	Direct	Imprecise	Unknown	Insufficient evidence to comment on the comparative safety of tinzaparin vs. enoxaparin on bleeding in patients with renal insufficiency
Mahe, 2007 <sup>30</sup>		High	Direct	Imprecise	Unknown	5 events/27 vs 4/28 ( p=0.67)
<b><i>Dabigatran vs. Enoxaparin</i></b>						
	VTE	Moderate	Direct	Imprecise	Unknown	Insufficient evidence to comment on effectiveness of dabigatran in reducing VTE in severe renal compromise patients vs. enoxaparin
Dahl, 2012 <sup>156</sup>		Moderate	Direct	Imprecise	Unknown	Insufficient evidence; 4.3% of patients receiving dabigatran experienced a VTE, compared with 6.4% of patients receiving enoxaparin (OR: 0.68, 95% CI: 0.31-1.48, p=0.334)
	Bleeding	Moderate	Direct	Precise	Unknown	Insufficient evidence to comment on the safety of dabigatran vs. Enoxaparin in terms of reducing major bleeding episodes in patients with renal compromise
Dahl, 2012 <sup>156</sup>		Moderate	Direct	Precise	Unknown	Insufficient evidence; no events in patients receiving dabigatran (0/96) experienced a major bleed versus 4.7% (6/128) of patients receiving enoxaparin (p=0.039)
<b><i>Desirudin vs. Enoxaparin</i></b>						
	VTE	Moderate	Direct	Precise	Unknown	Insufficient evidence to comment on effectiveness of desirudin in reducing VTE in severe renal compromise patients vs. enoxaparin
Storr, 2012 <sup>155</sup>		Moderate	Direct	Precise	Unknown	Insufficient evidence; 4.9% of patients receiving desirudin experienced a VTE, compared with 7.6% of patients receiving enoxaparin (p=0.019)
	Bleeding	Moderate	Direct	Imprecise	Unknown	Insufficient evidence to comment on the safety of desirudin vs. Enoxaparin in terms of reducing major bleeding episodes in patients with renal compromise
Storr, 2012 <sup>155</sup>		Moderate	Direct	Imprecise	Unknown	Insufficient evidence; 0.8% of patients receiving desirudin experienced a major bleed versus 0.2% of patients receiving enoxaparin (p=0.109)

**Table 34. Body of evidence for pharmacological prophylaxis of venous thromboembolism in patients with renal insufficiency (continued)**

Author, Year	Outcomes	Risk of Bias	Directness	Precision	Consistency	Strength of Evidence and Magnitude of Effect
<b><i>Unfractionated Heparin vs. Enoxaparin</i></b>						
	<b>Bleeding</b>	<b>High</b>	<b>Direct</b>	<b>Precise</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on the safety of unfractionated heparin vs. Enoxaparin in terms of reducing major bleeding episodes in patients with renal compromise</b>
Elsaid, 2012 <sup>157</sup>		High	Direct	Precise	Unknown	Insufficient evidence to comment on the safety of unfractionated heparin vs. Enoxaparin in terms of reducing major bleeding episodes in patients with renal compromise. 4.1% vs. 13.5%, RR: 0.31, 95% CI: 0.14-0.71).
<b><i>UFH in Severe Renal Compromise vs. All Other Renal Status</i></b>						
	<b>VTE</b>	<b>Moderate</b>	<b>Direct</b>	<b>Imprecise</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of UFH in reducing VTE in severe renal compromise patients vs. all other renal patients</b>
Bauersachs, 2011 <sup>51</sup>		Moderate	Direct	Imprecise	Unknown	Insufficient evidence; 2.6% of patients had a VTE event
	<b>Bleeding</b>	<b>Moderate</b>	<b>Direct</b>	<b>Imprecise</b>	<b>Unknown</b>	<b>Insufficient evidence to comment on effectiveness of UFH in increasing bleeding in severe renal compromise patients vs. all other renal patients</b>
Bauersachs, 2011 <sup>51</sup>		Moderate	Direct	Imprecise	Unknown	Insufficient evidence; 13 events in 92 patients

UFH = unfractionated heparin; VTE = venous thromboembolism

## Discussion

Our systematic review summarizes the current state of the evidence on the role of pharmacologic and mechanical prophylaxis for the prevention of VTE among these special populations. Our review demonstrates a paucity of evidence from high quality studies to inform these Key Questions for these special populations.

### Evidence

#### Key Question 1. What are the comparative effectiveness and safety of IVC filters to prevent PE in hospitalized patients with trauma?

The strength of evidence is low that prophylactic IVC filter placement when compared with no filter use is associated with a lower incidence of PE and fatal PE in hospitalized patients with trauma. We also found insufficient evidence that prophylactic IVC filter placement is associated with an increased incidence of DVT in hospitalized patients with trauma when compared with no use of filters. We found insufficient evidence to comment on mortality associated with prophylactic IVC filter placement in hospitalized patients with trauma.

We noted the different filter brands may be associated with different complications but we did not have enough comparisons among different filter subtypes to evaluate the comparative effectiveness and safety of various filter subtypes.

We found insufficient evidence from the comparative observational studies that rates of filter-associated thrombosis were higher when prophylactic filters were placed compared with not in this patient population. The evidence was insufficient about rates of other filter complications. Several uncontrolled observational studies provided information on the rare occurrences of filter complications such as strut fracture, insertion site thrombosis, arterial-venous fistulas, filter misplacement, filter tilt, filter migration and IVC thrombosis. The low rates of such complications, the significant risks of bias in the included studies, and the lack of control groups precluded any definitive assessment of the comparative safety of different filter types in patients with trauma. Our review did not evaluate the safety of IVC filters in patients when used for treatment or prevention of recurrent PE where complication rates may be different.

We identified only a single RCT addressing this KQ and it had significant methodological limitations.<sup>52</sup> This pilot trial randomized patients to usual care plus IVC filters versus usual care but was underpowered for all outcomes. Most studies in our database were assessed as having a high risk of bias except five observational studies which were assessed as having a moderate risk of bias. There was significant heterogeneity among the included studies in design and eligibility, and inconsistency in efficacy and safety outcome assessment methods. Although many of the studies reported on the VTE outcomes, most did not provide details about anatomic locations of the DVTs or PEs. Some studies did not distinguish between DVT and PE. However prophylactic IVC filters may have opposing effects on DVTs and PEs, increasing the rates of DVTs and reducing the risk of PE. There were also differences in reporting and duration of follow-up. The included studies lacked adequate details about enrolled patient characteristics, such as race and gender, and details of the extent and severity of the trauma limiting our ability to generalize findings from these studies to other ethnic groups or age categories. There has been a wide variation in the use of IVCs in trauma centers which cannot be explained by

patient characteristics.<sup>158</sup> This variation could lead to selection bias for any observational studies of IVCs.

Our current finding should be interpreted in the context of other systematic reviews on this topic. A recent review conducted a qualitative synthesis of data from 24 studies and found increasing use of retrievable filters and low rates of filter related complications.<sup>159</sup> The authors concluded that there was a lack of high quality data, and therefore the true efficacy of prophylactic IVC filters for prevention of PE in trauma patients remains unclear. They reported that data from case series suggested a reduction in PE and fatal PE in high-risk poly-trauma patients who may have contraindications to DVT prophylaxis. A review from 2006, endorsed by the American Venous Forum, found that the evidence on optional IVC filters was not sufficient to support evidence-based recommendations.<sup>160</sup> Similarly, we only found low grade evidence that IVC filter placement compared with no IVC filter placement is associated with a lower incidence of PE and fatal PE in hospitalized patients with trauma, and insufficient evidence that prophylactic IVC filters placement is associated with an increased incidence of DVT in hospitalized patients with trauma.

There are conflicting guidelines on this topic. The practice guideline from the Eastern Association for the Surgery of Trauma recommends that insertion of a prophylactic IVC filters *should be considered* in very high risk trauma patients.<sup>35</sup> These include patients who cannot receive anticoagulation because of increased bleeding risk and have severe closed head injury (GCS < 8), incomplete spinal cord injury with part or quadriplegia, complex pelvic fractures with associated long-bone fractures, or multiple long-bone fractures (Level 3 recommendation). However, this guideline is 10 years old and was based primarily on data using permanent IVCs. A recent American College of Chest Physicians (ACCP) review suggested that that placement of an IVC filter probably reduces the risk of PE over the short term, but notes that the complications are “frequent” and long term outcomes are unclear.<sup>161</sup> This group noted that removable filters may mitigate the long-term complication rate, but also noted that they are often not removed. Thus the ACCP guidelines *recommends against* IVC filters for primary VTE prevention in patients with trauma (Grade 2C).<sup>161</sup>

**Key Question 2a. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with traumatic brain injury?**

**Key Question 2b. What is the optimal timing of initiation and duration of pharmacologic prophylaxis to prevent VTE in hospitalized patients with traumatic brain injury?**

Eight studies evaluated pharmacologic and mechanical strategies in hospitalized patients with traumatic brain injury. We found low grade evidence that UFH reduced the rates of total mortality compared with no pharmacoprophylaxis in hospitalized patients with traumatic brain injury. We also found low grade evidence that enoxaparin reduced the rates of DVT when compared with no pharmacoprophylaxis in traumatic brain injury patients. The strength of evidence is insufficient to comment on the comparative effectiveness and safety of any other pharmacological and mechanical strategies on VTE outcome and bleeding.

There was insufficient evidence to support that enoxaparin is more effective than unfractionated heparin in preventing PE and lowering mortality in hospitalized patients with traumatic brain injury. We also found insufficient evidence to support that enoxaparin when compared with heparin led to fewer bleeding complications. We found insufficient evidence to support that enoxaparin is more effective than intermittent pneumatic compression in preventing DVTs. We found insufficient evidence to support that intermittent pneumatic compression devices are more effective than enoxaparin in preventing PEs.

We found only two RCTs that addressed DVT prophylaxis in patients with traumatic brain injury. The remaining studies were single-center cohort studies, the majority of which were retrospective. Although the studies in this review asked similar questions (i.e., enoxaparin vs. heparin, pharmacologic prophylaxis vs. IPCs) and had similar patient populations, due the lack of high quality studies having minimal risk of bias, we were unable to comment on the comparative effectiveness of pharmacological and mechanical prophylaxis of venous thromboembolism in hospitalized patients with traumatic brain injury.

When looking at progression of ICH, we found insufficient evidence favoring enoxaparin when compared with unfractionated heparin or no use of chemoprophylaxis. When compared with intermittent pneumatic compression, there was insufficient evidence to support that enoxaparin reduces the risk of ICH exacerbation.

Five retrospective cohort studies evaluated the timing of pharmacologic prophylaxis in patients with traumatic brain injury. We found insufficient evidence to support that early (< 72 hours) compared with late administration of enoxaparin (> 72 hours) led to differences in progressions of ICH. The lack of high quality studies precludes definitive conclusions about the timing and initiation of prophylaxis in patients with brain trauma.

Our results should be interpreted in the context of other systematic reviews and existing guidelines. We did not identify any existing systematic reviews about the role of DVT prophylaxis, and its optimal timing and initiation in patients with traumatic brain injury. The two organizations, EAST and the Traumatic Brain Foundation, that provide guidelines for the care of the patients with trauma and patients with traumatic brain injury, respectively, do not make specific recommendations about DVT prophylaxis in these patients. The Eastern Association for the Surgery of Trauma (EAST) practice guidelines address DVT prophylaxis in the general trauma patient but do not make specific recommendations about patients with brain trauma. In 2007, the Brain Foundation Guidelines for the Management of Severe Traumatic Brain Injury found no good quality data to support the use of DVT prophylaxis in TBI patients. They found level III evidence for IPC and chemoprophylaxis, while stating that “there is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of pharmacologic prophylaxis for deep vein thrombosis.” Additionally, the ACCP guidelines do not specifically address DVT prophylaxis in these patients.

### **Key Question 3. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns?**

The strength of evidence was insufficient about the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns.

The only included cohort study of IVC filter placement was at high risk of bias with significant methodological limitations. It included just 20 patients and did not have a control group. The very high mortality rate in this study (9 out of 20 participants) was likely related to

multi-organ failure. Thus, we could not draw any meaningful conclusions<sup>126</sup> on the comparative effectiveness and safety of IVC filters. We did not find any studies that evaluated the comparative effectiveness and safety of pharmacologic strategies in the prevention of VTE among patients with burns.

There are several unanswered clinical questions for patients with burns. These patients are at elevated risk of both VTE and bleeding and the optimal prophylaxis remains unknown. Although the study we reviewed reported that the burned body surface area was not associated with thrombotic complications,<sup>162</sup> this remains unclear.

Clinicians, policymakers, and other decision makers should interpret our findings in the context of existing recommendations for VTE prevention among hospitalized patients with burns. The ACCP 2012 guidelines do not provide specific recommendations for preventing VTE in patients with burns.<sup>163</sup> The 2008 ACCP guidelines recommend routine thromboprophylaxis for burn patients having additional risk factors for VTE (Grade 1A).<sup>164</sup> The guidelines also recommend either low-dose unfractionated heparin or low molecular weight heparin as soon as it is safe (Grade 1C). For patients at risk of bleeding, the guidelines recommend mechanical thromboprophylaxis with graduate compression stockings and or intermittent pneumatic compression until the bleeding risk decreases (Grade 1A).<sup>164</sup>

#### **Key Question 4. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with liver disease?**

We found no studies that directly address the comparative effectiveness and safety of pharmacologic strategies among patients with liver disease. Previous studies have estimated that 0.5 to 6.3 percent of patients with chronic liver disease experience VTE. These studies characterize chronic liver disease as a condition complicated by thrombocytopenia and by prevalent portal vein thrombosis.<sup>165</sup> The correlation between international normalized ratio values and VTE risk remains unclear.<sup>166</sup>

There are no specific recommendations for prophylaxis in patients with chronic liver disease. The specific reasons for the lack of evidence on hospitalized patients with liver disease are unclear, but may include exclusion of such high-risk patients from trials.

#### **Key Question 5. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients receiving antiplatelet therapy?**

We found no studies that directly addressed the comparative effectiveness of pharmacologic strategies among hospitalized patients receiving antiplatelet therapy. However, two large pooled analysis of randomized controlled trials of pharmacoprophylaxis of VTE reported on this KQ.<sup>127,128</sup> There was no difference in the risk of bleeding among patients on antiplatelets when dabigatran was compared with enoxaparin, or rivaroxaban was compared with enoxaparin. These drugs were used for a limited duration, and bleeding was recorded within the study time period that did not exceed 30 days. However these findings are not generalizable to patients taking high dose ASA (> 160 mg/day) or those taking other potent antiplatelets such as ticlopidine or clopidogrel, because such patients were not included.



## Key Question 6. What are the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in patients having bariatric surgery?

We found low grade evidence to support that IVC filters do not reduce the risk of PE. Other complications of filter placement occasionally occur, some of which may be fatal.<sup>147</sup> Only a subset of studies reported on filter retrieval rates. Physicians ultimately removed more than two-thirds of the retrievable filters placed. Because bariatric surgery requires close followup and medical compliance, there may be relatively high rates of filter retrieval in this patient population and a lesser likelihood of long-term filter-related complications. There was marked practice variation in filter use for VTE prophylaxis among hospitalized patients undergoing bariatric surgery, beyond what could be explained by differences in the patient populations. Additionally, the process of selecting patients for filters based on real or perceived VTE risk may bias toward a lack of filter efficacy, or the appearance of harm.<sup>149</sup>

In the absence of high quality studies, we were unable to determine the comparative effectiveness and safety, or the optimal timing and duration of prophylactic pharmacotherapy. The observational studies did not provide a clear association between the use of pre-operative initiation of pharmacologic prophylaxis and perioperative bleeding, or between post-operative initiation of pharmacologic prophylaxis and thrombosis. A study of extended prophylaxis versus inpatient prophylaxis suggested that continuing enoxaparin therapy for 10 days discharge may be associated with a lower risk of VTE, when compared with shorter therapy.<sup>129</sup> However, since this cohort study adopted longer-term treatment during its later years, there were other changes that may have impacted VTE rates favorably, such as shorter surgery durations, fewer open procedures, and shorter lengths of stay, which precludes any definitive conclusions. The rate of fatal pulmonary emboli appears to be low in patients receiving pharmacologic prophylaxis.

Pharmacokinetic data from two studies suggest that “subtherapeutic” anti-Xa levels are common when patients receive standard prophylactic doses of enoxaparin, particularly 30 mg twice daily, and that “supratherapeutic” levels are common when patients receive doses of 60 mg twice daily.<sup>132 133</sup> However, the extent to which anti-Xa levels predict bleeding in obese patients undergoing bariatric surgery is unknown. Consistent with current practice, the majority of the studies emphasized the use of IPC devices, compression stockings, and early ambulation. Additionally, the studies that focused on IVC filters generally included patients receiving concurrent pharmacologic prophylaxis. The efficacy and safety of these modalities of prophylaxis remains unclear. One study, not included in our review, reported low rates of adverse outcomes in patients undergoing bariatric surgery who did not receive either IVC filters or pharmacologic prophylaxis.<sup>167</sup> This study excluded patients with prior VTE. The study used a prophylactic strategy that included calf-length pneumatic compression devices and early ambulation, and the authors sought to maintain short operative times (averaging 106 minutes). This study, which included 957 patients, reported rates of DVT at 0.31 percent, PE at 0.10 percent, and major bleeding at 0.73 percent. Notable in this study, as well as many studies we included, is that ambulation is often possible within 24 hours of bariatric surgery. The relatively short operative times, laparoscopic approach, and early ambulation may attenuate the VTE risk of laparoscopic bariatric surgeries, despite the large body habitus of those patients undergoing bariatric surgery.

Our results suggest that there may be a higher rate of bleeding with augmented dosing regimens, with no evidence of increased efficacy. These results are generally consistent with the findings from a previous systematic review and meta-analysis conducted by Becattini et al.<sup>168</sup> In

contrast to our comparative effectiveness review, which evaluated only comparative studies of pharmacologic regimens, Becattini et al. also included uncontrolled single-arm studies of pharmacologic prophylaxis. They concluded that the incidence of symptomatic postoperative VTE appeared to be less than 1 percent with either prophylactic strategy, but that with screening, the rate was approximately 2 percent. Because definitions of major bleeding varied, the authors applied, where possible, the International Society of Thrombosis and Haemostasis definition of major bleeding in an effort to standardize the bleeding rates across studies.<sup>169</sup> Using this standardized definition, bleeding rates were approximately 1 percent for standard-dose regimens, and 1.6 percent for weight-adjusted (augmented) pharmacological prophylaxis. The authors concluded that there might be a higher rate of bleeding with augmented dosing regimens with no evidence of increased efficacy similar to our findings.

In the absence of high quality studies among patients undergoing bariatric surgery, the ACCP evidence-based clinical practice guidelines used data from trials in other populations such as patients undergoing abdominal and pelvic surgery.<sup>170</sup> These guidelines suggest that clinicians follow the manufacturer's recommendations for dosing of pharmacotherapy, but also state that it may be prudent to consult with a pharmacist regarding dosing in bariatric surgery patients and other patients who are obese who may require higher doses of unfractionated heparin or low molecular weight heparin. The guidelines do not make any recommendations regarding the use of filters in bariatric surgery patients.

### **Key Question 7. What are the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of obese and underweight patients?**

We found only one subgroup analysis of an RCT that reported on the comparative effectiveness and safety of fixed low-dose dalteparin 5000 IU/day versus placebo among hospitalized obese patients with a BMI less than 40kg/m<sup>2</sup>. However the strength of evidence was insufficient on the composite endpoint of DVT, PE and sudden death; and the outcomes of mortality and bleeding. We did not find any evidence about the role of other pharmacologic or mechanical strategies among hospitalized obese patients. There were no studies among patients who are underweight. Previous ACCP guidelines recommended a weight based administration of low molecular weight heparins among obese patients.<sup>164</sup> The FDA-approved dosing provides no specific dose adjustment for obese patients.

The other pertinent study to this Key Question, the Freeman study, although small and not powered to determine clinical efficacy or safety is a pilot study whose findings is consistent with the current ACCP guidelines that recommends the use of weight based administration of low molecular weight heparins in obese patients. The limitations of the study besides its small size include that the primary outcome measured- anti-factor Xa level, is a surrogate marker of adequate anticoagulation and by extension effective prophylaxis against VTE and not the desired clinical outcome itself. Given the median length of stay of 3 days, the outcome was only followed for a maximum of 3 days, and given prior evidence that enoxaparin may accumulate during longer treatment periods (especially in patients with renal impairment) longer periods of follow up will be warranted to give complete picture of the outcome. Finally, the study did not include medically ill but non-obese patients they are not able to exclude that similar findings could be seen in non-obese patients.

## Key Question 8. What are the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis?

Patients with compromised renal function who require pharmacologic VTE prophylaxis are very common. However, we found insufficient evidence in the published literature to guide treatment decisions. The published evidence regarding the relative safety and efficacy of several agents versus enoxaparin are limited to single studies with a moderate-to-high risk of bias. Our findings are consistent with two other recently published reviews. The ACCP guidelines make dosing recommendations for the *therapeutic* use of LMWH.<sup>171 172</sup> However, we agree with the ACCP guidelines' assessment that the data are insufficient to make direct recommendations about *prophylaxis*. Their assessment of the indirect evidence regarding bioaccumulation and increased anti-Xa levels are also consistent with ours. The ACCP guidelines suggest that decreased clearance of LMWHs has been associated with increased risk of bleeding events for patients with severe renal insufficiency. However, the cited study compares patients with and without severe renal dysfunction who received the same therapy. Therefore, it is not possible to determine the additional risk conveyed by LMWH therapy, that is, above the baseline increased risk of bleeding among patients with renal insufficiency.

The product labeling for the drugs in our review all recommend decreased dosing for VTE prophylaxis in patients with renal insufficiency. However, these recommendations are not backed by cited peer-reviewed literature. Therefore, we see a great need for future studies to assess the relative safety and efficacy of VTE prophylaxis regimens in patients with compromised renal function.

## Limitations

Our systematic review identified important weaknesses in the literature. We did not identify high quality RCTs on any of these KQs. The RCTs identified for some of these KQs were small and had methodological limitations. The majorities of observational studies included in this review were at high risk of bias and did not report on several quality items of interest. The greatest risk to their validity was confounding by indication in that the sicker patients received more intense prophylaxis than the less sick patients, with no or inadequate adjustment for differences between treatment groups. The studies were heterogeneous in definition of VTE and bleeding outcomes precluding any meaningful pooling in a meta-analysis. We also did not find data on several pharmacologic comparisons of interest or details about appropriate dosing strategies in these special populations.

Our systematic review has several limitations. Although our search strategy was comprehensive, we may have missed studies. Although we included study designs other than randomized controlled trials in our review, the identification and indexing of observational studies is far more challenging than that of randomized controlled trials. So it is possible we may have missed a few observational studies. The potential impact of this on the strength of our inference is unknown. We were unable to assess the possibility of publication bias or selective outcomes reporting and its impact on our findings. It is difficult to determine the impact of unpublished data on the findings of the systematic review. Although we evaluated a range of important outcomes, we did not evaluate some potential long term complications such as phlegmasia and functional impairment which were beyond the scope of this review.

## Future Research

Our report highlights the need for additional research on the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE among these special populations. For many of the questions, multicenter clinical trials may be prohibitively expensive or impossible. We describe here options for observational research as well as trials.

There remains a significant research gap regarding the efficacy and safety for IVC filters for PE prophylaxis in trauma patients. The American Venous Forum and the Society of Interventional Radiology Multidisciplinary Consensus Conference have placed a high priority on studies of filters in trauma.<sup>160</sup> If feasible, a large, multi-center RCT could definitively answer the question on the efficacy and safety of IVC filters in patients with trauma including patients with traumatic brain injury.<sup>160</sup> We recognize that this may be prohibitively complex and expensive; therefore, answering this question with well-designed observational research may be optimal. These observational studies could be prospective cohort studies with the exposed group defined as individuals with trauma receiving filters and with a carefully matched comparison group of individuals - having comparable injuries and comorbid conditions - who do not receive filters. Additionally, observational research could be facilitated with use of registry data, such as from the National Trauma Data Bank.<sup>33</sup> Although presently there is insufficient detail about filter placement in this registry, this could be rectified. This would then allow cohort studies to be nested within this registry. The information that would need to be captured would be filter related information including timing, indication, type of filter, as well as complications from placement. Such studies should also adequately determine the utility of surveillance for VTE prophylaxis.

Retrospective cohort studies may also be valuable for this question but there needs to be much better control for confounding by indication than was done in the studies included in this review. The major flaw of the included retrospective studies was that the authors compared the outcomes for patients receiving filters with patients not receiving filters with little attention to differences among these patients. Commonly, the patients receiving filters were at greater risk for thrombotic complications (or other adverse outcomes) than patients without filters. With careful risk adjustment through regression or the use of other methods such as propensity score matching or instrumental variable analyses, valid inferences can be drawn from retrospective studies. We identified very few studies that used propensity score methods, and even the use of multivariate regression techniques was limited.

Future studies should also attempt to determine the reasons for low filter retrieval rates. Filter related complications may be obviated by timely removal of filters; if this is not happening, there needs to be better understanding of why not and a testing of interventions to improve retrieval rates.

We found that few studies reported on post-thrombotic syndrome as an outcome for filter studies. Future studies should report on these outcomes. These studies should help inform the degree to which the recurrent DVT episodes, potentially associated with filters, result in long-term sequelae from post-thrombotic syndrome.

Additional studies among patients with traumatic brain injury are still needed to determine whether pharmacologic DVT prophylaxis should be used for these patients, and the optimal timing of administration. This very well may require trials. The level of detail about timing of dosing in observational data may be limited. Studies should also determine how to better risk stratify patients to inform decisions about pharmacologic prophylaxis. This could be addressed with observational studies describing outcomes of patients in different strata of risk.

Unquestionably, severe burns may induce pathophysiological changes that alter the pharmacokinetic parameters of drugs, such as volume of distribution and clearance.<sup>173</sup> For this systematic review, we searched for studies that measured the effect of pharmacologic strategies on anti-Xa concentration, which is a reasonable surrogate for bleeding risk, for the Key Questions addressing patients with renal insufficiency and obesity and underweight. Pharmacokinetic studies are needed in other patient populations to determine whether altered pharmacokinetics of enoxaparin may result in inadequate dosing in burn patients, and whether dose-adjustment of enoxaparin based on serum anti-Xa monitoring is warranted.<sup>174</sup> Observational studies using electronic health records should be feasible and can answer this question. Electronic health record data would provide sufficient information about the exposures to the pharmacologic and mechanical interventions, and outcomes; and should allow for controlling for confounding by indication with information about comorbid conditions, burn severity and surface area affected. Given that there are likely important institutional differences in practice patterns regarding prophylaxis of burns, the use of the institution as an instrumental variable is conceivable (assuming that the patient mix is comparable across institutions). Future studies should adequately consider the role of specific risk factors for VTE in burn patients such as body surface area, age, body mass index, concomitant injuries, mobility states and the presence of central venous lines.

Future research should include high-quality observational studies to determine the comparative effectiveness and safety of various pharmacological and mechanical strategies among patients with liver disease. Such studies should characterize the relative risks of bleeding and thrombosis across stages of liver disease, which will require clinical information such as from electronic health records.

The question of elevated risk of bleeding with dual therapy with prophylactic anticoagulation and aspirin therapy remains unanswered. Rare events such as bleeding from prophylactic doses of anticoagulation are difficult to answer in trials; this question too will require high-quality observational studies that control for confounding by indication with the use of propensity score methods or possibly instrumental variables.

Trials of IVC filters in patients undergoing bariatric surgery might not be warranted. There is established value of pharmacologic prophylaxis in this patient population, so that RCTs that do not allow pharmacological treatment might be considered to be unethical. Similarly, because the rates of events are so low in patients with pharmacological treatment, exposing individuals to filter placement in an RCT may expose them to complication risk while there is little opportunity to demonstrate improvement in PE rates over the existing low rates. Such trials should include only those patients deemed to be at highest risk for VTE complications, such as those with prior VTE. RCTs might address whether standard doses of prophylaxis that have been proven safe and effective in other types of surgery (such as 5,000 units of subcutaneous unfractionated heparin three times daily, enoxaparin 30 mg twice daily, or enoxaparin 40 mg once daily) are adequate for patients undergoing bariatric surgery. We suggest that weight-based dosing compared with fixed-dosing, rather than BMI-based dosing compared with fixed-dosing, is the more relevant scientific question.

RCTs should evaluate the comparative effectiveness and safety of LMWHs in obese patients. Such trials need to ensure that those at both extremes of weight the underweight (BMI < 18 kg/m<sup>2</sup>) and severely obese (BMI > 40 kg/m<sup>2</sup>) are adequately represented in these trials. RCTs of VTE prevention will ideally report data on subgroups of obese and overweight patients, as well as subgroups of patients defined by renal impairment status. Future trials

should seek to enroll a subpopulation of patients with renal insufficiency to add to this body of evidence. Observational analyses may be useful for this question as well. We propose that large trials that have been completed should report subgroup results, including subgroups that were not specified at the start of the trial, so that this information is available to researchers doing meta-analysis.<sup>175</sup> Whereas the results in these subgroups might be considered exploratory in the context of the parent trial, when pooled across studies, the added power may allow for stronger, yet cautious, conclusions.

Even with evidence for the above, it still may not be clear as to what is the best practice as this may depend on patients' preferences for the possible outcomes. Post-thrombotic syndrome is an unfortunate outcome that is not often addressed in studies of prophylaxis, but which may importantly affect a patient's quality of life. An individual's tolerance of risk without an intervention may exceed his tolerance of a different risk with an intervention, and this has importance for decision making. These questions are best answered with qualitative methods or possibly with quantitative methods designed for learning patients' preferences. These can then be used in decision-analytic models that may be informative to clinicians and patients.

## **Conclusion**

Our systematic review summarizes the current state of the evidence on the role of pharmacologic and mechanical prophylaxis for the prevention of VTE among these special populations. Our review demonstrates a paucity of evidence from high quality studies to inform these Key Questions for these special populations. Our systematic review identified important weaknesses in the literature. Future research using high quality observational studies that control for confounding by indication, such as provider and practice patterns, and confounding by disease severity may be needed as randomized controlled trials typically exclude or do not report on these special populations.

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## Appendix A. Acronyms and Abbreviations

AIS	Abbreviated Injury Scale
BMI	Body Mass Index
CAT	Computed Axial Tomography
CT	Computed Tomography
CTA	Computed Tomography Angiography
CUS	Compression Ultrasonography
DVT	Deep Vein Thrombosis
GCS	Glasgow Coma Scale
Hr(s)	Hour(s)
ICU	Intensive Care Unit
INR	International Normalized Ratio
IPG	Impedance Phlebography
ISS	Injury Severity Score
IVC	Inferior Vena Cava
IVCF	Inferior Vena Cava Filter
LE	Lower Extremity
LMWH	Low Molecular Weight Heparin
Mg	Milligram
NIH	National Institutes of Health
NR	Not Reported
PE	Pulmonary Embolism
P-IVCF	Prophylactic Inferior Vena Cava Filter
RCT	Randomized Controlled Trial
R-IVCF	Retrievable Inferior Vena Cava Filter
RYGB	Roux-en-Y gastric bypass
SCD	Sequential Compression Device
SCI	Spinal Cord Injury
SQ	Subcutaneous
TBI	Traumatic Brain Injury
UFH	Unfractionated Heparin
USS	Ultrasound Scan
U	Units
VCF	Vena Cava Filter
V/Q Scan	Ventilation Perfusion Scan
VTE	Venous Thromboembolism

## Appendix B. Detailed Search Strategies

July 9th, 2012

Pubmed search string=14239

((“pulmonary embolism”[mh] OR PE[tiab] OR “Pulmonary embolism”[tiab] OR thromboembolism[mh] OR thromboembolism[tiab] OR thromboembolisms[tiab] OR Thrombosis[mh] OR thrombosis[tiab] OR DVT[tiab] OR VTE[tiab] OR clot[tiab]) AND (Anticoagulants[mh] OR Anticoagulants[tiab] OR Anticoagulant[tiab] OR “thrombin inhibitors”[tiab] OR Aspirin[mh] OR aspirin[tiab] OR aspirins[tiab] OR clopidogrel[nm] OR clopidogrel[tiab] OR Plavix[tiab] OR ticlopidine[mh] OR ticlopidine[tiab] OR ticlid[tiab] OR prasugrel[nm] OR prasugrel[tiab] OR effient[tiab] OR ticagrelor[NM] OR ticagrelor[tiab] OR Brilinta[tiab] OR cilostazol[NM] OR cilostazol[tiab] OR pletal[tiab] OR warfarin[mh] OR warfarin[tiab] OR coumadin[tiab] OR coumadine[tiab] OR Dipyridamole[mh] OR dipyridamole[tiab] OR persantine[tiab] OR dicoumarol[MH] OR dicoumarol[tiab] OR dicumarol[tiab] OR Dextran sulfate[mh] OR dextran sulfate[tiab] OR “thrombin inhibitors”[tiab] OR “thrombin inhibitor”[tiab] OR heparin[mh] OR Heparin[tiab] OR Heparins[tiab] OR LMWH[tiab] OR LDUH[tiab] OR Enoxaparin[mh] OR Enoxaparin[tiab] OR Lovenox[tiab] OR Dalteparin[tiab] OR Fragmin[tiab] OR Tinzaparin[tiab] OR innohep[tiab] OR Nadroparin[tiab] OR Fondaparinux[nm] OR Fondaparinux[tiab] OR Arixtra[tiab] OR Idraparinux[nm] OR Idraparinux[tiab] OR Rivaroxaban[nm] OR Rivaroxaban[tiab] OR novastan[tiab] OR Desirudin[nm] OR Desirudin[tiab] OR Iprivask[tiab] OR “direct thrombin inhibitor”[tiab] OR Argatroban[nm] OR Argatroban[tiab] OR Acova[tiab] OR Bivalirudin[nm] OR Bivalirudin[tiab] OR Angiomax[tiab] OR Lepirudin[nm] OR Lepirudin[tiab] OR Refludan[tiab] OR Dabigatran[nm] OR Dabigatran[tiab] OR Pradaxa[tiab] OR “factor xa”[mh] OR “factor Xa”[tiab] OR vena cava filters[mh] OR filters[tiab] OR filter[tiab] OR compression stockings[mh] OR intermittent pneumatic compression devices[mh] OR compression [tiab] OR “Venous foot pump”[tiab] )) AND(prevent\*[tiab] OR prophyla\*[tiab] OR prevention and control[subheading]) NOT (animals[mh] NOT humans[mh]) NOT (editorial[pt] OR comment[pt]) NOT ((infant[mh] OR infant[tiab] OR child[mh] OR child[tiab] OR children[tiab] OR adolescent[mh] OR adolescent[tiab] OR "teen-age"[tiab] OR pediatric[tiab] OR perinatal[tiab]) NOT (adult[tiab] OR adults[tiab] OR adult[mh])) NOT ("mechanical valve"[tiab] OR “heart valve”[tiab] OR “atrial fibrillation”[mh] OR “atrial fibrillation”[tiab] OR thrombophilia[mh] OR thrombophilia[tiab] OR pregnancy[mh])

CINAHL = 2856

International pharmaceutical abstracts = 13337

TX “Pulmonary embolism” OR TX thromboembolism OR TX thromboembolisms OR TX Thrombosis OR TX DVT OR TX VTE OR TX clot  
AND

TX Anticoagulants OR TX Anticoagulant OR TX “thrombin inhibitors” OR TX “thrombin inhibitor” OR TX aspirin OR TX aspirins OR TX clopidogrel OR TX Plavix OR TX ticlopidine OR TX ticlid OR TX prasugrel OR TX effient OR TX ticagrelor OR TX Brilinta OR TX cilostazol OR TX pletal OR TX warfarin OR TX coumadin OR TX coumadine OR TX dipyridamole OR Tx persantine OR TX dicoumarol OR TX dicumarol OR TX dextran sulfate

OR TX Heparin OR TX Heparins OR TX LMWH OR TX LDUH OR TX Enoxaparin OR TX Lovenox OR TX Dalteparin OR TX Fragmin OR TX Tinzaparin OR TX innohep OR TX Nadroparin OR TX Fondaparinux OR TX Arixtra OR TX Idraparinux OR TX Rivaroxaban OR TX novastan OR TX Desirudin OR TX Iprivask OR TX “direct thrombin inhibitor” OR TX Argatroban OR TX Acova OR TX Bivalirudin OR TX Angiomax OR TX Lepirudin OR TX Refludan OR TX Dabigatran OR TX Pradaxa OR TX “factor Xa” OR TX vena cava filters OR TX filters OR TX filter OR TX compression stockings OR TX intermittent pneumatic compression devices OR TX compression OR TX “Venous foot pump”TX Anticoagulants OR TX Anticoagulant OR TX “thrombin inhibitors” OR TX “thrombin inhibitor” OR TX Heparin OR TX Heparins OR TX LMWH OR TX LDUH OR TX Enoxaparin OR TX Lovenox OR TX Dalteparin OR TX Fragmin OR TX Tinzaparin OR TX innohep OR TX Nadroparin OR TX Fondaparinux OR TX Arixtra OR TX Idraparinux OR TX Rivaroxaban OR TX novastan OR TX Desirudin OR TX Iprivask OR TX “direct thrombin inhibitor” OR TX Argatroban OR TX Acova OR TX Bivalirudin OR TX Angiomax OR TX Lepirudin OR TX Refludan OR AND TX prevent\* OR TX prophyla\*

#### EMBASE : 9473

'thromboembolism'/exp OR 'pulmonary embolism':ab,ti OR thromboembolism:ab,ti OR thromboembolisms:ab,ti OR thrombosis:ab,ti OR dvt:ab,ti OR vte:ab,ti OR clot:ab,ti AND ('thrombin inhibitor'/exp OR aspirin:ab,ti OR aspirins:ab,ti OR clopidogrel:ab,ti OR warfarin:ab,ti OR coumadin:ab,ti OR coumadine:ab,ti OROR heparins:ab,ti OR 'lmwh':ab,ti OR lduh:ab,ti OR enoxaparin:ab,ti OR lovenox:ab,ti OR dalteparin:ab,ti OR fragmin:ab,ti OR tinzaparin:ab,ti OR innohep:ab,ti OR nadroparin:ab,ti OR fondaparinux:ab,ti OR arixtra:ab,ti OR idraparin:ab,ti OR rivaroxaban:ab,ti OR novastan:ab,ti OR desirudin:ab,ti OR iprivask:ab,ti OR 'direct thrombin inhibitor':ab,ti OR argatroban:ab,ti OR acova:ab,ti OR bivalirudin:ab,ti OR angiomax:ab,ti OR lepirudin:ab,ti OR refludan:ab,ti OR dabigatran:ab,ti OR pradaxa:ab,ti OR 'factor xa':ab,ti OR 'vena cava filters':ab,ti OR 'compression stockings':ab,ti OR 'intermittent pneumatic compression devices':ab,ti OR compression:ab,ti OR 'venous foot pump':ab,ti) AND (prevent\*:ab,ti OR prophyla\*:ab,ti) NOT ('infant'/exp OR infant:ab,ti OR 'child'/exp OR child:ab,ti OR children:ab,ti OR 'adolescent'/exp OR adolescent:ab,ti OR 'teen-age':ab,ti OR pediatric:ab,ti OR perinatal:ab,ti NOT (adult:ab,ti OR adults:ab,ti) NOT ('animal'/exp OR animal:ab,ti NOT ('human'/exp OR human:ab,ti)) NOT ('mechanical valve':ab,ti OR 'heart valve':ab,ti OR 'atrial fibrillation':ab,ti OR 'elective knee replacement':ab,ti OR 'elective hip replacement':ab,ti OR thrombophilia:ab,ti OR pregnancy:ab,ti))

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- Dalteparin:ti,ab,kw OR Fragmin:ti,ab,kw OR Tinzaparin:ti,ab,kw OR innohep:ti,ab,kw OR Nadroparin:ti,ab,kw OR Fondaparinux:ti,ab,kw OR Arixtra:ti,ab,kw OR Idraparinux:ti,ab,kw OR Rivaroxaban:ti,ab,kw OR novastan:ti,ab,kw OR Desirudin:ti,ab,kw OR Iprivask:ti,ab,kw OR "direct thrombin inhibitor":ti,ab,kw OR Argatroban:ti,ab,kw
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- #34 Dalteparin:ti,ab,kw OR Fragmin:ti,ab,kw OR Tinzaparin:ti,ab,kw OR innohep:ti,ab,kw OR Nadroparin:ti,ab,kw OR Fondaparinux:ti,ab,kw OR Arixtra:ti,ab,kw OR Idraparinux:ti,ab,kw OR Rivaroxaban:ti,ab,kw OR novastan:ti,ab,kw OR Desirudin:ti,ab,kw OR Iprivask:ti,ab,kw OR "direct thrombin inhibitor":ti,ab,kw OR Argatroban:ti,ab,kw OR Acova:ti,ab,kw OR Bivalirudin:ti,ab,kw 9740 edit delete
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- #35 Dalteparin:ti,ab,kw OR Fragmin:ti,ab,kw OR Tinzaparin:ti,ab,kw OR innohep:ti,ab,kw OR Nadroparin:ti,ab,kw OR Fondaparinux:ti,ab,kw OR Arixtra:ti,ab,kw OR Idraparinux:ti,ab,kw OR Rivaroxaban:ti,ab,kw OR novastan:ti,ab,kw OR Desirudin:ti,ab,kw OR Iprivask:ti,ab,kw OR "direct thrombin inhibitor":ti,ab,kw OR Argatroban:ti,ab,kw OR Acova:ti,ab,kw OR Bivalirudin:ti,ab,kw OR Angiomax:ti,ab,kw 9743 edit delete
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- #36 Dalteparin:ti,ab,kw OR Fragmin:ti,ab,kw OR Tinzaparin:ti,ab,kw OR innohep:ti,ab,kw OR Nadroparin:ti,ab,kw OR Fondaparinux:ti,ab,kw OR Arixtra:ti,ab,kw OR Idraparinux:ti,ab,kw OR Rivaroxaban:ti,ab,kw OR novastan:ti,ab,kw OR Desirudin:ti,ab,kw 9745 edit delete

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 Argatroban:ti,ab,kw OR Acova:ti,ab,kw OR Bivalirudin:ti,ab,kw OR  
 Angiomax:ti,ab,kw OR Lepirudin:ti,ab,kw
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 LDUH:ti,ab,kw OR Enoxaparin:ti,ab,kw OR Lovenox:ti,ab,kw OR  
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 #37 innohep:ti,ab,kw OR Nadroparin:ti,ab,kw OR Fondaparinux:ti,ab,kw 9745 edit delete  
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 Rivaroxaban:ti,ab,kw OR novastan:ti,ab,kw OR Desirudin:ti,ab,kw  
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 #38 innohep:ti,ab,kw OR Nadroparin:ti,ab,kw OR Fondaparinux:ti,ab,kw 9762 edit delete  
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 Rivaroxaban:ti,ab,kw OR novastan:ti,ab,kw OR Desirudin:ti,ab,kw  
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 Angiomax:ti,ab,kw OR Lepirudin:ti,ab,kw OR Refludan:ti,ab,kw OR  
 Dabigatran:ti,ab,kw OR Pradaxa:ti,ab,kw
- Anticoagulants:ti,ab,kw OR Anticoagulant:ti,ab,kw OR "thrombin  
 inhibitors":ti,ab,kw OR "thrombin inhibitor":ti,ab,kw OR  
 heparin:ti,ab,kw OR Heparins:ti,ab,kw OR LMWH:ti,ab,kw OR  
 #40 LDUH:ti,ab,kw OR Enoxaparin:ti,ab,kw OR Lovenox:ti,ab,kw 9808 edit delete  
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 innohep:ti,ab,kw OR Nadroparin:ti,ab,kw OR Fondaparinux:ti,ab,kw  
 OR Arixtra:ti,ab,kw OR Idraparinux:ti,ab,kw OR



- Rivaroxaban:ti,ab,kw OR novastan:ti,ab,kw OR Desirudin:ti,ab,kw  
OR Iprivask:ti,ab,kw OR "direct thrombin inhibitor":ti,ab,kw OR  
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Angiomax:ti,ab,kw OR Lepirudin:ti,ab,kw OR Refludan:ti,ab,kw OR  
Dabigatran:ti,ab,kw OR Pradaxa:ti,ab,kw OR "factor xa":ti,ab,kw  
Anticoagulants:ti,ab,kw OR Anticoagulant:ti,ab,kw OR "thrombin  
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LDUH:ti,ab,kw OR Enoxaparin:ti,ab,kw OR Lovenox:ti,ab,kw OR  
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innohep:ti,ab,kw OR Nadroparin:ti,ab,kw OR Fondaparinux:ti,ab,kw  
#41 OR Arixtra:ti,ab,kw OR Idraparinux:ti,ab,kw OR 9822 edit delete  
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OR Iprivask:ti,ab,kw OR "direct thrombin inhibitor":ti,ab,kw OR  
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Angiomax:ti,ab,kw OR Lepirudin:ti,ab,kw OR Refludan:ti,ab,kw OR  
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inhibitors":ti,ab,kw OR "thrombin inhibitor":ti,ab,kw OR  
heparin:ti,ab,kw OR Heparins:ti,ab,kw OR LMWH:ti,ab,kw OR  
LDUH:ti,ab,kw OR Enoxaparin:ti,ab,kw OR Lovenox:ti,ab,kw OR  
Dalteparin:ti,ab,kw OR Fragmin:ti,ab,kw OR Tinzaparin:ti,ab,kw OR  
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Angiomax:ti,ab,kw OR Lepirudin:ti,ab,kw OR Refludan:ti,ab,kw OR  
Dabigatran:ti,ab,kw OR Pradaxa:ti,ab,kw OR "factor xa":ti,ab,kw OR  
"vena cava filters":ti,ab,kw OR filters:ti,ab,kw  
Anticoagulants:ti,ab,kw OR Anticoagulant:ti,ab,kw OR "thrombin  
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OR Arixtra:ti,ab,kw OR Idraparinux:ti,ab,kw OR  
#43 OR Arixtra:ti,ab,kw OR Idraparinux:ti,ab,kw OR 11914 edit delete  
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Dabigatran:ti,ab,kw OR Pradaxa:ti,ab,kw OR "factor xa":ti,ab,kw OR  
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- Anticoagulants:ti,ab,kw OR Anticoagulant:ti,ab,kw OR "thrombin inhibitors":ti,ab,kw OR "thrombin inhibitor":ti,ab,kw OR heparin:ti,ab,kw OR Heparins:ti,ab,kw OR LMWH:ti,ab,kw OR LDUH:ti,ab,kw OR Enoxaparin:ti,ab,kw OR Lovenox:ti,ab,kw OR Dalteparin:ti,ab,kw OR Fragmin:ti,ab,kw OR Tinzaparin:ti,ab,kw OR innohep:ti,ab,kw OR Nadroparin:ti,ab,kw OR Fondaparinux:ti,ab,kw OR Arixtra:ti,ab,kw OR Idraparinux:ti,ab,kw OR
- #44 Rivaroxaban:ti,ab,kw OR novastan:ti,ab,kw OR Desirudin:ti,ab,kw 11970 edit delete  
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- Anticoagulants:ti,ab,kw OR Anticoagulant:ti,ab,kw OR "thrombin inhibitors":ti,ab,kw OR Aspirin:ti,ab,kw OR aspirins:ti,ab,kw OR clopidogreal:ti,ab,kw OR warfarin:ti,ab,kw OR coumadin:ti,ab,kw OR coumadina:ti,ab,kw OR "thrombin inhibitor":ti,ab,kw OR heparin:ti,ab,kw OR Heparins:ti,ab,kw OR LMWH:ti,ab,kw OR LDUH:ti,ab,kw OR Enoxaparin:ti,ab,kw OR Lovenox:ti,ab,kw OR Dalteparin:ti,ab,kw OR Fragmin:ti,ab,kw OR Tinzaparin:ti,ab,kw OR innohep:ti,ab,kw OR Nadroparin:ti,ab,kw OR Fondaparinux:ti,ab,kw OR Arixtra:ti,ab,kw OR Idraparinux:ti,ab,kw OR
- #45 Rivaroxaban:ti,ab,kw OR novastan:ti,ab,kw OR Desirudin:ti,ab,kw 14236 edit delete  
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- #46 (#8 OR #45) 16191 edit delete
- #47 prevent\*:ti,ab,kw OR prophyla\*:ti,ab,kw 103114 edit delete
- #48 (#7 AND #46 AND #47) 3120 edit delete

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(TITLE-ABS-KEY("pulmonary embolism") OR TITLE-ABS-KEY(thromboembolism) OR TITLE-ABS-KEY(thromboembolisms) OR TITLE-ABS-KEY(thrombosis) OR TITLE-ABS-KEY(dvt) OR TITLE-ABS-KEY("VTE") OR TITLE-ABS-KEY(clot)) AND (TITLE-ABS-KEY(anticoagulants) OR TITLE-ABS-KEY(anticoagulant) OR TITLE-ABS-KEY("thrombin

inhibitors”) OR TITLE-ABS-KEY(“thrombin inhibitor”) OR TITLE-ABS-KEY(Aspirin) OR TITLE-ABS-KEY(clopidogrel) OR TITLE-ABS-KEY(ticlopidine) OR TITLE-ABS-KEY(prasugrel) OR TITLE-ABS-KEY(warfarin) OR TITLE-ABS-KEY(coumadin) OR TITLE-ABS-KEY(coumadine) OR TITLE-ABS-KEY(heparin) OR TITLE-ABS-KEY(heparins) OR TITLE-ABS-KEY("LMWH") OR TITLE-ABS-KEY("LDUH") OR TITLE-ABS-KEY(enoxaparin) OR TITLE-ABS-KEY(lovenox) OR TITLE-ABS-KEY(dalteparin) OR TITLE-ABS-KEY(fragmin) OR TITLE-ABS-KEY(tinzaparin) OR TITLE-ABS-KEY(innohep) OR TITLE-ABS-KEY(nadroparin) OR TITLE-ABS-KEY(fondaparinux) OR TITLE-ABS-KEY(arixtra) OR TITLE-ABS-KEY(idraparinux) OR TITLE-ABS-KEY(rivaroxaban) OR TITLE-ABS-KEY(novastan) OR TITLE-ABS-KEY(desirudin) OR TITLE-ABS-KEY(iprivask) OR TITLE-ABS-KEY(“direct thrombin inhibitor ")OR TITLE-ABS-KEY(Argatroban)OR TITLE-ABS-KEY(Acova)OR TITLE-ABS-KEY(Bivalirudin)OR TITLE-ABS-KEY(Angiomax)OR TITLE-ABS-KEY(Lepirudin)OR TITLE-ABS-KEY(Refludan)OR TITLE-ABS-KEY(Dabigatran)OR TITLE-ABS-KEY(Pradaxa)OR TITLE-ABS-KEY(“factor xa”)OR TITLE-ABS-KEY(" vena cava filters ")OR TITLE-ABS-KEY(filters)OR TITLE-ABS-KEY(filter)OR TITLE-ABS-KEY(" compression stockings ")OR TITLE-ABS-KEY(" intermittent pneumatic compression devices ") OR TITLE-ABS-KEY(compression)OR TITLE-ABS-KEY(“Venous foot pump”)) AND (TITLE-ABS-KEY(prevent\*) OR TITLE-ABS-KEY(prophyla\*))

# Appendix C. Screening and Data Abstraction Forms

## Title Review

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Rethnam U, Yesupalan RS, Sinha A.

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☐ No  
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☒ No, this article DOES NOT apply to any of the Key Questions (check all of the reasons that apply)

☐ No original data (systematic reviews, editorial, commentary)  
☐ Does not evaluate a population of interest  
☐ Drug is not available in the U.S.  
☐ Not conducted in humans  
☐ Treatment of VTE  
☐ Not relevant to key questions  
☐ Other

☐ Yes, this article may apply to one or more of the key questions

☐ Unclear - No abstract or cannot tell from abstract alone

Is the article written in a language other than English?

☐ Yes (no response needed if language is English)  
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☐ No, this article DOES NOT apply to any of the Key Questions (check all of the reasons that apply)

☒ Yes, this article may apply to one or more of the key questions

☐ Unclear - No abstract or cannot tell from abstract alone

Is the article written in a language other than English?

☐ Yes (no response needed if language is English)


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**Does this article POTENTIALLY apply to ANY of the key questions?**

☒ NO, this article DOES NOT apply to any of the Key Questions (check only one reason):

- ☐ No original data (systematic reviews, editorial, commentary)
- ☐ Not conducted in humans
- ☐ Does not evaluate a population of interest
- ☐ Treatment of VTE
- ☐ Comparator drug is not available in the U.S. and intervention arm has no data on subgroup
- ☐ Subgroup data is not available for our special populations (Trauma, antiplatelet, liver disease, obesity, underweight, renal disease)
- ☐ Case report of known complications of drugs (e.g. Bleeding, HIT)
- ☐ Not relevant to key questions
- ☐ Other

☐ Yes, this article may apply to one or more of the following key questions (CHECK ALL THAT APPLY):


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Does this article POTENTIALY apply to ANY of the key questions?

☐ NO, this article DOES NOT apply to any of the Key Questions (check only one reason):

☒ Yes, this article may apply to one or more of the following key questions (CHECK ALL THAT APPLY):

☐ KQ1a:What is the comparative effectiveness and safety of inferior vena cava filters to prevent pulmonary embolism in hospitalized patients with trauma?

☐ KQ1b:What is the comparative effectiveness and safety of pharmacological and mechanical strategies to prevent venous thromboembolism in hospitalized patients with trauma?

☐ KQ2a:What is the comparative effectiveness and safety of pharmacological and mechanical strategies to prevent venous thromboembolism in hospitalized patients with traumatic brain injury?

☐ KQ2b:What is the optimal timing of initiation and duration of pharmacological prophylaxis to prevent venous thromboembolism in hospitalized patients with traumatic brain injury?

☐ KQ3:What is the comparative effectiveness and safety of pharmacological and mechanical strategies to prevent venous thromboembolism in hospitalized patients with burns?

☐ KQ4:What is the comparative effectiveness and safety of pharmacological and mechanical strategies to prevent venous thromboembolism in hospitalized patients with liver failure with or without thrombocytopenia or

☐ KQ5:What is the comparative effectiveness and safety of pharmacological and mechanical strategies to prevent venous thromboembolism in hospitalized patients receiving antiplatelet therapy?

☐ KQ6:What is the comparative effectiveness and safety of pharmacological and mechanical strategies to prevent venous thromboembolism in patients having bariatric surgery?


☐ KQ7:What is the comparative effectiveness and safety of pharmacological prophylaxis for prevention of venous thromboembolism during hospitalization of obese and underweight patients?

☐ KQ8:What is the comparative effectiveness and safety of pharmacological prophylaxis for prevention of venous thromboembolism during hospitalization of patients with acute kidney injury, moderate renal impairment,

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1. Please select the study intervention

☐ Pharmacologic agent versus placebo/control

☐ Pharmacologic agent versus pharmacologic agent

☐ Pharmacologic agent versus mechanical agent

☐ Pharmacologic agent versus IVC filter

☐ Pharmacologic agent versus pharmacological + mechanical agents (or vice versa)

☐ Mechanical agent versus placebo/control

☐ Mechanical agent versus mechanical agent

☐ Mechanical agent versus IVC filter

☐ IVC filter versus No IVC filter

☐ Prolonged versus standard duration pharmacological prophylaxis

☐ Others (SPECIFY)


**Concurrent Standard Therapies/Interventions (therapies which given to all patients regardless of arm to which they were randomized)**

☐ Yes

☒ No

**R2 only: If you are reviewing R1 data entry, enter you initials when you have completed the audit**  

Submit Form and go to or Skip to Next



ritu.sharma  
Yoha.Chelladurai

kemi.fawole  
tokunbo

Margaret.Peterson

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Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.

Retniam U, Yesupalan RS, Sinha A.

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1. Please select the study intervention

☐ Pharmacologic agent versus placebo/control

☐ Pharmacologic agent versus pharmacologic agent

☐ Pharmacologic agent versus mechanical agent

☐ Pharmacologic agent versus IVC filter

☐ Pharmacologic agent versus pharmacological + mechanical agents (or vice versa)

☐ Mechanical agent versus placebo/control

☐ Mechanical agent versus mechanical agent

☐ Mechanical agent versus IVC filter

☐ IVC filter versus No IVC filter

☐ Prolonged versus standard duration pharmacological prophylaxis

☐ Others (SPECIFY)

Concurrent Standard Therapies/Interventions (therapies which given to all patients regardless of arm to which they were randomized)

☒ Yes

☐ Concurrent mechanical (e.g. stockings):

☐ Mobilization regimen:

☐ Concurrent medications:

☐ Other:

☐ No

ARM1 - always use for control group	Arm 2	Arm 3	Arm 4	Arm 5
<div><input type="checkbox"/> No control/all arms were active</div> <div><input type="checkbox"/> Usual care/ No Intervention</div> <div><input type="checkbox"/> Other <div></div></div>	<div><input type="checkbox"/> Name of the Arm 2 <div></div></div> <div><input type="checkbox"/> Pharmacologic</div> <div><input type="checkbox"/> Mechanical</div> <div><input type="checkbox"/> Inferior vena cava filter</div>	<div><input type="checkbox"/> Name of the Arm 3 <div></div></div> <div><input type="checkbox"/> Pharmacologic</div> <div><input type="checkbox"/> Mechanical</div> <div><input type="checkbox"/> Inferior vena cava filter</div>	<div><input type="checkbox"/> Name of the Arm 4 <div></div></div> <div><input type="checkbox"/> Pharmacologic</div> <div><input type="checkbox"/> Mechanical</div> <div><input type="checkbox"/> Inferior vena cava filter</div>	<div><input type="checkbox"/> Name of the Arm 5</div> <div><input type="checkbox"/> Pharmacologic</div> <div><input type="checkbox"/> Mechanical</div> <div><input type="checkbox"/> Inferior vena cava filter</div>

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Submit Form

 and go to  or 


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Study characteristics

5/2/2012 12:15 PM

C-7



ritu.sharma kemil.fawole Margaret.Peterson  
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**Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.**  
Rethnam U, Yesupalan RS, Sinha A.

[Submit Form](#) and go to [or Skip to Next](#)  
Please click her for [helpful points](#)

1. Should this study be included? If no, please specify reason for exclusion

☒ Yes  
☐ No
3. Does this study have a name/ NCT (clinical trial registration number) ?

☐ Yes, specify   
☐ No
4. Is this a secondary study of a large clinical trial? (If yes, please include the author and year of the study)

☐ Yes, specify   
☐ No
5. Please select a study design:

☐ RCT  
☐ Controlled trial, non-randomized  
☐ Prospective cohort  
☐ Retrospective cohort  
☐ Case control  
☐ Case report  
☐ Cross sectional  
☐ Case series  
☐ Other study design
6. Study site

☐ Single center  
☐ Multiple center
7. Study location - Check all that apply

☐ North America  
☐ South America  
☐ Europe  
☐ Asia  
☐ Africa  
☐ Australia
8. Recruitment/Enrollment (Please enter only YEAR)

☐ Start year of recruitment   
☐ End year of recruitment   
☐ Not Reported
9. Planned length of follow-up

☐ Please specify:   
☐ Not Reported
10. Did the article report the method of **surveillance for VTE?**

☐ No  
☐ Yes- specify the method and frequency
11. Funding source:

☐ Government

- ☐ Non-profit
- ☐ Industry
- ☐ Other-please specify
- ☐ Not Reported

Please specify Inclusion/Exclusion criteria for all populations (Specify the additional criteria for Trauma and Liver failure at the end of the form)

Age	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
Male	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
Female	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
Pregnancy	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
Weight	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
BMI	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
INR	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
APTT	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
Platelets	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
Liver disease or Cirrhosis	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
Length of stay -Overall	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
Length of stay - ICU	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
Creatinine clearance	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
Creatinine level	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
History of VTE	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
History of GI bleeding	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported
On antiplatelet (Aspirin)	<input type="radio"/> Inclusion <input type="text"/>	<input type="radio"/> Exclusion <input type="text"/>	<input type="radio"/> Not Reported

On anti-coagulants
<input type="radio"/> Inclusion <input type="text"/> <input type="radio"/> Exclusion <input type="text"/> <input type="radio"/> Not Reported
Type of surgery (elective knee or hip arthroplasty)
<input type="radio"/> Inclusion <input type="text"/> <input type="radio"/> Exclusion <input type="text"/> <input type="radio"/> Not Reported
Immobility
<input type="radio"/> Inclusion <input type="text"/> <input type="radio"/> Exclusion <input type="text"/> <input type="radio"/> Not Reported
1991 NIH guidelines ( <b>Only for Bariatric surgery patients</b> )
<input type="radio"/> Inclusion <input type="text"/> <input type="radio"/> Exclusion <input type="text"/> <input type="radio"/> Not Reported <a href="#">Clear Response</a>
Total body surface area burnt ( <b>Only for Burn patients</b> )
<input type="radio"/> Inclusion <input type="text"/> <input type="radio"/> Exclusion <input type="text"/> <input type="radio"/> Not Reported <a href="#">Clear Response</a>
Other please specify
<input type="radio"/> Inclusion <input type="text"/> <input type="radio"/> Exclusion <input type="text"/> <a href="#">Clear Response</a>
Other please specify
<input type="radio"/> Inclusion <input type="text"/> <input type="radio"/> Exclusion <input type="text"/> <a href="#">Clear Response</a>


Please click below for additional criteria for Trauma and Liver Failure

☐ Trauma ☐ Liver Failure

**R2 only: If you are reviewing R1 data entry, enter your initials when you have completed the audit**

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**Participant Characteristics**



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Rethnam U, Yesupalan RS, Sinha A.

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**Participant Characteristics at Baseline**

1. Total N at baseline  
☐ N   
☐ Not reported

Define Groups

**INSTRUCTIONS:**  
If information is available for the total populations at baseline, complete the first column and ONLY the first column.  
If information is only available by intervention/exposure groups, complete the Groups columns.  
If information is not available by intervention/exposure groups, select *other* and briefly describe group.  
If the Group Ns at baseline do not add up to the Total Population N at baseline, please contact the 2nd reviewer before abstracting.  
**Specify the additional criteria for Trauma and Liver failure at the end of the form**  
Be consistent in Arm designations. This should match the Arm/Group you described in the Interventions form.  
If the study is reported not only by intervention arm, but also by subgroup use the "other" option for the arm and describe.

Overall group	2. Arm 1 (always use for control) Leave blank if there is no control group <input type="text"/>	3. Arm 2 <input type="text"/>	4. Arm 3 <input type="text"/>	5. Arm 4 <input type="text"/>	6. Arm 5 <input type="text"/>
7. <input type="checkbox"/> N <input type="text"/>	8. <input type="checkbox"/> n <input type="text"/>	9. <input type="checkbox"/> n <input type="text"/>	10. <input type="checkbox"/> n <input type="text"/>	11. <input type="checkbox"/> n <input type="text"/>	12. <input type="checkbox"/> n <input type="text"/>

13. Sex  
☒ reported  

Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
14. <input type="checkbox"/> Male, n <input type="text"/> <input type="checkbox"/> Male, % <input type="text"/>	15. <input type="checkbox"/> Male, n <input type="text"/> <input type="checkbox"/> Male, % <input type="text"/>	16. <input type="checkbox"/> Male, n <input type="text"/> <input type="checkbox"/> Male, % <input type="text"/>	17. <input type="checkbox"/> Male, n <input type="text"/> <input type="checkbox"/> Male, % <input type="text"/>	18. <input type="checkbox"/> Male, n <input type="text"/> <input type="checkbox"/> Male, % <input type="text"/>	19. <input type="checkbox"/> Male, n <input type="text"/> <input type="checkbox"/> Male, % <input type="text"/>

20. If sex differs by group, please describe/ Other comments

☐ not reported

21. Age  
☒ reported  

Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
22. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	23. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	24. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	25. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	26. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	27. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> median <input type="text"/> <input type="checkbox"/> range <input type="text"/>

28. If age differs by group, please describe/Other comments

☐ not reported

29. Race/ethnicity  
☒ Reported  

	Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
White, non-Hispanic	30. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	31. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	32. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	33. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	34. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	35. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>
Black, non-Hispanic	36. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	37. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	38. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	39. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	40. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	41. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>

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Latino/Hispanic	42. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	43. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	44. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	45. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	46. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	47. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>
Asian/Pacific Islander	48. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	49. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	50. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	51. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	52. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	53. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>
American Indian/Alaska Native	54. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	55. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	56. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	57. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	58. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	59. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>
60. Other <input type="text"/>	61. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	62. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	63. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	64. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	65. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	66. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>
67. Other <input type="text"/>	68. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	69. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	70. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	71. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	72. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	73. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>
74. Other <input type="text"/>	75. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	76. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	77. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	78. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	79. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	80. <input type="checkbox"/> 2n <input type="text"/> <input type="checkbox"/> % <input type="text"/>

81. If race/ethnicity differs by group, please describe/ Other comments

☐ not reported

82. EMI

☒ reported

Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
83. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	84. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	85. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	86. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	87. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	88. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> median <input type="text"/> <input type="checkbox"/> range <input type="text"/>

89. If EMI differs by group, please describe/Other comments

☐ not reported

90. Weight

☒ reported

Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
91. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	92. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	93. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	94. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	95. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> Median <input type="text"/> <input type="checkbox"/> Range <input type="text"/>	96. <input type="checkbox"/> mean <input type="text"/> <input type="checkbox"/> median <input type="text"/> <input type="checkbox"/> range <input type="text"/>

97. If Weight differs by group, please describe/Other comments

☐ not reported

98. Prior history of VTE

☒ reported

Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
99. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	100. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	101. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	102. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	103. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>	104. <input type="checkbox"/> n <input type="text"/> <input type="checkbox"/> % <input type="text"/>

105. If prior history of VTE differs by group, please describe/ Other comments

☐ not reported

106. Please click for Trauma and Burn

☐ Trauma

☐ Burn

283. Other Comments

284. **R2 only: if you are reviewing R1 data entry, enter your initials when you have completed the audit**

Submit Form and go to ☐ or [Skip to Next](#)



## Primary DistillerSR

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Rethnam U, Yesupalan RS, Sinha A.

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or Skip to Next

Definitions:

Total VTE: includes total number of DVT and PE

Lower extremity DVT: proximal or distal is used only for deep veins of the leg. Saphenous vein is a superficial vein and will not be classified as proximal/deep. Deep veins from popliteal above (including the superficial femoral vein) are proximal. Veins below the popliteal vein are distal.

Upper limb DVT: will be classified as catheter associated or not

PE: will be classified as central and peripheral. Central venous zones include the main pulmonary artery, the left and right main pulmonary arteries, the anterior trunk, the right and left interlobar arteries, the left upper lobe trunk, the right middle lobe artery, and the right and left middle lobe, the right lower lobe, the left upper lobe, the lingula, and the left lower lobe.

If the article has reported outcomes by interventions other than the ones specified in methods section please try to capture those interventions and outcomes (For e.g. In an article comparing the rates of DVT in UFH vs control article has also provided outcomes by doses of UFH, say low dose vs high dose, try to capture those interventions and outcomes in Arm 3 and 4. This can be used in other scenarios too:

- Time of treatment, early vs late etc

- Varying doses; Enoxaparin 50 mg vs 40 mg etc

- Renal status; moderate renal failure vs severe, normal renal function vs renal impairment etc

- BMI; obese vs normal, moderate obese vs morbid obese etc

Please submit one Form per ARM

Please make a note in the comments box if there are overlapping events in the same patient (eg are any DVTs also counted as PEs)

1. How was DVT/PE confirmed? Please specify the n or percentage of participants diagnosed in the text box if available

DVT

DVT

Venography

Ultrasoundography

MRI

Plethysmography

CT scan

Autopsy

Other

PE

PE

Angiography

CT scan

MRI

V/Q Scan (Ventilation/perfusion scan or lung scintigraphy)

Echocardiography

Autopsy

Other

Study did not describe primary outcomes

Please select the Arm/Group

Select an Answer

Nfor analysis

6. Time point	Outcomes	Outcome measures	Point estimate	95% CI
Select an Answer	<div> <div>Total VTE only ( only if VTE events are unspecified, you should choose this option)</div> <div>Total DVT only ( Similarly this is for unspecified DVT)</div> <div>Total PE only ( Unspecified PE)</div> <div>Total DVT + PE only</div> <div>Lower extremity DVT</div> <div>Upper extremity DVT</div> <div>PE</div> <div>Clear Response</div> </div>	<div> <div>n patient</div> <div>% patient</div> <div>n events</div> <div>Other- please specify</div> </div>	Select an Answer	
21. Time point	Outcomes 2	Outcome 2 measures	Point estimate	95% CI
Select an Answer	<div> <div>Total VTE only ( only if VTE events are unspecified, you should choose this option)</div> <div>Total DVT only ( Similarly this is for unspecified DVT)</div> <div>Total PE only ( Unspecified PE)</div> <div>Total DVT + PE only</div> <div>Lower extremity DVT</div> <div>Upper extremity DVT</div> <div>PE</div> <div>Clear Response</div> </div>	<div> <div>n patient</div> <div>% patient</div> <div>n events</div> <div>Other- please specify</div> </div>	Select an Answer	

156. Comments

157. R2 only: If you are reviewing R1 data entry, enter you initials when you have completed the audit

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Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.

Retnam U, Yesupalan RS, Sinha A.

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**Please submit one Form per ARM**

Study did not describe secondary outcomes

☐ Check this box

Please select the Arm/Group and specify

[Select an Answer](#)

N for analysis	4. Time point <a href="#">Select an Answer</a>	Outcomes-1 <input type="radio"/> Total Mortality <input type="radio"/> Mortality due to bleeding <input type="radio"/> Fatal PE <input type="radio"/> Post-thrombotic syndrome <input type="radio"/> Length of hospital stay <input type="radio"/> Length of ICU stay -days <input type="radio"/> Filter retrieval rate <input type="radio"/> INR level <input type="radio"/> PTT level <input type="radio"/> Factor Xa level <input type="radio"/> Quality of life <input type="radio"/> Cost of therapy <a href="#">Clear Response</a>	8. Definition	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Mean <input type="checkbox"/> Median <input type="checkbox"/> Range <input type="checkbox"/> Other- please specify	Point estimate <a href="#">Select an Answer</a>	95% CI
N for analysis	14. Time point <a href="#">Select an Answer</a>	Outcomes-2 <input type="radio"/> Total Mortality <input type="radio"/> Mortality due to bleeding <input type="radio"/> Fatal PE <input type="radio"/> Post-thrombotic syndrome <input type="radio"/> Length of hospital stay <input type="radio"/> Length of ICU stay -days <input type="radio"/> Filter retrieval rate <input type="radio"/> INR level <input type="radio"/> PTT level <input type="radio"/> Factor Xa level <input type="radio"/> Quality of life <input type="radio"/> Cost of therapy <a href="#">Clear Response</a>	16. Definition	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Mean <input type="checkbox"/> Median <input type="checkbox"/> Range <input type="checkbox"/> Other- please specify	Point estimate <a href="#">Select an Answer</a>	95% CI
N for analysis	24. Time point <a href="#">Select an Answer</a>	Outcomes-3 <input type="radio"/> Total Mortality <input type="radio"/> Mortality due to bleeding <input type="radio"/> Fatal PE <input type="radio"/> Post-thrombotic syndrome <input type="radio"/> Length of hospital stay <input type="radio"/> Length of ICU stay -days <input type="radio"/> Filter retrieval rate <input type="radio"/> INR level <input type="radio"/> PTT level <input type="radio"/> Factor Xa level <input type="radio"/> Quality of life <input type="radio"/> Cost of therapy <a href="#">Clear Response</a>	26. Definition	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Mean <input type="checkbox"/> Median <input type="checkbox"/> Range <input type="checkbox"/> Other- please specify	Point estimate <a href="#">Select an Answer</a>	95% CI
N for analysis	34. Time point <a href="#">Select an Answer</a>	Outcomes-4 <input type="radio"/> Total Mortality <input type="radio"/> Mortality due to bleeding <input type="radio"/> Fatal PE <input type="radio"/> Post-thrombotic syndrome <input type="radio"/> Length of hospital stay <input type="radio"/> Length of ICU stay -days <input type="radio"/> Filter retrieval rate <input type="radio"/> INR level <input type="radio"/> PTT level <input type="radio"/> Factor Xa level <input type="radio"/> Quality of life <input type="radio"/> Cost of therapy <a href="#">Clear Response</a>	36. Definition	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Mean <input type="checkbox"/> Median <input type="checkbox"/> Range <input type="checkbox"/> Other- please specify	Point estimate <a href="#">Select an Answer</a>	95% CI
N for analysis	44. Time point <a href="#">Select an Answer</a>	Outcomes-5 <input type="radio"/> Total Mortality <input type="radio"/> Mortality due to bleeding <input type="radio"/> Fatal PE <input type="radio"/> Post-thrombotic syndrome	46. Definition	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events	Point estimate <a href="#">Select an Answer</a>	95% CI

- ☐ Length of hospital stay
- ☐ Length of ICU stay -days
- ☐ Filter retrieval rate
- ☐ INR level
- ☐ PTT level
- ☐ Factor Xa level
- ☐ Quality of life
- ☐ Cost of therapy
- [Clear Response](#)


- ☐ Mean
- ☐ Median
- ☐ Range
- ☐ Other- please specify


<b>N for analysis</b> <input type="text"/>	54. Time point <input type="text" value="Select an Answer"/>	Outcomes-6 <ul style="list-style-type: none"> <li><input type="radio"/> Total Mortality</li> <li><input type="radio"/> Mortality due to bleeding</li> <li><input type="radio"/> Fatal PE</li> <li><input type="radio"/> Post-thrombotic syndrome</li> <li><input type="radio"/> Length of hospital stay</li> <li><input type="radio"/> Length of ICU stay -days</li> <li><input type="radio"/> Filter retrieval rate</li> <li><input type="radio"/> INR level</li> <li><input type="radio"/> PTT level</li> <li><input type="radio"/> Factor Xa level</li> <li><input type="radio"/> Quality of life</li> <li><input type="radio"/> Cost of therapy</li> </ul> <a href="#">Clear Response</a>	56. Definition <input type="text"/>	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Mean <input type="checkbox"/> Median <input type="checkbox"/> Range <input type="checkbox"/> Other- please specify	Point estimate <input type="text" value="Select an Answer"/>	95% CI <input type="text"/>
<b>N for analysis</b> <input type="text"/>	64. Time point <input type="text" value="Select an Answer"/>	Outcomes-7 <ul style="list-style-type: none"> <li><input type="radio"/> Total Mortality</li> <li><input type="radio"/> Mortality due to bleeding</li> <li><input type="radio"/> Fatal PE</li> <li><input type="radio"/> Post-thrombotic syndrome</li> <li><input type="radio"/> Length of hospital stay</li> <li><input type="radio"/> Length of ICU stay -days</li> <li><input type="radio"/> Filter retrieval rate</li> <li><input type="radio"/> INR level</li> <li><input type="radio"/> PTT level</li> <li><input type="radio"/> Factor Xa level</li> <li><input type="radio"/> Quality of life</li> <li><input type="radio"/> Cost of therapy</li> </ul> <a href="#">Clear Response</a>	68. Definition <input type="text"/>	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Mean <input type="checkbox"/> Median <input type="checkbox"/> Range <input type="checkbox"/> Other- please specify	Point estimate <input type="text" value="Select an Answer"/>	95% CI <input type="text"/>
<b>N for analysis</b> <input type="text"/>	74. Time point <input type="text" value="Select an Answer"/>	Outcomes-8 <ul style="list-style-type: none"> <li><input type="radio"/> Total Mortality</li> <li><input type="radio"/> Mortality due to bleeding</li> <li><input type="radio"/> Fatal PE</li> <li><input type="radio"/> Post-thrombotic syndrome</li> <li><input type="radio"/> Length of hospital stay</li> <li><input type="radio"/> Length of ICU stay -days</li> <li><input type="radio"/> Filter retrieval rate</li> <li><input type="radio"/> INR level</li> <li><input type="radio"/> PTT level</li> <li><input type="radio"/> Factor Xa level</li> <li><input type="radio"/> Quality of life</li> <li><input type="radio"/> Cost of therapy</li> </ul> <a href="#">Clear Response</a>	76. Definition <input type="text"/>	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Mean <input type="checkbox"/> Median <input type="checkbox"/> Range <input type="checkbox"/> Other- please specify	Point estimate <input type="text" value="Select an Answer"/>	95% CI <input type="text"/>
<b>N for analysis</b> <input type="text"/>	84. Time point <input type="text" value="Select an Answer"/>	Outcomes-9 <ul style="list-style-type: none"> <li><input type="radio"/> Total Mortality</li> <li><input type="radio"/> Mortality due to bleeding</li> <li><input type="radio"/> Fatal PE</li> <li><input type="radio"/> Post-thrombotic syndrome</li> <li><input type="radio"/> Length of hospital stay</li> <li><input type="radio"/> Length of ICU stay -days</li> <li><input type="radio"/> Filter retrieval rate</li> <li><input type="radio"/> INR level</li> <li><input type="radio"/> PTT level</li> <li><input type="radio"/> Factor Xa level</li> <li><input type="radio"/> Quality of life</li> <li><input type="radio"/> Cost of therapy</li> </ul> <a href="#">Clear Response</a>	86. Definition <input type="text"/>	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Mean <input type="checkbox"/> Median <input type="checkbox"/> Range <input type="checkbox"/> Other- please specify	Point estimate <input type="text" value="Select an Answer"/>	95% CI <input type="text"/>
<b>N for analysis</b> <input type="text"/>	94. Time point <input type="text" value="Select an Answer"/>	Outcomes-10 <ul style="list-style-type: none"> <li><input type="radio"/> Total Mortality</li> <li><input type="radio"/> Mortality due to bleeding</li> <li><input type="radio"/> Fatal PE</li> <li><input type="radio"/> Post-thrombotic syndrome</li> <li><input type="radio"/> Length of hospital stay</li> <li><input type="radio"/> Length of ICU stay -days</li> <li><input type="radio"/> Filter retrieval rate</li> <li><input type="radio"/> INR level</li> <li><input type="radio"/> PTT level</li> <li><input type="radio"/> Factor Xa level</li> <li><input type="radio"/> Quality of life</li> <li><input type="radio"/> Cost of therapy</li> </ul> <a href="#">Clear Response</a>	96. Definition <input type="text"/>	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Mean <input type="checkbox"/> Median <input type="checkbox"/> Range <input type="checkbox"/> Other- please specify	Point estimate <input type="text" value="Select an Answer"/>	95% CI <input type="text"/>

103. Comments

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**Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.**  
Rethnam U, Yesupalan RS, Sinha A.

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**Please submit one Form per ARM**

**Please select the Arm/Group and enter the Arm name**

Select an Answer

N for analysis	Time point Select an Answer	Outcomes 1 <input type="radio"/> Bleeding <input type="radio"/> Heparin-induced thrombocytopenia <input type="radio"/> Allergic reaction <input type="radio"/> Mechanical device complications - please specify <input type="radio"/> Filter complications <input type="radio"/> Infections <a href="#">Clear Response</a>	Definition	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Other - Please specify
N for analysis	Time point Select an Answer	Outcomes 2 <input type="radio"/> Bleeding <input type="radio"/> Heparin-induced thrombocytopenia <input type="radio"/> Allergic reaction <input type="radio"/> Mechanical device complications - please specify <input type="radio"/> Filter complications <input type="radio"/> Infections <a href="#">Clear Response</a>	Definition	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Other - Please specify
N for analysis	Time point Select an Answer	Outcomes 3 <input type="radio"/> Bleeding <input type="radio"/> Heparin-induced thrombocytopenia <input type="radio"/> Allergic reaction <input type="radio"/> Mechanical device complications - please specify <input type="radio"/> Filter complications <input type="radio"/> Infections <a href="#">Clear Response</a>	19. Definition	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Other - Please specify
N for analysis	24. Time point Select an Answer	Outcomes 4 <input type="radio"/> Bleeding <input type="radio"/> Heparin-induced thrombocytopenia <input type="radio"/> Allergic reaction <input type="radio"/> Mechanical device complications - please specify <input type="radio"/> Filter complications <input type="radio"/> Infections <a href="#">Clear Response</a>	26. Definition	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Other - Please specify
N for analysis	31. Time point Select an Answer	Outcomes 5 <input type="radio"/> Bleeding <input type="radio"/> Heparin-induced thrombocytopenia <input type="radio"/> Allergic reaction <input type="radio"/> Mechanical device complications - please specify <input type="radio"/> Filter complications <input type="radio"/> Infections <a href="#">Clear Response</a>	33. Definition	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Other - Please specify
N for analysis	38. Time point Select an Answer	Outcomes 6 <input type="radio"/> Bleeding <input type="radio"/> Heparin-induced thrombocytopenia <input type="radio"/> Allergic reaction <input type="radio"/> Mechanical device complications - please specify <input type="radio"/> Filter complications <input type="radio"/> Infections <a href="#">Clear Response</a>	40. Definition	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Other - Please specify
N for analysis	45. Time point Select an Answer	Outcomes 7 <input type="radio"/> Bleeding <input type="radio"/> Heparin-induced thrombocytopenia <input type="radio"/> Allergic reaction <input type="radio"/> Mechanical device complications - please specify <input type="radio"/> Filter complications <input type="radio"/> Infections <a href="#">Clear Response</a>	47. Definition	Outcome measures <input type="checkbox"/> n patient <input type="checkbox"/> % patient <input type="checkbox"/> n events <input type="checkbox"/> Other - Please specify

51. Comments:

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**Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.**

Rethnam U, Yesupalan RS, Sinha A.

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**For case studies and case series please check unable to determine for questions 11,12,13,21,22, and 23**

### Checklist for measuring study quality

#### Reporting

Question	Description	Answer
1. Is the hypothesis/aim/objective of the study clearly described?		1. <input type="radio"/> Yes <input type="radio"/> No
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	<i>If the main outcomes are first mentioned in the Results section, the question should be answered 'no.'</i>	2. <input type="radio"/> Yes <input type="radio"/> No
3. Are the characteristics of the patients included in the study clearly described?	<i>In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.</i>	3. <input type="radio"/> Yes <input type="radio"/> No
4. Are the interventions of interest clearly described?	<i>Treatments and placebo (where relevant) that are to be compared should be clearly described.</i>	4. <input type="radio"/> Yes <input type="radio"/> No
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	<i>A list of principal confounders is provided.</i>	5. <input type="radio"/> Yes <input type="radio"/> Partially <input type="radio"/> No
6. Are the main findings of the study clearly described?	<i>Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).</i>	6. <input type="radio"/> Yes <input type="radio"/> No
7. Does the study provide estimates of the random variability in the data for the main outcomes?	<i>In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered 'yes.'</i>	7. <input type="radio"/> Yes <input type="radio"/> No
8. Have all important adverse events that may be a consequence of the intervention been reported?	<i>This should be answered 'yes' if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).</i>	8. <input type="radio"/> Yes <input type="radio"/> No
9. Have the characteristics of patients lost to follow-up been described?	<i>This should be answered 'yes' where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered 'no' where a study does not report the number of patients lost to follow-up.</i>	9. <input type="radio"/> Yes <input type="radio"/> No
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?		10. <input type="radio"/> Yes <input type="radio"/> No

#### External Validity



Question	Description	Answer
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	<i>The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered 'unable to determine.'</i>	11. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	<i>The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.</i>	12. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine
13. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	<i>For the question to be answered 'yes' the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered 'no' if, for example, the intervention was undertaken in a specialist center unrepresentative of the hospitals most of the source population would attend.</i>	13. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine

**Internal Validity-bias**

Question	Description	Answer
14. Was an attempt made to blind study subjects to the intervention they have received?	<i>For studies where the patients would have no way of knowing which intervention they received, this should be answered 'yes.'</i>	14. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine
15. Was an attempt made to blind those measuring the main outcomes of the intervention?		15. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine
16. If any of the results of the study were based on "data dredging", was this made clear?	<i>Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer 'yes.'</i>	16. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	<i>Where follow-up was the same for all study patients the answer should be 'yes.' If different lengths of follow-up were adjusted, for example, by survival analysis, the answer should be 'yes.' Studies where differences in follow-up are ignored should be answered 'no.'</i>	17. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine
18. Were the statistical tests used to assess the main outcomes appropriate?	<i>The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered 'yes.' If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered 'yes.'</i>	18. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine
19. Was compliance with the intervention/s reliable?	<i>Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered 'no.' For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered 'yes.'</i>	19. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine
20. Were the main outcome measures used accurate (valid and reliable)?	<i>For studies where the outcome measures are clearly described, the question should be answered 'yes.' For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered 'yes.'</i>	20. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine

**Internal Validity-confounding and selection bias**



Question	Description	Answer
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	<i>For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.</i>	21. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	<i>For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.</i>	22. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine
23. Were study subjects randomized to intervention groups?	<i>Studies which state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example alternate allocation would score no because it is predictable.</i>	23. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	<i>All non-randomized studies should be answered 'no.' If assignment was concealed from patients but not from staff, it should be answered 'no.'</i>	24. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	<i>This question should be answered 'no' for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomized studies, if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered 'no.'</i>	25. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine
26. Were losses of patients to follow-up taken into account?	<i>If the numbers of patients lost to follow-up are not reported, the question should be answered 'unable to determine.' If the proportion lost to follow-up was too small to affect the main findings, the question should be answered 'yes.'</i>	26. <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> unable to determine

**Power**

Question	Description	Answer
27. Did they report a power calculation?		27. <input type="radio"/> Yes <input type="radio"/> No

**28. Comments**

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# Appendix D. Excluded Studies

Appendix D lists studies that were excluded from this review, categorized by reason for exclusion and alphabetized.

## Case Reports

Famularo G, Gasbarrone L, Minisola G, De Simone C. Systemic bleeding in a patient with enoxaparin-induced thrombocytopenia. *Am J Emerg Med* 2009; 27(6):756.e1-2.

Fargen KM, Bhasin RR, Murad GJ. Abdominal craniectomy implantation and thromboembolism prophylaxis resulting in wound hematoma. *Neurosurgery* 2010; 67(2):495-7.

Fryburg K, Nguyen HS, Cohen-Gadol AA. Spontaneous acute subdural hematoma due to fondaparinux: Report of two cases. *Surg Neurol Int* 2011; 2:44.

Han IS, Chung EY, Hahn YJ. Spinal epidural hematoma after epidural anesthesia in a patient receiving enoxaparin -A case report-. *Korean J Anesthesiol* 2010; 59(2):119-22.

LaBan MM, Whitmore CE, Taylor RS. Bilateral adrenal hemorrhage after anticoagulation prophylaxis for bilateral knee arthroplasty. *Am J Phys Med Rehabil* 2003; 82(5):418-20.

McLaughlin JA, Paulson MM, Rosenthal RE. Delayed onset of anterior tibial compartment

syndrome in a patient receiving low-molecular-weight heparin. A case report. *J Bone Joint Surg Am* 1998; 80(12):1789-90.

Plath J, Schulze R, Barz D et al. Necrotizing skin lesions induced by low-molecular-weight heparin after total knee arthroplasty. *Arch Orthop Trauma Surg* 1997; 116(6-7):443-5.

Rowland CH, Woodford PA, De Lisle-Hammond J, Nair B. Heparin-induced thrombocytopenia-thrombosis syndrome and bilateral adrenal haemorrhage after prophylactic heparin use. *Aust N Z J Med* 1999; 29(5):741-2.

Salem M, Elrefai S, Shrit MA, Warkentin TE. Fondaparinux thromboprophylaxis-associated heparin-induced thrombocytopenia syndrome complicated by arterial thrombotic stroke. *Thromb Haemost* 2010; 104(5):1071-2.

Tsapatsaris NP. Low-dose heparin. A cause of hematoma of rectus abdominis. *Arch Intern Med* 1991; 151(3):597-9.

Wessler S, Avioli LV. Anticoagulants in treatment of patients with hip fracture. *JAMA* 1968; 204(2):140-4.

## Data Not Abstractable

A Prospective Comparison of Warfarin to Aspirin for Thromboprophylaxis in Total Hip and Total Knee Arthroplasty. *J Arthroplasty* 2011.

Abernethy EA, Hartsuck JM. Postoperative pulmonary embolism. A prospective study utilizing low dose heparin. *Am J Surg* 1974; 128(6):739-42.

AbuRahma AF, Robinson PA, Boland JP et al. Therapeutic and prophylactic vena caval interruption for pulmonary embolism: caval and venous insertion site patency. *Ann Vasc Surg* 1993; 7(6):561-8.

Agno W. Rivaroxaban for the prevention of venous thromboembolism following major orthopedic surgery: the RECORD trials. *Expert Rev Cardiovasc Ther* 2009; 7(6):569-76.

Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. *Br J Surg* 2005; 92(10):1212-20.

- Agnelli G, Cosmi B, Di Filippo P et al. A randomised, double-blind, placebo-controlled trial of dermatan sulphate for prevention of deep vein thrombosis in hip fracture. *Thromb Haemost* 1992; 67(2):203-8.
- Agnelli G, Haas S, Ginsberg JS, Krueger KA, Dmitrienko A, Brandt JT. A phase II study of the oral factor Xa inhibitor LY517717 for the prevention of venous thromboembolism after hip or knee replacement. *J Thromb Haemost* 2007; 5(4):746-53.
- Ahmad I, Yeddula K, Wicky S, Kalva SP. Clinical sequelae of thrombus in an inferior vena cava filter. *Cardiovasc Intervent Radiol* 2010; 33(2):285-9.
- Akanmu AS, Nnodu OE, Giwa SO et al. Efficacy and safety of enoxaparin, a low molecular weight heparin in the prevention of deep vein thrombosis in Nigerian patients after orthopaedic surgery. *Afr J Med Med Sci* 2004; 33(4):335-40.
- Alexander JJ, Yuh JP, Piotrowski JJ. Is the increasing use of prophylactic percutaneous IVC filters justified? *Am J Surg* 1994; 168(2):102-6.
- Alfaro MJ, Paramo JA, Rocha E. Prophylaxis of thromboembolic disease and platelet-related changes following total hip replacement: a comparative study of aspirin and heparin-dihydroergotamine. *Thromb Haemost* 1986; 56(1):53-6.
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## Treatment

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## Appendix E. Evidence Tables

**Table 1. Risk of Bias**

Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q8	Q10	Q14	Q15	Q20	Q23	Q24	Q25	Q26	Risk of Bias
<b>KQ1</b>																
Rajasekhar A, 2011 <sup>1</sup>	Yes	Yes	Yes	Yes	No	No	No	No	No	U/D	N/A	Yes	U/D	N/A	N/A	High
O'Keffe, T., 2011 <sup>2</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	U/D	N/A	N/A	Yes	U/D	High
Roberts, A., 2010 <sup>3</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	No	High
Rosenthal D., 2009 <sup>4</sup>	N/A	Yes	No	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	U/D	High
Doody O, 2009 <sup>5</sup>	N/A	Yes	No	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	No	High
Gorman PH, 2009 <sup>6</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	Yes	Yes	Moderate
Cherry RA, 2008 <sup>7</sup>	N/A	Yes	Yes	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	No	High
Zakhary EM, 2008 <sup>8</sup>	N/A	Yes	Yes	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Hermesen JL, 2008 <sup>9</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	Yes	Yes	Moderate
Mahier A, 2008 <sup>10</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	U/D	High
Rosenthal D., 2007 <sup>11</sup>	N/A	Yes	No	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Keller IS., 2007 <sup>12</sup>	N/A	No	No	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	Yes	High
Karmy-Jones R, 2007 <sup>13</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	Yes	Yes	Moderate
Stefanidis D, 2006 <sup>14</sup>	N/A	Yes	No	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	No	High
Gonzalez RP, 2006 <sup>15</sup>	N/A	Yes	No	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	No	High
Binkert CA, 2006 <sup>16</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	Yes	High
Rosenthal, D., 2006 <sup>17</sup>	N/A	Yes	No	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	Yes	High

Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q8	Q10	Q14	Q15	Q20	Q23	Q24	Q25	Q26	Risk of bias
<b>KQ1</b>																
Rosenthal, D., 2005 <sup>18</sup>	N/A	Yes	No	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	U/D	High
Rosenthal D, 2004 <sup>19</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	Yes	Yes	Moderate
Hoff WS, 2004 <sup>20</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	U/D	High
Kurtoglu M, 2003 <sup>21</sup>	N/A	Yes	No	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	Yes	Yes	High
Offner, P.J., 2003 <sup>22</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	U/D	High
Duperier T, 2003 <sup>23</sup>	N/A	Yes	No	Yes	No	N/A	N/A	N/A	N/A	N/A	U/D	N/A	N/A	No	U/D	High
Carlin AM, 2002 <sup>24</sup>	N/A	No	Yes	No	Partially	N/A	N/A	N/A	N/A	N/A	U/D	N/A	N/A	U/D	No	High
Conners MS, 2002 <sup>25</sup>	N/A	Yes	Yes	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	U/D	High
Sekharan, J., 2001 <sup>26</sup>	N/A	Yes	Yes	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	U/D	High
Wojcik R, 2000 <sup>27</sup>	N/A	Yes	Yes	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Tola JC, 1999 <sup>28</sup>	N/A	Yes	No	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	No	High
Langan EM, 1999 <sup>29</sup>	N/A	Yes	No	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	No	High
McMurtry AL, 1999 <sup>30</sup>	N/A	Yes	Yes	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Rogers, F.B., 1997 <sup>31</sup>	N/A	Yes	No	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	No	High
Nunn, C.R., 1997 <sup>32</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Rogers FB, 1997 <sup>33</sup>	N/A	Yes	No	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	Yes	High
Gosin JS, 1997 <sup>34</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	No	High
Patton, J.H. Jr, 1996 <sup>35</sup>	N/A	Yes	No	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Rodriguez, J.L., 1996 <sup>36</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High

Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q8	Q10	Q14	Q15	Q20	Q23	Q24	Q25	Q26	Risk of bias
<b>KQ1</b>																
Rogers FB, 1995 <sup>37</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	No	High
Zolfaghari D, 1995 <sup>38</sup>	N/A	Yes	Yes	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Millward, S.F., 1994 <sup>39</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Wilson JT, 1994 <sup>40</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Leach TA, 1994 <sup>41</sup>	N/A	Yes	No	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	U/D	High
Meier, C., 2006 <sup>42</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Smoot RL, 2010 <sup>43</sup>	N/A	Yes	Yes	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	No	High
Sing RF, 2001 <sup>44</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	No	High
Greenfield LJ, 2000 <sup>45</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	Yes	Yes	Moderate
Khansarinia, S, 1995 <sup>46</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	No	High
Rogers, F.B., 1993 <sup>47</sup>	N/A	Yes	No	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
<b>KQ2a</b>																
Scudday, T., 2010, <sup>48</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Salottolo, K., 2010, <sup>49</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Dudley, R.R., 2010, <sup>50</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	Yes	Yes	Moderate
Gersin, K., 1992, <sup>51</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Kurtoglu, M., 2004, <sup>52</sup>	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	U/D	High
Minshall, C.T., 2011, <sup>53</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	No	High
Sadeh, Y., 2012 <sup>54</sup>	Yes	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	High

Phelan, H.A., 2012 <sup>55</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
<b>KQ2b</b>																
Koehler D.M., 2011, <sup>56</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	Yes	High
Salotto K., 2011, <sup>49</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Kim J., 2002, <sup>57</sup>	N/A	Yes	Yes	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	U/D	High
Reiff D.A., 2009, <sup>58</sup>	N/A	Yes	Yes	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	U/D	High
Depew A.J., 2008, <sup>59</sup>	N/A	No	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	No	High
<b>KQ5</b>																
Eriksson,B.I., 2012 <sup>60</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U/D	Yes	Low
Friedman,R.J., 2012 <sup>61</sup>	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	U/D	Yes	Low
<b>KQ6</b>																
Singh, K., 2011 <sup>62</sup>	N/A	Yes	Yes	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Vaziri, K., 2010 <sup>63</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	No	High
Overby, D. W., 2009 <sup>64</sup>	N/A	Yes	No	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	Yes	High
Raftopoulos, I., 2008 <sup>65</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	Yes	High
Simone, E. 2008 <sup>66</sup>	N/A	Yes	Yes	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Ojo, P., 2008 <sup>67</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	No	High
Borkgren-Okonek, M. 2008 <sup>68</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	U/D	High
Rowan, B. O. 2008 <sup>69</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	Yes	U/D	High
Kardys, C. M. 2008 <sup>70</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	Yes	High
Obeid, F. N., 2007 <sup>71</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	U/D	High
Schuster, R., <sup>72</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	Yes	Yes	High

Piano, G., Ketteler, 2007 <sup>73</sup>	N/A	Yes	Yes	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	Yes	High
Gargiulo, N.J., 2006 <sup>74</sup>	N/A	Yes	No	Yes	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	U/D	Yes	High
Hamad, G.G., 2005 <sup>75</sup>	N/A	Yes	Yes	Yes	Partially	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	Yes	U/D	High
Scholten, D. J., 2002 <sup>76</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No	No	High
Kothari, S. 2007 <sup>77</sup>	N/A	No	Yes	Yes	Partially	N/A	N/A	N/A	N/A	N/A	U/D	N/A	N/A	U/D	No	High
Van Ha, T. G., 2011 <sup>78</sup>	N/A	Yes	No	Yes	No	Yes	Yes	No	No	No	Yes	No	No	U/D	Yes	High
Li, W., 2012 <sup>79</sup>	N/A	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	N/A	High
Birkmeyer, N. J., 2013 <sup>80</sup>	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	Yes	N/A	Yes	U/D	High
<b>KQ7</b>																
Kucher, N., 2005 <sup>81</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U/D	Yes	Yes	Moderate
Freeman A, 2012 <sup>82</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	No	Yes	Moderate
<b>KQ8</b>																
Bauersachs, 2011 <sup>83</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Mahe, 2007 <sup>84</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	N/A	Yes	No	N/A	N/A	High
Dahl, 2012 <sup>85</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U/D	Yes	Yes	Moderate
Storr, 2012 <sup>86</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	U/D	No	Yes	Moderate
Elsaid, 2012 <sup>87</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	U/D	Yes	High

N/A= Not applicable, U/D = Unable to determine,

Q1- Hypothesis/aim/objective of the study clearly described; Q2- Main outcomes to be measured clearly described in the Introduction or Methods section; Q3- Characteristics of the patients included in the study clearly described; Q4- interventions of interest clearly described; Q5- principal confounders in each group of subjects to be compared clearly described; Q6- main findings of the study clearly described; Q8-all important adverse events that may be a consequence of the intervention been reported; Q10- Actual probability values been reported; Q14- attempt made to blind study subjects to the intervention; Q15- attempt made to blind those measuring the main outcomes of the intervention; Q20- main outcome measures used accurate; Q23- study subjects randomized to intervention groups; Q24- randomized intervention assignment concealed from both patients and health care staff; Q25- adequate adjustment for confounding in the analyses from which the main findings were drawn; Q26- losses of patients to follow-up taken into account

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**Evidence Table 2. Study characteristics for KQ1**

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
<b>IVCF versus IVCF</b>								
Karmy-Jones R, 2007 <sup>17</sup>	Cohort-retro	Multiple center- N. America	2005-2005	NR	6 of the 21 centers had formal protocols to screen for DVT with lower extremity duplex ultrasound in high risk patients	NR	R-IVCF or P-IVCF	NR
Keller IS., 2007 <sup>18</sup>	Cohort-retro	Single center- Europe	1996-2005	NR	All patients with optional IVC filters used as permanent filters were followed-up once between Dec 2005 & June 2006 by means of clinical examination, venous duplex US from the popliteal vein to the IVC, and plain radiography of abdomen	NR	Filter	NR
O'Keffe, T., 2011 <sup>30</sup>	Cohort-retro	Single center- N. America	2006-2006	NR	No	NR	Age: 13<x<89 BMI Type of trauma: TBI or spinal cord injury, complex pelvic fractures with associated long bone fracture, multiple long bone fractures ICU Filter Contraindication to heparin anticipated to exceed 72 hours	NR
Rosenthal D., 2007 <sup>43</sup>	Cohort-retro	Single center- N. America	2003-2006	NR	Venous color flow duplex	NR	Male Female Multiple trauma patients with relative or	NR

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
							absolute contraindications to low dose heparin therapy or barriers to prevent sequential compression devices ICU Filter	
Rosenthal D., 2009 <sup>42</sup>	Cohort-retro	Single center- N. America	2004-2008	NR	No	NR	Filter: Retrievable Gunther Tulip or Celect IVC catheter	NR
Smoot RL, 2010 <sup>52</sup>	Cohort-retro	Single center- N. America	2001-2005	NR	During the study years, no specific venous thromboembolism (VTE) surveillance protocols were in effect at our institution. Specifically, duplex ultrasound evaluation of extremities was not used for screening of patients but was only obtained when there was clinical suspicion for the presence of a DVT.	NR	Filter	NR
<b>IVCF Versus Control</b>								
Gorman PH, 2009 <sup>11</sup>	Cohort-retro	Single center- N. America	2002-2003	NR	No	NR	Length of stay at facility > 7 days Acute spinal cord injury between C3 and L3	NR
Gosin JS, 1997 <sup>12</sup>	Cohort-pros	Single center- N. America	1994-1996	NR	PE documented by ventilation perfusion, Angiogram or autopsy	NR	Age: 17 ≤ Length of stay-ICU: ≥48 hours Must meet one or more of the high-risk injury criteria: severe closed head injuries (abbreviated injury score of 4 or 5), complex pelvic fractures (disruption of the pelvic ring), spinal cord injuries,	NR

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
							or lower-extremity injuries concomitant with significant injury to another body system *injury severity score >15 ICU	
Khansarinia S, 1995 <sup>19</sup>	Prospective cohort with historical controls	Single center- N. America	1992-1994	All Patients Monitored Until Discharge And If Readmitted To Hospital For Any Reason	Evaluation by B-mode ultrasonography, V/Q scanning, or pulmonary arteriography to document presence or absence of PE. Weekly or twice-weekly lower extremity ultrasonograms obtained before any delayed PGF insertions and on all patients with ICU status greater than 3 days.	NR	ISS: >9 Trauma Center: admitted to level I trauma center Expected to survive longer than 48 hrs Must meet one of the following: severe head injury with prolonged ventilator dependence, severe head injury with multiple lower extremity fractures, spinal cord injury with or without paralysis, major abdominal or pelvic penetrating venous injury, or pelvic fracture with lower extremity fractures	NR
Rajasekhar A, 2011 <sup>34</sup>	RCT	Single center- N. America	2008-2010	6 Months Post Discharge	CUS for DVT, spiral CT for PE	Industry	Age: >18 years BMI: >35 kg/m <sup>2</sup> Immobility: ≥ 7 days Type of trauma: spinal cord injury with paralysis, multiple complex pelvic fractures, bilateral LE bone fracture except fibula, pelvic + one or more LE bone fracture excluding fibula Trauma Center: <96 hours Expected admission: ≥ 1 week	Pregnancy Filter: previous placement, contraindications Terminally ill or anticipated survival <24 hours
Rodriguez JL, 1996 <sup>36</sup>	Cohort-retro	Single center- N. America	1991-1993	NR	Patients with lower extremity edema underwent ultrasound and	NR	Survived > 48 hours and had three or more of the following risk factors for PE: age greater than 55 years, Injury Severity Score (ISS) > 15, the presence of severe trauma (Abbreviated Injury	NR

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
					pulse Doppler scan. All patients had noninvasive evaluation of lower extremities and vena cava was performed before and after discharge.		Scale (AIS) > 2) of the head, chest, or abdomen, multiple lower extremity fractures, pelvic fractures, spinal trauma, and/or subclavian vein cannulation	
Rogers FB, 1995 <sup>39</sup>	Cohort-pros	Single center- N. America	1991-1994	NR	To assess for deep vein thrombosis, impedance plethysmography was done within 48 hours of filter insertion and weekly thereafter until death or discharge. Venous duplex ultrasound was used to confirm or rule out DVT if plethysmography was abnormal.	NR	Type of trauma: all trauma patients Trauma Center Filter: was placed in one of the four injury groups (spinal cord injury, severe head injury with coma lasting longer than 48 hrs, isolated hip fractures in elderly and complex pelvic fractures with concomitant long bone fracture) and who had relative or absolute contraindications to use of heparin	Elderly patients with isolated hip fractures
Rogers FB, 1997 <sup>38</sup>	Cohort-pros	Single center- N. America	1991-	NR	Weekly impedance plethysmography	NR	Type of trauma: Pelvis, femur and/or tibial fracture Trauma Center: Admission to study center Lower extremity fracture requiring prolonged bed rest >6weeks Low impact injury or poor chance of survival	NR
Wilson JT, 1994 <sup>55</sup>	Cohort-pros	Single center- N. America	1986-1993	6 Months To 24 Months	Weekly impedance plethysmograph	NR	Type of trauma: Traumatic spinal cord injury resulting in paraplegia or quadriplegia	NR

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
					y		Trauma Center: Admission to study center Filter: prospective cohort had IVC filter	
<b>IVCF Only</b>								
Rosenthal D, 2004 <sup>46</sup>	Cohort-retro	Single center- N. America	2002-2003	Until Event (Thromboembolic Complication) Occurrence, Discharge Or Death Of Patient	Color flow duplex ultrasound after 2 weeks of IVCF placement	NR	Type of trauma: multiple trauma with relative or absolute contraindications to low dose heparin or barriers to placement of SCD	History of VTE Documented DVT or Pulmonary embolism
Bach JR, 1990 <sup>1</sup>	Case report	Single center- N. America	1988-1988	NR	No	NR	NR	NR
Benjamin ME, 1999 <sup>2</sup>	Series	Single center- N. America	NR	Until Discharge Or Death	Weekly duplex imaging	NR	All patients who were referred to the vascular surgery service for filter placement over a six month period were included in the study Trauma Center ICU	
Binkert CA, 2006 <sup>3</sup>	Cohort-retro	Multiple center- N. America	2004-2005	NR	IVC venography at the time of retrieval of filter	NR	Recovery filter removal after more than 180days after placement	NR
Bochicchio GV, 2001 <sup>4</sup>	Case report	Single center- N. America	NR	NR	No	NR	Type of trauma: Building collapse accident: complete open pelvic ring disruption with right acetabular and femur fracture Type of surgery: Emergent angiography, Exploratory laparotomy for control of bleeding from liver laceration and perforations from the IVCF Trauma Center Filter	NR
Carlin AM, 2002 <sup>5</sup>	Cohort-retro	Single center- N. America	1991-2001	NR	No	NR	Type of trauma: BLUNT Trauma Center: Admission to study trauma center Filter: Prophylactic or therapeutic IVCF placement	NR
Cherry RA, 2008 <sup>6</sup>	Cohort-pros	Single center- N. America	2004-2006	NR	No	NR	Age: ≥ 18 years Trauma Center	Therapeutic IVC filter



Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
							Filter: Prophylactic IVC filter placement	placement, major burns, deviation from a modified EAST protocol, deaths
Conners MS, 2002 <sup>7</sup>	Cohort-retro	Single center-N. America	1995-2000	1 Year	No	NR	Filter: Duplex-directed IVCF placement	NR
Doody O, 2009 <sup>8</sup>	Cohort-retro	Single center-Australia	2005-2007	NR	Venogram at 2 months after filter insertion	NR	NR	NR
Duperier T, 2003 <sup>9</sup>	Cohort-retro	Single center-N. America	1999-2000	NR	Duplex before discharge	NR	Filter: Greenfield filter insertion during study period	NR
Gonzalez RP, 2006 <sup>10</sup>	Cohort-pros	Single center-N. America	1999-2003	NR	No	NR	Trauma Center: all traumatized patient in the study centre were included Filter	NR
Greenfield LJ, 2000 <sup>13</sup>	Case series of consecutive patients who received Vena cal filters after Traumatic surgery (from Michigan Filter Registry which contains prospectively collected data for IVCF patients	Single center-N. America	1990-1999	Average Follow Up Time Stated In Article Is 42 Months (0-172 Months)	Follow up data obtained prospectively from routine examinations, duplex USS, plain radiographs, and CT scan.	NR	History of VTE Inclusion criteria for therapeutic group in this study Type of trauma: patients who had trauma as primary or secondary diagnosis during the study period Trauma Center: all trauma patients who had IVCF Filter	NR
Hermesen JL, 2008 <sup>14</sup>	Cohort-retro	Single center-N. America	2004-2007	NR	Preprocedure outpatient computed abdominal tomographic (CAT) scan of the abdomen	Government	Trauma Center: level 1 trauma center Filter: receiving a Bard Recovery™ or G2™ R-IVCF (Bard Peripheral Vascular, Inc., Tempe, AZ) for PE prophylaxis.	NR

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
					and pelvis			
Hoff WS, 2004 <sup>15</sup>	Cohort-pros	Single center-N. America	2002-2003	NR	Ultrasound	NR	Head injury (intracerebral hemorrhage) Thoracoabdominal injury Type of trauma: severe/multiple orthopedic injury Spinal cord injury lower extremity external fixation device/traction device/splints	NR
Hughes GC, 1999 <sup>16</sup>	Case report	Single center-N. America	NR	NR	No	NR	Type of trauma: closed head injury	NR
Kurtoglu M, 2003 <sup>20</sup>	Cohort-pros	Single center-Europe	1999-2002	6 Months, 1 Year, And 2 Years	During follow-up Duplex ultrasound of the inferior vena cava and lower extremity was performed to assess patency	NR	Trauma Center: Trauma and Surgical Emergency Service of Istanbul Medical Faculty Filter	NR
Langan EM, 1999 <sup>21</sup>	Cohort-pros	Single center-N. America	1991-1998	NR	Duplex scans	NR	Immobility: all patients anticipated to have prolonged immobility were eligible for inclusion All patients with contraindication to anticoagulation were eligible for inclusion All trauma patients expected to have prolonged immobilization (criteria used to determine this not specified) All trauma patients with a contraindication to anticoagulation (criteria used to determine this not specified)	NR
Leach TA, 1994 <sup>22</sup>	Cohort-pros	Single center-N. America	1986-conflicting sentences on page 293: “...During the 5 years beginning July 1986...” and “...During the 6 year study	NR	No	NR	History of VTE Immobility: Extended Immobilization Any patient who evidenced 4 or more of the following risk factors for DVT: 1. History of DVT 2.Age >40 years 3. Congestive heart failure 4. Obesity 5. Malignancy 6. Extended immobilization 7. Spinal cord injury: Any patient exhibiting any one of 1. Previous VTE 2. Free floating	NR

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
			period...”				ileofemoral thrombus 3. Documented DVT, anticoagulation contraindicated 4 Recent lower extremity venous suture line Trauma Center: Level 1 Trauma Center Filter	
Lo CH, 2008 <sup>23</sup>	Series	Single center- Australia	2001-2005	NR	No	NR	Filter Lower limb flap reconstruction(s)	NR
Mahier A, 2008 <sup>24</sup>	Cohort-retro	Single center- Asia	2002-2005	NR	Patients with clinical suspicion of VTE had imaging	NR	Trauma Center: tertiary trauma center Filter patients who cannot be treated with anticoagulation or suffer from lower extremity trauma precluding the use of pneumatic calf compression	NR
McMurtry AL, 1999 <sup>25</sup>	Cohort-retro	Single center- N. America	1992; 1989-1996; 1991	NR	No	NR	Absolute contraindication to coagulation (criteria not stated in the paper) Trauma Center: all patients admitted with VCFs after trauma	NR
Meier, C., 2006 <sup>27</sup>	Cohort-retro	Single center- Europe	1998-2004	NR	No	NR	ISS: ≥16 Filter: Prophylactic IVC filter placement	NR
Meier, C., 2006 <sup>26</sup>	Series	Single center- Europe	2003-	NR	No	NR	ISS: ≥16	Filter: Therapeutic filter placement
Millward, S.F., 1994 <sup>28</sup>	Cohort-pros	Multiple center- N. America	1992-1993	1 Month After Filter Removal	The presence of recurrent PE following filter removal was determined by means of clinical assessment. Duplex sonography of the insertion vein and IVC was scheduled to be performed between 1 week and 1 month following filter removal	NR	NR	NR
Nunn, C.R.,	Cohort-pros	Single center-	1995-1996	NR	Doppler US of	NR	Type of trauma: open abdominal	Patients who

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
1997 <sup>29</sup>		N. America			Lower extremities prior to IVC filter placement and after placement looking for DVT		wounds ISS: >15 Trauma Center: Admission to study center Filter: Prophylactic Greenfield filter placement	refused to consent
Offner, P.J., 2003 <sup>31</sup>	Cohort-pros	Single center- N. America	2001-2002	Until Death Or Discharge	Duplex sonography was not performed unless clinically indicated by unilateral leg swelling, calf tenderness, tenderness with passive heel stretch, or suspected pulmonary embolism. PE was evaluated using tomography of the chest or formal pulmonary angiography if the tomography was negative.	NR	Patients at high risk for venous thromboembolism with relative or absolute contraindications to low-dose anticoagulant therapy or barriers to the placement of sequential compression devices Type of trauma: major pelvic and/or acetabular fractures with or without associated lower extremity long bone fractures, bilateral lower extremity long bone fractures, spinal cord injury with neurologic deficit, and severe head injury	NR
Patton, J.H. Jr, 1996 <sup>32</sup>	Cohort-retro	Single center- N. America	1991-1995	NR	Duplex ultrasonography was used or patients with suspicion for DVT; patients who exhibited signs of PE were assessed with ventilation/perfusion scan;	NR	Type of trauma: (1) with spinal cord injury and deficit, (2) with pelvic fracture and/or long bone fracture requiring immobilization, and (3) with significant head injury and prolonged immobilization. Trauma Center ICU Filter	NR

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
					patients with moderate probability scans were taken to pulmonary angiography if stable enough to leave ICU, otherwise treated as if they had had a PE			
Phelan, H.A., 2009 <sup>33</sup>	Series	Single center- N. America	1992-2001	NR	No	Industry	Prophylactic permanent Greenfield filters placed after injury, survival to discharge from hospital Type of trauma: Severe traumatic brain injury, spinal cord injury, major pelvic or lower extremity long bone fracture, pelvic or abdominal penetrating venous injury Filter: Permanent prophylactic Greenfield filter placement	Age: Less than 18 years at time of study Preg: Pregnant at time of study Death before discharge from hospital, therapeutic filter placement, prisoners at time of study
Roberts, A., 2010 <sup>35</sup>	Cohort-retro	Single center- N. America	2003-2009	12 Months Post Insertion	No	Industry	Type of trauma: spinal cord injury resulting in quadriplegia or quadriparesis Trauma Center Filter severe cervical SCI resulting in quadriplegia or quadriparesis and relative contraindications to anticoagulation relative contraindications to LMWH or UFH (eg. need for spinal surgery stabilization, concomitant injuries such as cranial trauma)	NR
Rogers, F., 2001 <sup>37</sup>	Case report	Single center- N. America	1999-not stated because this is case report	NR	No	NR	Type of trauma: Multiple injuries after falling off a ladder: grade III splenic laceration, Anterior column fracture of 2nd thoracic vertebra, Posterior column	NR

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
			; patient was discharged from hospital after 45 days				fracture of 1st thoracic vertebra, spinal cord lesion Trauma Center ICU Filter	
Rogers, F.B., 1993 <sup>40</sup>	two studies: one is a retrospective study, the other was prospective	Single center-N. America	1991-1992	NR	Weekly impedance plethysmography after filter insertion. If IPG equivocal or abnormal then duplex u/s done	NR	1. Relative or absolute contraindication to anticoagulants 2. Spinal cord injury with complete paraplegia or quadriplegia 3. Severe Pelvic fracture and long bone fractures; 4. Severe head injury with GCS $\leq$ 8 Type of trauma: as stated in inclusion criteria Glasgow Coma Scale: Severe head injury with a GCS $\leq$ 8 Trauma Center: Trauma center Filter	Warfarin therapy
Rogers, F.B., 1997 <sup>41</sup>	Cohort-pros	Single center-N. America	1991-1996	Until Hospital Discharge	In the first 2 years of the study, patients underwent impedance plethysmography, duplex sonography or both after 48 hours of VCF insertion and then weekly thereafter till discharge. Later on, patients were only screened for DVT if they developed clinical signs	NR	severe pelvic fracture (type III or IV) Long bone fracture Type of trauma: Spinal cord injury with paraplegia or quadriplegia Glasgow Coma Scale: $\leq$ 8 Trauma Center: all patients admitted with contraindication to anticoagulation	NR
Rosenthal, D., 2005 <sup>44</sup>	Cohort-pros	Single center-N. America	2002-2004	Until Hospital Discharge Or Death	Yes	NR	Multiple trauma patients with relative or absolute contraindication to anticoagulation (not specified)	NR
Rosenthal, D., 2006 <sup>45</sup>	Cohort-retro	Single center-N. America	2002-2004	NR	Lower extremity venous color-	NR	Multiple Trauma Patients, Relative or absolute contra-indications	NR

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
					flow duplex USS within 14d of placement, and prior to retrieval		to heparin or barriers to placement of sequential compression devices, ICU patients, Retrievable filters Type of trauma: multiple trauma patients ICU Filter: Retrievable (Gunther tulip, recovery and Optease)	
Sekharan, J., 2001 <sup>47</sup>	Cohort-retro	Single center- N. America	1992-1994	Follow Up Was Attempted In All Patients With At Least 5 Years' Duration Since Placement Of Prophylactic Green Filter	Each patient who presented for follow up had duplex USS to assess presence of DVT	NR	Type of trauma: Severe head injury with prolonged ventilator dependence; Severe head injury with multiple lower extremities fractures; Spinal cord injury with or without paralysis; Major abdominal or pelvic penetrating venous injury; Pelvic fracture with lower extremity fractures ISS: ISS greater than 9 Trauma Center: Level 1 Filter Be expected to survive longer than 48 hours	NR
Shang, E.K., 2011 <sup>48</sup>	Case report	Single center- N. America	NR	NR	Yes	Not funded	NR	NR
Sing RF, 2001 <sup>49</sup>	Series	Single center- N. America	NR	Case 2 Was Followed Up For 4years	No	NR	Type of trauma: Multiple trauma Trauma Center Filter	NR
Sing RF, 2001 <sup>50</sup>	Prospective Observational study	Single center- N. America	1996-2000	Long-Term Follow Up Consists Of Annual Outpatient Visits And Duplex USS Surveillance.	Duplex ultrasonographic surveillance annually	NR	All patients who received IVCF during the study period , ICU patients ICU Filter	NR
Sing, RF <sup>51</sup>	Series	Single center- N. America	NR	NR	No	NR	Immobility Trauma Center: Admission to study center ICU Filter: Bedside IVC placement in ICU	NR
Stefanidis D, 2006 <sup>53</sup>	Cohort-pros	Single center- N. America	2004-2005	At Least 1 Month Post	No	NR	Filter: optional VCF placement	NR

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
				Hospital Discharge				
Tola JC, 1999 <sup>54</sup>	Cohort-retro	Single center-N. America	1997-1998	Duration Of Hospital Stay	Clinical monitoring for signs and symptoms of PE/venous thrombosis	NR	Severely injured patients with contraindication to anticoagulation (criteria not specified)	NR
Wojcik R, 2000 <sup>56</sup>	Cohort-retro	Single center-N. America	1993-1997	NR; The Mean Duration Of Follow Up Is 28.9 months (Range:5-62)	Yes-Duplex USS	NR	History of VTE: only for patients who had VCF for therapeutic indications Trauma Center Patients admitted to trauma service who had VCF placed Filter	NR
Zakhary EM, 2008 <sup>57</sup>	Cohort-retro	Single center-N. America	2003-2005	Attempts To Contact Patients Were Made 3 Months After Insertion; The Mean Time Between Insertion Of IVC And Retrieval Was 165 Days (90-360)	No	NR	All patients who had Recovery Filters Type of trauma Filters were inserted in blunt trauma patients who had head injury, pelvic fractures and or long bone fractures Trauma Center: Level 1 trauma center Filter: Recovery filter excluding patients with new generations recovery filters	Patients with new generations of recovery filters Patients who received G2 filter which replaced recovery filter
Zolfaghari D, 1995 <sup>58</sup>	Cohort-retro	Single center-N. America	1990-1991	NR	Venous duplex scan	NR	All patients who received IVC filter at Level 1 Trauma center Trauma Center : Level 1 Filter	NR

AIS= Abbreviated Injury Scale; BMI= Body Mass Index; CAT= Computed Axial Tomography; CT= Computed Tomography; CUS= Compression Ultrasonography; DVT= Deep Vein Thrombosis; GCS= Glasgow Coma Scale; ICU= Intensive Care Unit; IPG= Impedance Phlebography; ISS= Injury Severity Score; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; LE= Lower Extremity; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; SCD= Sequential Compression Device; SCI= Spinal Cord Injury; TBI= Traumatic Brain Injury; UFH= Unfractionated Heparin; USS= Ultrasound Scan; VCF= Vena Cava Filter; VTE= Venous Thromboembolism



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**Evidence Table 3. Participant characteristics for KQ1**

Author, Year	Arm, n	Age (years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI	Weight	Prior History of VTE, n (%)	Trauma, n (%)	ICU Duration
Bach, J.R., 1990 <sup>1</sup>	Total, 1	NR	Overall Male, 0 (0)	NR	NR	NR	NR	NR	NR
Benjamin, M.E., 1999 <sup>2</sup>	Arm 2 (Prophylactic DGFI only), 23	Mean:46 Range:19-79	Male, 20 (86.95)	NR	NR	NR	41	Other fracture (combined pelvic and lower extremity fracture): 1 (4.35)	Arm 2: Mean:14.1 Range:1-150
Binkert, C.A., 2006 <sup>3</sup>	(Overall), 13	Mean:46.2 Range:21-70	Male, 6	NR	NR	NR	NR	Pelvis fracture (overall): 2 Other fracture (overall):1 comment: long bone fracture	NR
Bochicchio, G.V., 2001 <sup>4</sup>	Arm 2 (Case Report), 1	Mean:48	Male, 1	Black: 1	NR	NR	NR	Pelvic fracture: 1 Spinal cord injury: 1	NR
Carlin, A.M., 2002 <sup>5</sup>	Arm 1 (control)	NR	NR	NR	NR	NR	NR	Pelvic fracture (overall): (38 ) Spinal cord injury (overall): 16 (12) Other fracture foot- ankle (overall): 21	NR
	Arm 2 (Prophylactic IVCF)	NR	NR	NR	NR	NR	NR	Other fracture (tibia- fibula): 29 Other fracture (femur- shaft): 20	NR
Cherry, R.A., 2008 <sup>6</sup>	Arm 1 (244 at baseline), 176	Mean:43.8	Male, (63.5)	NR	NR	NR	NR	Ventilator days mean:7 Range:0-42 ISS Mean:26.7 Pelvic fracture:99 Long bone fracture:109 Spine fracture:87 Complex fracture: 53	NR
Conners, M.S., 2002 <sup>7</sup>	(Overall ) 284	Mean:41 Range:15-87	Male, 203 (71)	NR	NR	NR	NR	Spinal cord injury: 19	NR
Doody O, 2009 <sup>8</sup>	Arm 2 (IVCF), 115	Mean:47.97 Range:19-84	Male, 74 (63.4)	NR	NR	NR	NR	NR	NR
Duperier T, 2003 <sup>9</sup>	Arm 2 (IVCF), 133	NR	NR	NR	NR	NR	NR	Pelvic fracture (overall): 6 (5)	NR

Author, Year	Arm, n	Age (years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI	Weight	Prior History of VTE, n (%)	Trauma, n (%)	ICU Duration
								Other fracture (overall)multiple long bones: 27 (20) Other fracture (overall) vertebral: 3 (2) Spinal cord injury: 3	
Gonzalez, R.P., 2006 <sup>10</sup>	Arm 2 (OR), 78	Mean:38.6	NR	NR	NR	NR	NR	Spinal cord injury (overall): 11 (30)	RN
	Arm 3 (STICU), 56	Mean:39.6	NR	NR	NR	NR	NR	NR	NR
Gorman P.H., 2009 <sup>11</sup>	Arm 1 (Control), 58	Mean:48.1	Male, 40 (69)	NR	NR	NR	NR	NR	NR
	Arm 2 (IVCF), 54	Mean:37.1	Male, 52 (96)	NR	NR	NR	24 (20.9)	NR	NR
Gosin J.S., 1997 <sup>12</sup>	Arm 1 (control) 249	NR	NR	NR	NR	NR	NR	NR	NR
	Arm 2 (Heparin), 151	NR	NR	NR	NR	NR	NR	NR	NR
	Arm 3 (IVCF), 99	Mean:42.6 Range:17-91	Male, 71	NR	NR	NR	NR	ISS mean: 23.4 Other fracture (femur): 27	NR
Greenfield, L.J., 2000 <sup>13</sup>	Arm 2 (P-IVCF), 249	Mean:43 Range:14-88	Male, 154	NR	NR	NR	16	ISS mean: 25, Range:4-75* Spinal cord injury: 43 (27)	NR
	Arm 3 (T-IVCF), 136	Mean:46 Range:11-93	Male, 81	NR	NR	NR	NR	ISS mean:20, Range:4-54*	NR
Hermesen, J.L., 2008 <sup>14</sup>	Arm 2 (R-IVC Filter), 74	Mean:38.4	Male, (68)	NR	NR	NR	NR	ISS Mean:32 Mechanism of injury blunt: (100)	NR
Hoff, W.S., 2004 <sup>15</sup>	(Overall), 35	Mean:34 Range:15-66	Male, 25 (71.4)	NR	NR	NR	NR	ISS- mean: 30, Range:6-75 Mechanism of injury blunt(overall): 35 (100) Pelvic fracture(overall): 17 (48.6) Other fracture	NR

Author, Year	Arm, n	Age (years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI	Weight	Prior History of VTE, n (%)	Trauma, n (%)	ICU Duration
								(overall)maxilla facial: 7 (20) Other fracture (overall)vertebral: 16 (45.7)	
Hughes, G.C., 1999 <sup>16</sup>	Arm 2 (Case 1), 1	Mean:47	Male, 1 (100)	NR	NR	NR		Other fracture (bilateral lower extremity#): 1 (100)	NR
	Arm 3 (Case 2), 1	NR	Male, 1 (100)	NR	NR	NR		Other fracture (bilateral lower extremity#): 1 (100)	NR
Karmy-Jones R, 2007 <sup>17</sup>	Arm 2 (R-IVCF), 446	Mean:39.8	Male, (69)	NR	NR	NR	NR	ISS- mean: 25.3 Mechanism of injury blunt : (92) Mechanism of injury penetrated: (8) Pelvic fracture: (44) Other fracture: (53)	NR
	Arm 3 (P-IVCF), 172	NR	NR	NR	NR	NR	NR	Pelvic fracture: (32) Other fracture: (37)	NR
Keller IS., 2007 <sup>18</sup>	Arm 2 (Gunther Tulip), 92	Mean:45.6 Range:16-84	Male, 64	NR	NR	NR	19 (7.7)	NR	NR
	Arm 3 (OptEase Group), 80	Mean:47.8 Range:17-86	Male, 47	NR	NR	NR	NR	NR	NR
Khansarinia, S., 1995 <sup>19</sup>	Arm 1 (control), 216	Mean:38.3	Male, (75.5)	NR	NR	NR	NR	ISS mean: 25.4 AIS head/neck: 55 AIS abdominal score: Mean:35 Glasgow coma scale score: Mean:11.8* Mechanism of injury	NR

Author, Year	Arm, n	Age (years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI	Weight	Prior History of VTE, n (%)	Trauma, n (%)	ICU Duration
	Arm 2 (PGF), 108	Mean:35.9	Male, (76)	NR	NR	NR	NR	blunt: (81) ISS- mean: 28.0 AIS head/neck: 40 AIS abdominal score: Mean:38 Glasgow coma scale score: Mean:10.3* Mechanism of injury blunt: (85)	NR
Kurtoglu M, 2003 <sup>20</sup>	Arm 2 (IVCF), 11	NR	NR	NR	NR	NR	NR	NR	Mean:10.3 Days Range:4-39
Langan, E.M., 1999 <sup>21</sup>	Arm 2 (IVCF)	NR	NR	NR	NR	NR	0 (0)	Mechanism of injury blunt (overall): 27 (14.4) Other fracture (lower extremity fracture): 4 (17.39) Spinal cord injury: 11 (47.83)	NR
Leach, T.A., 1994 <sup>22</sup>	NR	NR	NR	NR	NR	NR	NR	NR	Mean:18.4 Days
Leach, T.A., 1994 <sup>22</sup>	Arm 1 (Control)			NR	NR	NR	NR	Other fracture (lower extremity fracture): 8*	NR
	Arm 2 (IVCF), 201	Mean:37.5	Male, (73)	NR	NR	NR	NR	Mechanism of injury blunt: (60) Mechanism of injury penetrating: (40) Other fracture (lower extremity fracture): 0 *	Mean:21.1 Days
Lo, C.H., 2008 <sup>23</sup>	Arm 2 (Gunther Tulip), 17	Median:37 Range:15-64	Male, 12	NR	NR	NR	NR	Mechanism of injury blunt: 17 Other fracture (Gustilo type IIIb tibia/fibula fractures): 11 Other fracture: (Gustilo type IIIc tibia/fibula	NR



Author, Year	Arm, n	Age (years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI	Weight	Prior History of VTE, n (%)	Trauma, n (%)	ICU Duration
								fractures and other lower limb injuries included open fractures of patella, tibial plateau and tibial plafond): 2	
Mahier, A., 2008 <sup>24</sup>	Arm 1 (overall), 80	Mean:38.5 Range:14-83	Male, 53 (66)	NR	NR	NR	NR	ISS Mean:33.5 Range:9-66	Mean:8
McMurtry, A.L., 1999 <sup>25</sup>	Arm 2 (Years of high PVCF use), 226	Mean:34.4	Male, (68.2)	NR	NR	NR	NR	ISS mean: 9.8 Mechanism of injury blunt: (82.7) Other fracture (tibia): (5.7) Other fracture, bilateral lower extremity long bone # (overall): 7 (33.3) Spinal cord injury (overall): 4 (19) Pelvic fracture (overall): 5 (23.8)	NR
	Arm 3 (Years of low PVCF use), 22	Mean:33	Male, (69.6)	NR	NR	NR	NR	ISS- mean: 10.2 Mechanism of injury blunt: (83.7) Other fracture (tibia): (5.5)	NR
Meier, C., 2006 <sup>27</sup>	Arm 2 (IVCF), 95	Overall: Mean:38 Range: 16-80	Overall: Male, 67 (70.5)	NR	NR	NR	Throughout hospitalization	Ventilator days comment: throughout hospitalization range: ISS-mean: Overall: Median:38 , Range:17-66 AIS head/neck: AIS face score comment: 3 (3) patients had AIS >2 AIS Chest score	NR

Author, Year	Arm, n	Age (years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI	Weight	Prior History of VTE, n (%)	Trauma, n (%)	ICU Duration
								comment: 64 (67.4)patients had AIS.2 AIS extremity score comment: 46 (48.4) patients had AIS >2 AIS external score comment: 1 (1.1) patient had AIS integument >2	
Meier, C., 2006 <sup>26</sup>	(Overall), 37	Mean:35 Range:17 - 73	Male, 23 (62)	NR	NR	NR	1	Ventilator days: Median:41, Range:17- 59	NR
Millward, S.F., 1994 <sup>28</sup>	Arm 2 (IVCF), 3	Mean:36 Range:22-55	Male, 3	NR	NR	NR	NR	Pelvic fracture: 23 Spinal cord injury: 25	NR
Nunn, C.R., 1997 <sup>29</sup>	Arm 2 (IVCF)	NR	NR	NR	NR	NR	0 (0)	Pelvic fracture: 1 (100) Other fracture (bilateral upper extremity #): 1 (100)	NR
O'Keffe, T., 2011 <sup>30</sup>	Arm 2(Trauma group) 91	Median:32	Male, (70)	NR	NR	NR	NR	ISS Median:29 AIS Abdominal scoreMedian:3 AIS Head/Neck score Mean:3.4 AIS Extremity score Median:2 Mechanism of injury penetrating: (4.4)	NR
	Arm 3 (Control - Non-trauma group), 76	Median:53	Male, (38)	NR	NR	NR	NR	AIS Head/Neck score Mean:3.4	NR
Offner, P.J., 2003 <sup>31</sup>	Arm 2 (IVCF), 44	Mean:37	Male, (55)	NR	NR	NR	12	ISS- mean: 33 Mechanism of injury blunt: (100) Pelvic fracture: 23 Other fracture (femur):15 Other fracture (multiple): 19	NR

Author, Year	Arm, n	Age (years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI	Weight	Prior History of VTE, n (%)	Trauma, n (%)	ICU Duration
Patton, J.H. Jr, 1996 <sup>32</sup>	Arm 2 (IVCF – acute complications), 110	Mean:47.2	Male, 68	NR	NR	NR	NR	ISS mean: 26 Glasgow coma score: mean:5	NR
Phelan, H.A., 2009 <sup>33</sup>	(Overall), 82	Mean:34.1	Male (63.4)	NR	NR	NR	NR	NR	NR
Rajasekhar, A., 2011 <sup>34</sup>	Arm 1 (Control), 16	Mean:53.7	Male, 10 (62.5)	NR	NR	NR	NR	ISS Mean:24.1 GCS Mean: 13.6 Uninsured; 5 Mechanism of injury penetrating; 15 Pelvic fracture;2 Bilateral LE fracture; 8 BLE fracture +SCI; 0	NR
	Arm 2 (IVCF), 18	Mean:41.2	Male, 13 (72.2)	NR	NR	NR	NR	ISS Mean:26.6 GCS Mean: 13.6 Uninsured: 6 Mechanism of injury penetrating: 18 Pelvic fracture;;5 Bilateral LE fracture: 4 BLE fracture +SCI 1	NR
Roberts, A., 2010 <sup>35</sup>	Arm 2 (IVCF), 45	Mean:39.7 Range:17-67	Male, 37	NR	NR	NR	NR	ISS Mean:34.2 AIS Abdominal score Arm 1 Mean:21.57, Arm 2 Mean:16.0, Arm 3 Mean:18.1, Arm 4 Mean:31.3 (not clear, reported for 4 arms), Head AIS score; (5)	NR
Rodriguez, J.L., 1996 <sup>36</sup>	Arm 1 (control), 80	Mean:41	Male, (68)	NR	NR	NR	NR	ISS mean: 29 AIS chest score: Mean:45 Glasgow coma scale: Mean:12 Mechanism of injury blunt: (98)	NR
	Arm 2 (IVCF), 40	Mean:44	Male, (58)	NR	NR	NR	NR	ISS mean: 31 AIS chest score: Mean:35	NR

Author, Year	Arm, n	Age (years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI	Weight	Prior History of VTE, n (%)	Trauma, n (%)	ICU Duration
								Glasgow coma scale: Mean:11 Mechanism of injury blunt: (98) Pelvic Fracture: 48 Other fracture (multiple long bone fracture): 39	
Rogers FB, 1997 <sup>38</sup>	Arm 1 (control), 905	Mean:38.9 *	NR	NR	NR	NR	NR	ISS mean: 9.83*	NR
	Arm 2 (IVCF), 35	Mean:58.4 *	NR	NR	NR	NR	NR	ISS mean: 22.8*	NR
Rogers, F., 2001 <sup>37</sup>	Arm 2 (Case Report), 1	Mean:48	Male, 1	NR	NR	NR	3	NR	NR
Rogers, F.B., 1993 <sup>40</sup>	Arm 2 (IVCF), 34	Mean:41.6	Sex ratio: 1.8 : 1.0	NR	NR	NR	NR	ISS mean: 28.9 Other fracture (head injury): 7	NR
Rogers, F.B., 1995 <sup>39</sup>	Arm 1 (Control)	NR	NR	NR	NR	NR	NR	Pelvic Fracture: (48) Other fracture (multiple lower extremity fractures): (75) Spinal cord injury: (24)	Mean:14 Range:1
	Arm 2 (PVCf), 63	Mean:38.9	Male, (73)	NR	NR	NR	NR	ISS mean: 31.5 Pelvic Fracture: (55) Other fracture (multiple lower extremity fractures): (80) Spinal cord injury: (25)	Mean:18 Range:6
	Arm 3 (All trauma patients), 3088	Mean:38.8	Male, (60)	NR	NR	NR	NR	ISS mean: 9.2	NR
Rogers, F.B., 1997 <sup>41</sup>	(Overall) 132	Mean:39.1	Male, (73)	NR	NR	NR	NR	ISS mean: 25.1 Other fracture : 43(32) Spinal Cord Injury: 47(35)	NR
Rosenthal D., 2007 <sup>43</sup>	Arm 2 (Filter dwell times <180days), 64	NR	NR	NR	NR	NR	NR	NR	NR

Author, Year	Arm, n	Age (years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI	Weight	Prior History of VTE, n (%)	Trauma, n (%)	ICU Duration
	Arm 3 (Filter dwell times >180 days), 41	NR	NR	NR	NR	NR	NR	NR	NR
Rosenthal D., 2009 <sup>42</sup>	Arm 1 (Overall), 187	Mean:44 Range:17-71	Male, 109	NR	NR	NR	NR	ISS Mean:28.5	NR
Rosenthal, D., 2004 <sup>46</sup>	(Overall), 94	Mean:38 Range:17-66	Male, 57 (60.6)	NR	NR	NR	NR	ISS- mean: 25.1 Mechanism of injury blunt (overall): 89 (94.75) Pelvic fracture (overall): 38 (40.4) Other fracture (overall): 44 (46.8) Spinal cord injury (overall): 31 (30.1)	NR
Rosenthal, D., 2005 <sup>44</sup>	(Overall), 103	Mean:40 Range:17-68	Male, 64 (62.1)	NR	NR	NR	NR	ISS- mean: 27.7 Mechanism of injury blunt (overall): 93(90.2) Pelvic fracture (overall): 41 (39.8) Other fracture (overall): 51 (49.5)	NR
Rosenthal, D., 2006 <sup>45</sup>	Arm 2 (Gunther Tulip), 127	Mean:42 Range:17-68	Male, 77 (60.6)	NR	NR	NR	NR	Spinal cord injury: (25)	NR
	Arm 3 (Celect)	NR	NR	NR	NR	NR	NR	Spinal cord injury: (25)	NR
Sekharan, J., 2001 <sup>47</sup>	Arm 2 (Follow up Patients), 33	Mean:38.1	Male, 25	NR	NR	NR	NR	Spinal cord injury (overall): 167 (59)	NR
Shang, E.K., 2011 <sup>48</sup>	Arm 2 (IVCF), 1	Mean: 46	Male, (0)	NR	NR	NR	NR	NR	NR
Sing, R.F., 1998 <sup>51</sup>	Arm 2 (IVCF), 8	Overall Range: 19-84	Overall: Male, 7	NR	NR	NR	NR	NR	NR
Sing, R.F., 2001 <sup>49</sup>	Arm 2 (Case 1), 1	Mean:54	Male, 1	NR	NR	NR	NR	Other fracture comment: Case 1: Depressed skull fracture, frontal lobe contusion, multiple facial fractures, distal right radius and ulna fractures, and thoracic spine fracture.	NR

Author, Year	Arm, n	Age (years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI	Weight	Prior History of VTE, n (%)	Trauma, n (%)	ICU Duration
	Arm 3 (Case 2), 1	Mean:69	Male, 0	NR	NR	NR	NR	NR	NR
Sing, R.F., 2001 <sup>50</sup>	Arm 2 (IVCF), 158	Mean:42.2	Male, 113	NR	NR	NR	NR	ISS- mean: 27.3	NR
Smoot RL, 2010 <sup>52</sup>	Arm 1 (Overall), 226	Mean:49	Male, 138	NR	NR	NR	NR	ISS Median:26 Range:1-59 Pelvic fracture:92 (41) Long bone fracture:129 (57) Spine fracture:76 (34)	NR
Stefanidis, D., 2006 <sup>53</sup>	(Overall), 83	Mean:43 Range:14 - 71	Male, 59 (71)	NR	NR	NR	NR	ISS- mean: 26	NR
Tola, J.C., 1999 <sup>54</sup>	Arm 2 (IVCF),25	52.6(31-86)	19(76)	NR	NR	NR	4(16)	Other fracture combined pelvic # and long bone# (overall): 3 (14.3)	NR
Wilson, J.T., 1994 <sup>55</sup>	Arm 1 (control), 111	Mean:30.0	NR	NR	NR	NR	NR	ISS mean: 29	NR
	Arm 2 (Greenfield Titanium), 15	Mean:31.4	NR	NR	NR	NR	16	ISS mean: 30	NR
Wojcik, R., 2000 <sup>56</sup>	Arm 2 (VCF Registry Patients), 105	Mean:54.8 Range:18-87	Male, 75	NR	NR	NR	NR	ISS- mean:26.1, Range:5-75	NR
Zakhary, E.M., 2008 <sup>57</sup>	Arm 2 (IVCF), 122	Mean:38.5 Range:15-58	Male, 86 (70.1)	NR	NR	NR	NR	ISS Mean:19.7 Range:5-42 Mechanism of injury blunt: 122 Spinal cord injury: 27	NR
Zolfaghari, D., 1995 <sup>58</sup>	Arm 2 (IVCF), 45	Median:37	Male, 23	NR	NR	NR	16	NR	NR

AIS= Abbreviated Injury Scale; BMI= Body Mass Index; CAT= Computed Axial Tomography; CT= Computed Tomography; CUS= Compression Ultrasonography; DGFI = duplex-guided IVC filter insertion; DVT= Deep Vein Thrombosis; GCS= Glasgow Coma Scale; ICU= Intensive Care Unit; IPG= Impedance Phlebography; ISS= Injury Severity Score; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; LE= Lower Extremity; PE= Pulmonary Embolism; PGF= Prophylactic Greenfield Filter; P-IVCF= Prophylactic Inferior Vena Cava Filter; PVCF= Prophylactic Vena Cava Filter ;RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; SCD= Sequential Compression Device; SCI= Spinal Cord Injury; TBI= Traumatic Brain Injury; UFH= Unfractionated Heparin; USS= Ultrasound Scan; VCF= Vena Cava Filter; VTE= Venous Thromboembolism

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**Evidence Table 4. Intervention characteristics for KQ1 – Part A**

Author, Year	Arm Name	Filter name	Filter type (temp or permanent)	Filter placed by	Setting	Planned duration of filter	Concurrent therapy
<b>IVCF versus IVCF Cohort- retro</b>							
Karmy-Jones R, 2007 <sup>17</sup>	Arm 2 (R-IVCF)	Gunther Tulip® - 152 OPTEASE® -37 Recovery- 224	NR	NR	NR	NR	No
	Arm 3 (P-IVCF)	Greenfield Stainless Steel® - 59 TRAPEASE® -46 VenaTech LGM® -23 Nitinol-14; bard non recovery-7; birds nest-4	NR	NR	NR	NR	No
	Arm 4 (R-IVCF - prophylactic)	Gunther Tulip® OPTEASE® Recovery	NR	NR	NR	NR	No
Keller, I.S., 2007 <sup>18</sup>	Arm 2 (Gunther Tulip)	Gunther Tulip®	Temp & Permanent	Interventional Radiologist	Angiography Suites	NR	No
	Arm 3 (OptEase)	OptEase	Temp & Permanent	Interventional Radiologist	Angiography suites	NR	No
O'Keffe, T., 2011 <sup>30</sup>	Arm 2 (Trauma Group)	Gunther Tulip® - 50 G2® -40 Other-1	NR	NR	NR	NR	No
	Arm 3 (Non trauma group - control)	Gunther Tulip® - 52 G2® -23 Other-1	NR	NR	NR	NR	No
Rosenthal D., 2007 <sup>43</sup>	Arm 2 (Filter dwell times <180 days)	Gunther Tulip®	Temp & Permanent	NR	NR	<180 days	No
	Arm 3 (Filter dwell times >180 days)	Gunther Tulip®	Temp & Permanent	NR	NR	>180days	No
Rosenthal D., 2009 <sup>42</sup>	Arm 2 (Gunther Tulip)	Gunther Tulip®	Temporary	NR	Bedside in ICU	NR	No

Author, Year	Arm Name	Filter name	Filter type (temp or permanent)	Filter placed by	Setting	Planned duration of filter	Concurrent therapy
	Arm 3 (Celect)	Celect <sup>®</sup>	Temporary	NR	Bedside in ICU	NR	No
<i>Cross sectional</i>							
Smoot RL, 2010 <sup>52</sup>	Arm 2 (Permanent)	Greenfield Stainless Steel <sup>®</sup> TRAPEASE <sup>®</sup> VenaTech LGM <sup>®</sup>	Permanent	Interventional Radiologist	NR	NR	No
	Arm 3 (Retrievable)	Gunther Tulip <sup>®</sup> Recovery	Temporary	Interventional Radiologist	NR	NR	No

**Evidence Table 4. Intervention characteristics for KQ1 continued**

Author, Year	Arm Name	Filter name	Filter type (temp or permanent)	Filter placed by	Setting	Planned duration of filter	Concurrent therapy	Comparator Arm
<b>IVCF versus Control RCT</b>								
Rajasekhar, A., 2011 <sup>34</sup>	Arm 1 (Usual care/ No Intervention)	NR	NR	NR	NR	NR	SCDs, enoxaparin 30 mg s.c twice a day/ 5000 units UFH s.c thrice a day/ fondaparinux 2.5mg s.c every day	NR
	Arm 2 (IVCF)	Celect®	Temporary	Trauma Surgeon, Vascular Surgeon	Bedside	NR	SCDs, enoxaparin 30 mg s.c twice a day/ 5000 units UFH s.c thrice a day/ fondaparinux 2.5mg s.c every day	NR
<b>Cohort- pros</b>								
Gosin JS, 1997 <sup>12</sup>	Arm 2 (DVT prophylaxis)	NR	NR	NR	NR	NR	NR	Heparin, 5000 units, S.C, every 8-12 hrs and pneumatic sequential compression devices
	Arm3 (IVCF)	Greenfield Titanium® - 65  Gianturco-Roehm Bird's nest	NR	Interventional Radiologist  Vascular surgeon	Operating room	NR	NR	NR
Rogers FB, 1995 <sup>39</sup>	Arm 2 (PVCF)	Greenfield Titanium®  Bird's nest filter (Cook, Bloomington)	NR	NR	Radiology suite	NR	SCD	NR

Author, Year	Arm Name	Filter name	Filter type (temp or permanent)	Filter placed by	Setting	Planned duration of filter	Concurrent therapy	Comparator Arm
	Arm 3 (All trauma patients)	Drug name: Heparin  Device name: Greenfield Titanium®  Bird's nest filter (Cook, Bloomington)	NR	NR	NR	NR	SCD	NR
Rogers FB, 1997 <sup>38</sup>	Arm 1 (Usual care/ No Intervention)	NR	NR	NR	NR	NR	Pneumatic compression devices	NR
	Arm 2 (IVCF)	NR	NR	Interventional Radiologist	Radiology suite	NR	Pneumatic compression devices	NR
Wilson JT, 1994 <sup>55</sup>	Arm 1 (Usual care/ No Intervention)	NR	NR	NR	NR	NR	Venous compression devices  Low dose subcutaneous heparin	NR
	Arm 2 (IVCF)	Greenfield Titanium® -15	NR	NR	NR	NR	Venous compression devices  Low dose subcutaneous heparin	NR
<i>Cohort- retro</i>								
Gorman PH, 2009 <sup>11</sup>	Arm 1 (Usual care/ No Intervention)	NR	NR	NR	NR	NR	Compression stockings Low weight heparin	NR
	Arm 2 (IVCF)	NR	NR	NR	NR	NR	Compression stockings Low weight heparin	NR
Rodriguez, J.L., 1996 <sup>36</sup>	Arm 1 (Usual care/ No	NR	NR	NR	NR	NR	No	NR

Author, Year	Arm Name	Filter name	Filter type (temp or permanent)	Filter placed by	Setting	Planned duration of filter	Concurrent therapy	Comparator Arm
	Intervention)							
	Arm 2 (IVCF)	Greenfield Titanium®-40	NR	Interventional Radiologist	NR	NR	No	NR
<i>Prospective cohort with historical control</i>								
Khansarinia, S, 1995 <sup>19</sup>	Arm 1 (Usual care/ No Intervention)	NR	NR	NR	NR	NR	SCD (if contraindication to LDH) LDH	NR
	Arm 2 (PGF)	Greenfield Stainless Steel® Greenfield Titanium®	NR	Interventional Radiologist, Trauma Surgeon, Vascular Surgeon	NR	NR	SCD (if contraindication to LDH) LDH	NR

**Evidence Table 4. Intervention characteristics for KQ1 continued**

Author, Year	Arm Name	Filter name	Filter type (temp or permanent)	Filter placed by	Setting	Planned duration of filter	Concurrent therapy
<b>IVCF Arm Only Cohort-pros</b>							
Cherry RA, 2008 <sup>6</sup>	Arm 2 (P-IVCF)	Greenfield Stainless Steel® Simon Nitinol® Vena Tech LP® Gunther Tulip® G2® Other: Cook Bird's nest, Bard Recovery	Temporary, permanent	NR	NR	NR	No
Gonzalez RP, 2006 <sup>10</sup>	Arm 2 (OR)	Greenfield Stainless Steel®	NR	Surgical residents	Bedside in operating room	NR	No
	Arm 3 (STICU)	Greenfield Stainless Steel®	NR	Surgical residents	ICU	NR	No
Hoff WS, 2004 <sup>15</sup>	Arm 2 (IVCF only)	Gunther Tulip® - 35	NR	NR	Interventional radiology	NR	No
Kurtoglu M, 2003 <sup>20</sup>	Arm 2 (Overall group)	Device name: VenaTech LGM®-10 Poliser- 1	Temporary and Permanent	Interventional Radiologist	Angiography room	NR	Patients continued to receive DVT prophylaxis with low-molecular-weight heparin during hospitalization
Langan EM, 1999 <sup>21</sup>	Arm 2 (IVCF)	Greenfield Stainless Steel®- not stated Greenfield Titanium®-not stated	NR	NR	NR	NR	SCD SC Heparin
Leach TA, 1994 <sup>22</sup>	Arm 2 (IVCF)	Greenfield Stainless Steel®- 205	NR	NR	NR	NR	No
Millward, S.F., 1994 <sup>28</sup>	No control/all arms were active	NR	Temporary (gunther)	NR	NR	NR	No
Nunn, C.R., 1997 <sup>29</sup>	Arm 2 (Overall group)	Greenfield Titanium®-49	NR	Vascular Surgeon, Assistance from experienced ultrasound	Bedside	NR	Lovenox 30mg sq bid



Author, Year	Arm Name	Filter name	Filter type (temp or permanent)	Filter placed by	Setting	Planned duration of filter	Concurrent therapy
				technician			
Offner, P.J., 2003 <sup>31</sup>	Arm 2 (IVCF)	Gunther Tulip <sup>®</sup>	Temp	Interventional Radiologist	Interventional radiology suite	14 days	Adjunctive measures, such as pneumatic compression devices, were used whenever possible Low-molecular-weight heparin therapy was instituted as soon as it was thought safe to do so by the attending physician and relevant consultants
Rogers, F.B., 1997 <sup>41</sup>	Arm 2 (IVCF only)	Greenfield Stainless Steel <sup>®</sup> -21 Greenfield Titanium <sup>®</sup> -93 Vena Tech LP <sup>®</sup> -10 Bird's nest filter-8	NR	NR	NR	NR	No
Rosenthal, D., 2005 <sup>44</sup>	Arm 2 (IVCF only)	Gunther Tulip <sup>®</sup> -38 OPTEASE <sup>®</sup> -35 Recovery -30	Retrievable (Temporary)	NR	103	NR	NR
Stefanidis D, 2006 <sup>53</sup>	Arm 2 (Overall group)	Gunther Tulip <sup>®</sup> G2 <sup>®</sup> OPTEASE <sup>®</sup> Recovery	Temporary	Interventional Radiologist, Trauma Surgeon, Vascular Surgeon	OR, ICU and interventional, radiology	1 month post hospital discharge	No
<i>Cohort-retro</i>							
Binkert CA, 2006 <sup>3</sup>	Arm 2 (Overall group)	Bard Recovery filter- 13 Intention to use	Temporary	NR	NR	NR	NR

Author, Year	Arm Name	Filter name	Filter type (temp or permanent)	Filter placed by	Setting	Planned duration of filter	Concurrent therapy
		filter (Temp. or Permanent): Temporary					
Carlin AM, 2002 <sup>5</sup>	Arm 2 (Prophylactic)	NR- 78	NR	Interventional Radiologist, Trauma Surgeon	NR	NR	No
Connors MS, 2002 <sup>7</sup>	Arm 2 (IVCF)	Greenfield Stainless Steel <sup>®</sup> -256 Simon Nitinol <sup>®</sup> -28 Gianturco-Roehm Bird's Nest <sup>®</sup> -2	NR	Vascular Surgeon	ICU, private rooms, vascular laboratories	NR	No
Doody O, 2009 <sup>8</sup>	Arm 2 (Overall group)	Celect <sup>®</sup> -115	Retrievable	NR	NR	NR	No
Duperier T, 2003 <sup>9</sup>	Arm 2 (Overall group)	Greenfield Titanium <sup>®</sup> -133	NR	Interventional Radiologist, Trauma Surgeon, only one placed by IR; the rest were trauma surgeons	OR (angiography suite in 1 patient)	NR	Pneumatic compression devices and/or graduated stockings Low molecular weight heparin (Lovenox) except patients with closed head injury and spinal cord injuries
Hermesen JL, 2008 <sup>14</sup>	Arm 2 (R-IVCF)	G2 <sup>®</sup> Bard Recovery	Temporary	Trauma Surgeon, Vascular Surgeon	NR	Removal occurred when patients were no longer at high risk for DVT/PE, had recovered completely from their injuries, and/or were able to be anticoagulated if indicated	No
Mahier A,	Arm 2 (Overall	Gunther Tulip <sup>®</sup>	Temp	Interventional	Angiography suite	2-3 weeks post	No

Author, Year	Arm Name	Filter name	Filter type (temp or permanent)	Filter placed by	Setting	Planned duration of filter	Concurrent therapy
2008 <sup>24</sup>	group)	OPTEASE <sup>®</sup>		Radiologist		insertion	
McMurtry AL, 1999 <sup>25</sup>	Arm 2 (PVCF during high VCF use)	NR	Permanent	Interventional Radiologist	Angiography suite	NR	SCDs, antiembolic stockings Adjusted dose heparin (IV)
	Arm 3 (PVCF during period of low VCF use)	NR	Permanent	Interventional Radiologist	Angiography suite	NR	SCDs, antiembolic stockings Adjusted dose heparin (IV)
	Arm 4 (PVCF [all])	NR	Permanent	Interventional Radiologist	NR	NR	SCDs, antiembolic stockings Adjusted dose heparin (IV)
Meier, C., 2006 <sup>27</sup>	Arm 2 (IVCF)	Gunther Tulip <sup>®</sup> - 65 OPTEASE <sup>®</sup> -30	Temporary (65), permanent (30)	Interventional Radiologist	Angiography suite	NR	High-thigh anti embolic stockings LDUH, LMWH, warfarin (in the absence of contraindications to anticoagulation)
Patton, J.H. Jr, 1996 <sup>32</sup>	Arm 2 (IVCF-acute complications)	Greenfield Titanium <sup>®</sup> -110	NR	Surgeons	Operating room	NR	prefilter and postfilter DVT prophylaxis using sequential compression devices unless they were unable to have compression boots placed prefilter and postfilter DVT prophylaxis consisting of SCH unless had a

Author, Year	Arm Name	Filter name	Filter type (temp or permanent)	Filter placed by	Setting	Planned duration of filter	Concurrent therapy
							contraindication to heparin
	Arm 3 (IVC filter - long-term)	Greenfield Titanium®-30	NR	Surgeons	Operating room	NR	prefilter and postfilter DVT prophylaxis using sequential compression devices unless they were unable to have compression boots placed prefilter and postfilter DVT prophylaxis consisting of SCH unless had a contraindication to heparin
Roberts, A., 2010 <sup>35</sup>	Arm 2 (IVCF)	NR	Temporary	Interventional Radiologist	Radiology suite	6-8 weeks	Patients were placed on subcutaneous lovenox or heparin 1 week after injury
Rosenthal D, 2004 <sup>46</sup>	Arm 2 (IVC filter only)	OPTEASE®	Temporary	Trauma Surgeon, Vascular Surgeon, general surgery resident	ICU bedside	NR	No
Rosenthal, D., 2006 <sup>45</sup>	Arm 2 (Overall group)	Gunther Tulip® OPTEASE® Recovery filters	Temp	NR	ICU, bedside, US guidance	Until anticoagulation safe	In patients with an initial contraindication to anticoagulation, LMWH was instituted as soon as it was believed to be safe by the attending

Author, Year	Arm Name	Filter name	Filter type (temp or permanent)	Filter placed by	Setting	Planned duration of filter	Concurrent therapy
							surgeon and pneumatic compression devices were used whenever possible.
Sekharan, J., 2001 <sup>47</sup>	Arm 2 (Follow up Patients)	Greenfield Stainless Steel®-33	NR	Interventional Radiologist, Trauma Surgeon, Vascular Surgeon, only 2 filters were inserted by Radiologists out of 108 baseline study population	NR	NR	Patient continued to receive DVT prophylaxis (Low dose subcutaneous heparin or Sequential Compression device) following filter placement
Tola JC, 1999 <sup>54</sup>	Arm 2 (IVC filter only)	Gianturco-Roehm Bird's Nest® Greenfield filter (type not specified) or B. Braun Vena Tech filter	NR	Surgery resident under supervision of trauma attending	25	NR	No
Wojcik R, 2000 <sup>56</sup>	Arm 2 (VCF Registry Patients), 105	Greenfield Stainless Steel®-72 (Green field Medi Tech) Simon Nitinol®-5 Bird's nest-28	NR	Interventional Radiologist Except 2 VCF (Who placed these filters not stated)	NR	NR	No
Zakhary EM, 2008 <sup>57</sup>	Arm 2 (All study populations)	Bard Peripheral Vascular, Recovery	Temp	Vascular Surgeon	Operating room in a single level 1 trauma center	Retrieval window of 180 days with contacting patients planned at 90d to arrange for retrieval	No
Zolfaghari D, 1995 <sup>58</sup>	Arm 2 (Patients Receiving an	VenaTech LGM®-45	NR	Vascular Surgeon	Operating Room	NA	No

Author, Year	Arm Name	Filter name	Filter type (temp or permanent)	Filter placed by	Setting	Planned duration of filter	Concurrent therapy
	IVC filter)						
<i>Case series/Case report</i>							
Bach JR, 1990 <sup>1</sup>	Arm 2 (IVC filter)	Greenfield Stainless Steel®-1	Permanent	NR	NR	NR	No
Benjamin ME, 1999 <sup>2</sup>	Arm 2 (IVC filter only)	Greenfield Titanium®-23	NR	NR	23	NR	Mechanical (17) and LMWH (4)
Bochicchio GV, 2001 <sup>4</sup>	Arm 2 (Case Report)	TRAPEASE®	NR	NR	NR	NR	No
Greenfield LJ, 2000 <sup>13</sup>	Arm 2 (IVCF -P), 249	Greenfield Stainless Steel®-131 patients Greenfield Titanium®-118 patients	NR	Interventional Radiologist	NR	NR (time from placement to last follow up is 2.4years	No
	Arm 3 (IVCF -T), 136	Greenfield Stainless Steel®-49 Greenfield Titanium®-87	NR	Interventional Radiologist	NR	Time from placement to last follow up is 1.9 years	No
Hughes GC, 1999 <sup>16</sup>	Arm 2 (Case 1)	Not specified	NR	NR	NR	NR	No
	Arm 3 (Case 2)	Not specified	NR	NR	NR	NR	No
Lo CH, 2008 <sup>23</sup>	Arm 2 (Overall group)	Gunther Tulip®-17	Temporary	NR	NR	NR	Compression on other (non-injured) 9 received enoxaparin, 1 received heparin Other: note- 16 prophylactic filters
Meier, C., 2006 <sup>26</sup>	Arm 2 (Overall group)	OPTEASE®	Temporary	Interventional Radiologist	Angiography suite	7 - 28 days	No
Phelan, H.A., 2009 <sup>33</sup>	Arm 2 (Overall group)	Greenfield Stainless Steel® Greenfield Titanium® One pt got non-	Permanent	Interventional Radiologist, Trauma Surgeon	NR	Permanent	No

Author, Year	Arm Name	Filter name	Filter type (temp or permanent)	Filter placed by	Setting	Planned duration of filter	Concurrent therapy
		Greenfield (not specified)					
Rogers, F., 2001 <sup>37</sup>	Arm 2 (Case Report)	Greenfield Stainless Steel®-1	NR	NR	NR	NR	No
Shang, E.K., 2011 <sup>48</sup>	Arm 2 (IVC filter only)	Gunther Tulip®-1	NR	NR	NR	NR	Heparin
Sing RF, 2001 <sup>49</sup>	Arm 2 (Case 1)	Vena Tech LP®-1	Temp	NR	NR	NR	No
	Arm 3 (Case 2)	Greenfield Stainless Steel®-1	Temp	NR	NR	NR	No
Sing, RF <sup>51</sup>	Arm 2 (IVCF)	Greenfield (6), Bird's Nest (2)	NR	Surgeons	Bedside in ICU	NR	No
<i>Prospective observational</i>							
Sing RF, 2001 <sup>50</sup>	Arm 2 (Study group)	Greenfield Stainless Steel®-8 Simon Nitinol® TRAPEASE® Greenfield Titanium® VenaTech LGM® Bird's Nest: 25; Simon Nitinol:5; TrapEase, 2 Green field filter:74	NR	Interventional Radiologist, General surgeon	ICU or Radiology dept	NR	NR
<i>Ambidirectional (retrospective and prospective studies)</i>							
Rogers, F.B., 1993 <sup>40</sup>	Arm 2 (IVCF)	Greenfield Stainless Steel®-32 Birds nest vena cava - 2	NR	NR	NR	NR	Venous compression boots

AIS= Abbreviated Injury Scale; BMI= Body Mass Index; CAT= Computed Axial Tomography; CT= Computed Tomography; CUS= Compression Ultrasonography; DGFI = duplex-guided IVC filter insertion; DVT= Deep Vein Thrombosis; GCS= Glasgow Coma Scale; ICU= Intensive Care Unit; IPG= Impedance Phlebography; ISS= Injury Severity Score; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; LE= Lower Extremity; PE= Pulmonary Embolism; OR= Operating Room; PGF= Prophylactic Greenfield Filter; P-IVCF= Prophylactic Inferior Vena Cava Filter; PVCf= Prophylactic Vena Cava Filter ;RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; SCD= Sequential Compression Device; SCI= Spinal Cord Injury; STICU=Surgical Trauma Intensive Care Unit; TBI= Traumatic Brain Injury; UFH= Unfractionated Heparin; USS= Ultrasound Scan; VCF= Vena Cava Filter; VTE= Venous Thromboembolism

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**Evidence Table 5. Patient-oriented Outcomes for KQ 1**

Author, Year	Outcome	Arm	N for analysis	Time point	Test to confirm DVT/PE	n (%) of Patients with Outcomes	n (%) of events	Measures of Association
Benjamin ME, 1999 <sup>1</sup>	Total DVT only	Arm 2 (P-IVCF only)	21 (Only 21 had prophylactic)	Hospital discharge	DVT: Ultrasonography	0 (0)	NR	NR
Bochicchio GV, 2001 <sup>2</sup>	NR	Arm 2 (Case Report – IVCF)	1	NR	DVT: Other	NR	NR	NR
	NR		1	NR	PE: Other	NR	NR	NR
Carlin AM, 2002 <sup>3</sup>	Total DVT only	Arm 2 (Prophylactic)	78	NR	NR	5 (6)	NR	NR
	Total PE only		78	NR	NR	0	NR	NR
Cherry RA, 2008 <sup>4</sup>	Total DVT only	Arm 2 (P-IVCF)	244	In hospital	DVT: Ultrasonography PE: CT scan	(9)	NR	NR
	Total PE only		244	In hospital	DVT: Ultrasonography PE: CT scan	4 (1.6)	NR	NR
Coners MS, 2002 <sup>5</sup>	Total PE only	Arm 2 (Overall)	284	NR	NR	1	NR	NR
Doody O, 2009 <sup>6</sup>	Total PE only	Arm 2 (IVCF)	115	2 months	DVT: Venography PE: CT angiography	1	NR	NR
	Lower extremity DVT		115	2 months	DVT: Venography PE: CT angiography	0	NR	NR
Duperier T, 2003 <sup>7</sup>	Total DVT only	Arm 2 (Overall)	133	NR	DVT: Ultrasonography PE: Autopsy	31	NR	NR
	Total PE only		133	NR	DVT: Ultrasonography PE: Autopsy	1	NR	NR
Gonzalez RP, 2005 <sup>8</sup>	Total VTE only	Arm 2 (OR))	NR	NR	NR	0	NR	NR
		Arm 3 (STICU)	No VTE	NR	NR	0	NR	NR
Gorman PH, 2009 <sup>9</sup>	Total DVT only	Arm 1 (control - No IVC filter)	58	In hospital	DVT: Ultrasonography	3 (5.2)	NR	p value: 0.021
		Arm 2 (IVC Filter)	54	In hospital	DVT: Ultrasonography PE: CT scan	11 (20.4)	NR	NR
	Total PE only	Arm 2 (IVC Filter)	54	In hospital	DVT: Ultrasonography PE: CT scan	1	NR	NR
Gosin JS, 1997 <sup>10</sup>	Total PE only	Arm 1 (control)	249	NR	PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy), Autopsy	12	NR	p value: <0.02
		Arm 2 (Heparin)	151	NR	PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy), Autopsy	4	NR	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Test to confirm DVT/PE	n (%) of Patients with Outcomes	n (%) of events	Measures of Association
		Arm 3 (IVCF)	99	NR	PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy), Autopsy	0	NR	NR
Greenfield LJ, 2000 <sup>11</sup>	Total DVT only	Arm 2 (Prophylactic Group)	197	NR	DVT: Ultrasonography PE: New PE=3; method of follow up include routine, autopsy, CT/cavogram	16 (10.8)	NR	NR
		Arm 3 (IVCF)	96	NR	DVT: Ultrasonography PE: Method of follow up include Routine, autopsy and CT/Cavogram	10 (8.6)	NR	NR
	PE	Arm 2 (Prophylactic Group)	197	NR	DVT: Ultrasonography PE: New PE=3; method of follow up include routine, autopsy, CT/cavogram	3 (1.5)	NR	NR
		Arm 3 (IVCF)	96	NR	DVT: Ultrasonography PE: Method of follow up include Routine, autopsy and CT/Cavogram	2 (2)	NR	NR
Hermesen JL, 2008 <sup>12</sup>	Total PE only	Arm 2 (R-IVC Filter)	92	NR	DVT: Ultrasonography PE: CT scan	3	NR	NR
Hoff WS, 2004 <sup>13</sup>	Total DVT only	Arm 2 (IVCF only)	35	Hospital discharge	DVT: Ultrasonography	3 (8.6)	NR	NR
	Total PE only		35	Hospital discharge	DVT: Ultrasonography	0 (0)	NR	NR
Hughes GC, 1999 <sup>14</sup>	PE	Arm 2 (Case 1)	1	Hospital discharge	NR	0 (0)	NR	NR
	Total VTE only	Arm 3 (Case 2)	1	Hospital discharge	NR	0 (0)	NR	NR
Karmy-Jones R, 2007 <sup>15</sup>	Total PE only	Arm 2 ( R-IVCF - all)	413	90 days	NR	2	NR	NR
	Total DVT only	Arm 4 (Prophylactic R-IVCF)	310	90 days	DVT: Ultrasonography	18 (20)	NR	NR
	Lower extremity DVT Distal		310	90 days	DVT: Ultrasonography	10 (2 iliofemoral & 8 suprapopliteal)	NR	NR
	Lower extremity DVT		310	90 days	DVT: Ultrasonography	8 (infrapopliteal)	NR	NR
Keller IS, 2007 <sup>16</sup>	PE	Arm 2 (Gunther Tulip)	92	Diagnosis made at 22 days	PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy)	2	2	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Test to confirm DVT/PE	n (%) of Patients with Outcomes	n (%) of events	Measures of Association
				and 1 year in the 2 cases of PE				
		Arm 3 (OptEase)	80	12 days after filter placement	PE: Angiography	1	1	NR
	Total DVT only	Arm 2 (Gunther Tulip)	92	Not specified	PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy)	1	1 patient in this arm had recurrent DVT but number not specified	NR
Khansarinia S, 1995 <sup>17</sup>	Total PE only	Arm 1 (control)	216	NR	DVT: Ultrasonography PE: Arteriography	13	NR	p value: <0.009
		Arm 2 (PGF)	108	NR	DVT: Ultrasonography PE: arteriography	0	NR	NR
Kurtoglu M, 2003 <sup>18</sup>	Total DVT only	Arm 2 (Overall)	11	17 months	DVT: Ultrasonography PE: Angiography	0	NR	NR
	Total PE only		11	17 months	DVT: Ultrasonography PE: Angiography	0	NR	NR
Langan EM, 1999 <sup>19</sup>	Total DVT only	Arm 2 (IVCF)	187	Hospital discharge	DVT: Ultrasonography PE: CT scan, VQ Scan (Ventilation/perfusion scan or lung scintigraphy)	24 (12.8)	NR	NR
	Total PE only		187	Hospital discharge	DVT: Ultrasonography PE: CT scan, VQ Scan (Ventilation/perfusion scan or lung scintigraphy)	1 (0.5)	NR	NR
Leach TA, 1994 <sup>20</sup>	Total DVT only	Arm 2 (IVCF)	201 patients (there 205 filters inserted)	NR	DVT: Method of diagnosis not reported	1	NR	NR
	PE		201 patients (there 205 filters inserted)	NR	DVT: Method of diagnosis not reported	0 (0)	NR	NR
Lo CH, 2008 <sup>21</sup>	Total PE only	Arm 2 (Gunther)	17	NR	PE: VQ Scan (Ventilation/perfusion scan	1	NR	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Test to confirm DVT/PE	n (%) of Patients with Outcomes	n (%) of events	Measures of Association
		Tulip)			or lung scintigraphy)			
	Upper extremity DVT		17	NR	PE: VQ Scan (Ventilation/perfusion scan or lung scintigraphy)	1	NR	NR
Mahier A, 2008 <sup>22</sup>	Lower extremity DVT	Overall Group	NR	NR	DVT: Ultrasonography	2	NR	NR
McMurtry AL, 1999 <sup>23</sup>	Total DVT only	Arm 4 (PVCF)	248	Period of study	PE: Angiography	6	NR	NR
		Arm 5 (All VCF [placed for prophylaxis and placed after 1]) episode of PE)	299	Period of study	PE: Angiography	9	NR	NR
	Total PE only	Arm 4 (PVCF)	248	Period of study	PE: Angiography	4	NR	NR
		Arm 5 (All VCF [placed for prophylaxis and placed after 1 episode of PE])	299	Period of study	PE: Angiography	6	NR	NR
Meier C, 2006 <sup>24</sup>	Total PE only	Arm 2 (OptEase)	37	30 days	DVT: Ultrasonography PE: CT scan	1	NR	NR
Meier C, 2006 <sup>25</sup>	Total DVT only	Arm 2 (IVCF)	95	Hospital discharge	DVT: Ultrasonography PE: CT scan	2	NR	NR
	Total PE only		95	21 days	DVT: Ultrasonography PE: CT scan	1	NR	NR
Milliard SF, 1994 <sup>26</sup>	Total PE only	Arm 2 (IVCF)	3	NR	PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy), Autopsy	0	NR	NR
Nunn CR, 1997 <sup>27</sup>	Total DVT only	Arm 2 (Greenfield Titanium)	49	Hospital discharge	NR	1	NR	NR
	Total PE only		49	Hospital discharge	NR	0	NR	NR
O'Keeffe T,	Total DVT only	Arm 2	91	90 days	DVT: Ultrasonography	10 (15 )	NR	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Test to confirm DVT/PE	n (%) of Patients with Outcomes	n (%) of events	Measures of Association
2011 <sup>28</sup>		(Trauma group)						
		Arm 3 (Non trauma group [control])	30	90 days	DVT: Ultrasonography	13 (43)	NR	NR
Offner PJ, 2003 <sup>29</sup>	Total PE only	Arm 2 (IVCF)	44	NR	PE: Angiography, helical computed tomography of the chest	0	NR	NR
	PE: Angiography, helical computed tomography of the chest		44	NR	PE: Angiography, helical computed tomography of the chest	NR	NR	NR
Patton JH Jr, 1996 <sup>30</sup>	Total PE only	Arm 2 (IVCF- acute complications )	110	NR	DVT: Ultrasonography PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy)	0	NR	NR
	Total DVT only	Arm 3 (IVC filter long term follow up)	110	Hospital discharge	DVT: Ultrasonography PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy)	7	NR	NR
		NR	30	4-42 months	DVT: Ultrasonography PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy)	30 (47)	14	NR
	Total PE only	NR	30	Hospital discharge	DVT: Ultrasonography PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy)	88 (0)	0	NR
Phelm HA, 2009 <sup>31</sup>	Total PE only	Arm 2	97	1 and 7 yrs post injury	NR	2 (2.1)	NR	NR
Rajasekhar A, 2011 <sup>32</sup>	Total DVT only	Arm 1 (control - No IVCF)	16	Hospital discharge	DVT: Ultrasonography PE:CT scan	0	NR	NR
		Arm 2 (Prophylactic IVCF)	18	Hospital discharge	DVT: Ultrasonography PE:CT scan	0 (0)	NR	NR
		Arm 1 (control - No IVCF)	16	30 days	DVT: Ultrasonography PE:CT scan	0	NR	NR
		Arm 2 (Prophylactic	18	30 days	DVT: Ultrasonography PE:CT scan	0 (0)	NR	NR



Author, Year	Outcome	Arm	N for analysis	Time point	Test to confirm DVT/PE	n (%) of Patients with Outcomes	n (%) of events	Measures of Association
		IVCF)						
		Arm 1 (control - No IVCF)	16	6 month follow up	DVT: Ultrasonography PE:CT scan	0	NR	NR
		Arm 2 (Prophylactic IVCF)	18	6 month follow up	DVT: Ultrasonography PE:CT scan	1	NR	NR
	Total PE only	Arm 1 (control - No IVCF)	16	Hospital discharge	DVT: Ultrasonography PE:CT scan	0	NR	NR
		Arm 2 (Prophylactic IVCF)	18	Hospital discharge	DVT: Ultrasonography PE:CT scan	0 (0)	NR	NR
		Arm 1 (control - No IVCF)	16	30 days	DVT: Ultrasonography PE:CT scan	0	NR	NR
		Arm 2 (P-IVCF)	18	30 days	DVT: Ultrasonography PE:CT scan	0 (0)	NR	NR
		Arm 1 (control - No IVCF)	16	6 month follow up	DVT: Ultrasonography PE:CT scan	1	NR	NR
		Arm 2 (P-IVCF)	18	6 month follow up	DVT: Ultrasonography PE:CT scan	0 (0)	NR	NR
Roberts A, 2010 <sup>33</sup>	Total VTE only	Arm 2	45	6 -8 weeks		0	NR	NR
Rodriguez JL, 1996 <sup>34</sup>	Lower extremity DVT	Arm 1 (control)	80	NR	DVT: Ultrasonography PE: Arteriogram	15	NR	NR
		Arm 2 (VCF)	40	NR	DVT: Ultrasonography PE: Arteriogram	6	NR	NR
	Total PE only	Arm 1 (control)	80	NR	DVT: Ultrasonography PE: Arteriogram	14	NR	Odd ratio: 8.27 95%CI:1.40 48.8 p value: 0.02
		Arm 2 (VCF)	40	NR	DVT: Ultrasonography PE: Arteriogram	1	NR	Odd ratio: 8.27 95% CI:1.40 48.8 p value: 0.02
Rogers FB, 1993 <sup>37</sup>	Total DVT only	Arm 2 (IVCF)	34	NR	DVT: Plethysmography	6 (17.6)	NR	NR
	PE		34	NR	DVT: Plethysmography	0 (0)	NR	NR
Rogers FB, 1995 <sup>36</sup>	Total PE only	Arm 2 (IVCF)	63	NR	DVT: Ultrasonography, Plethysmography PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy)	1	NR	NR
	Total DVT only		63	NR	DVT: Ultrasonography, Plethysmography	13	NR	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Test to confirm DVT/PE	n (%) of Patients with Outcomes	n (%) of events	Measures of Association
					PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy)			
Rogers FB, 1997 <sup>35</sup>	Total PE only	Arm 1 (control)	905	Hospital discharge	PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy)	1	NR	NR
		Arm 2 (IVCF)	35	Hospital discharge	PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy)	1	NR	NR
Rogers FB, 1997 <sup>38</sup>	Total PE only	Arm 2 (IVCF only)	132	Hospital discharge	DVT: Ultrasonography PE: Angiography, Autopsy, Abdominal ultrasonography	3 (2.3)	NR	NR
	Total DVT only		132	Hospital discharge	DVT: Ultrasonography PE: Angiography, Autopsy, Abdominal ultrasonography	12 (9)	NR	NR
Rosenthal D, 2004 <sup>42</sup>	Lower extremity DVT Proximal	Arm 2 (IVCF)	94	Within 2 weeks	DVT: Ultrasonography	1	NR	NR
	PE		94	After filter retrieval time unspecified	DVT: Ultrasonography	1	NR	NR
Rosenthal D, 2005 <sup>40</sup>	Total PE only	Arm 2 (IVCF only)	103	Hospital discharge	DVT: Ultrasonography PE: CT scan	1	NR	NR
	Total DVT only	Arm 2 (IVCF only)	103	Hospital discharge	DVT: Ultrasonography PE: CT scan	2	NR	NR
		Arm 3 (Subset of patients who underwent uneventful filter removal)	44	Hospital discharge	DVT: Ultrasonography	3	NR	NR
Rosenthal D, 2006 <sup>41</sup>	Lower extremity DVT	Arm 2 (Gunther Tulip)	NR	NR	DVT: Ultrasonography PE: CT scan	4	NR	NR
	PE		NR	NR (following filter retrieval)	DVT: Ultrasonography PE: CT scan	1	NR	NR
Rosenthal D, 2009 <sup>39</sup>	Total DVT only	Arm 2 (Gunther Tulip)	97	NR	PE:CT scan	2	NR	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Test to confirm DVT/PE	n (%) of Patients with Outcomes	n (%) of events	Measures of Association
	Total PE only	Arm 2 (Gunther Tulip)	97	NR	PE:CT scan	1	NR	NR
		Arm 3 (Celect)	90	NR	NR	1	NR	p value: >0.20
Sekharan J, 2001 <sup>43</sup>	Total DVT only	Arm 2 (Data available for follow up participants)	33	End of follow up	DVT: Ultrasonography PE: No PE	2 (6)	NR	NR
	PE		33	End of follow up	DVT: Ultrasonography PE: No PE	0 (0)	NR	NR
Shang EK, 2011 <sup>44</sup>	Total PE only	Arm 2 (IVCF only)	1	5 years after IVCF placement	PE: CT angiography	0	NR	NR
	Total DVT only		1	5 years after IVCF placement	PE: CT angiography	0	NR	NR
Sing RF <sup>46</sup>	Total DVT only	Arm 2 (IVCF)	8	3weeks post IVCF insertion	DVT: Autopsy	1	NR	NR
Sing RF, 2001 <sup>45</sup>	Total DVT only	Arm 2 (IVCF)	158	NR	DVT: Ultrasonography PE: 1 by pulmonary arteriography	8	NR	NR
	Total PE only	Arm 2 (IVCF)	158	NR	DVT: Ultrasonography PE: 1 by pulmonary arteriography	1	NR	NR
Smoot RL, 2010 <sup>47</sup>	Total DVT only	Arm 2 (Permanent)	86	NR	NR	NR	NR	NR
	Total PE only	Arm 2 (Permanent)	86	Follow up median of 11 months	NR	2	NR	NR
		Arm 3 (Retrievable)	140	Follow up median of 11 months	NR	6	NR	NR
Stefanidis D, 2006 <sup>48</sup>	Lower extremity DVT	Arm 2 (IVCF)	83	Hospital discharge	DVT: Ultrasonography	2	NR	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Test to confirm DVT/PE	n (%) of Patients with Outcomes	n (%) of events	Measures of Association
	Upper extremity DVT		83	Hospital discharge	DVT: Ultrasonography	1	NR	NR
	PE		83	60 days post hospital discharge	DVT: Ultrasonography	0	NR	NR
Tola JC, 1999 <sup>49</sup>	PE	Arm 2 (IVCF only)	25	Hospital discharge	NR	0 (0)	NR	NR
Wilson JT, 1994 <sup>50</sup>	Total PE only	Arm 1 (control)	111	NR	PE: Angiography, VQ Scan (Ventilation/perfusion scan or lung scintigraphy), Autopsy	7 (6.3)	8	NR
		Arm 2 (Greenfield Titanium)	15	Hospital discharge	NR	0	NR	NR
	Total DVT only	Arm 2 (Greenfield Titanium)	15	NR	NR	0	NR	NR
Wojcik R, 2000 <sup>51</sup>	Total DVT only	Arm 2 (VCF Registry Patients)	105	NR	DVT: Ultrasonography	28/64 patients who had VCF inserted for prophylactic indications	NR	NR
Wojcik R, 2000 <sup>51</sup>	PE	Arm 2 (VCF Registry Patients)	105	NR	DVT: Ultrasonography PE: No PE	0	NR	NR
Zakhary EM, 2008 <sup>52</sup>	Lower extremity DVT	Arm 2 (IVCF)	122	90-360	DVT: Venography, Ultrasonography	116	9	NR
			116	90 -360	DVT: Venography	NR	9	NR
			116	NR	DVT: Venography	NR	9	NR
			116	NR	DVT: Ultrasonography	9 (7.8)	NR	NR
			116	90 -360	DVT: Ultrasonography	9 (7.8)	9	NR
Zolfaghari D, 1995 <sup>53</sup>	PE	Arm 2 (Patients Receiving an IVC filter)	45	NR	PE: No post placement PEs in any of the 45 patients who received a filter	0	0	NR

AIS= Abbreviated Injury Scale; BMI= Body Mass Index; CAT= Computed Axial Tomography; CT= Computed Tomography; CUS= Compression Ultrasonography; DGFI = duplex-guided IVC filter insertion; DVT= Deep Vein Thrombosis; GCS= Glasgow Coma Scale; ICU= Intensive Care Unit; IPG= Impedance Phlebography; ISS= Injury Severity Score; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; LE= Lower Extremity; PE= Pulmonary Embolism; OR= Operating Room; PGF= Prophylactic Greenfield Filter; P-IVCF= Prophylactic Inferior Vena Cava Filter; PVCF= Prophylactic Vena Cava Filter ;RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; SCD= Sequential Compression Device; SCI= Spinal

Cord Injury; STICU=Surgical Trauma Intensive Care Unit; TBI= Traumatic Brain Injury; UFH= Unfractionated Heparin; USS= Ultrasound Scan; VCF= Vena Cava Filter; VTE= Venous Thromboembolism

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**Evidence Table 6. Other Patient-oriented Outcomes for KQ 1**

Author, Year	Outcome	Arm	N for Analysis	Time Point	Definition	N(%) of Patients with Outcomes	N Events	Mean/Median /Range	Measures of Association
Benjamin ME, 1999 <sup>1</sup>	Cost of therapy	Arm 2 (P-IVCF only)	23	Hospital discharge	Average charge of bedside DGFI	NR	NR	Mean: \$3200	NR
	Fatal PE	Arm 2 (P-IVCF only)	23	Hospital discharge	Deaths due to PE	0 (0)	NR	NR	NR
	Total Mortality	Arm 2 (P- IVCF only)	23	Hospital discharge	3 in hospital deaths	0 (0)	NR	NR	NR
Binkert CA, 2006 <sup>2</sup>	Filter retrieval rate	Arm 2 (Overall)	13	>180 days after IVCF insertion	Filter retrieval rate after 6 months	13(100)	NR	NR	NR
Bochicchio GV, 2001 <sup>3</sup>	Total Mortality	Arm 2 (Case Report)	1	NR	Died 3.5 weeks after admission	1	NR	NR	NR
Carlin AM, 2002 <sup>4</sup>	Total Mortality	Arm 2 (Prophylactic)	78	NR	NR	2 (4)	NR	NR	NR
	Length of hospital stay		78	NR	NR	NR	NR	NR	NR
Cherry RA, 2008 <sup>5</sup>	Filter retrieval rate	Arm 2 (P-IVCF)	140	18 months	Of all retrievable filters inserted (140)	82 (58.6)	NR	NR	NR
Conners MS, 2002 <sup>6</sup>	Total Mortality	Arm 2 (Overall)	284	NR	NR	36	NR	NR	NR
	Cost of therapy		284	NR	NR	NR	NR	Mean: \$2170	NR
Doody O, 2009 <sup>7</sup>	Filter retrieval rate	Arm 2	115	2 months	Successful retrieval rate from attempted retrieval	57 (49.6)	NR	NR	NR
Duperier T, 2003 <sup>8</sup>	Total Mortality	Arm 2 (IVCF)	133	NR	From injuries (not including the fatal PE)	4	NR	NR	NR
	Fatal PE		133	NR	NR	1	NR	NR	NR
Greenfield LJ, 2000 <sup>9</sup>	Total Mortality	Arm 2 (Prophylactic group) (IVCF)	249	NR	NR	(15.6)	NR	NR	NR
		Arm 3 (IVCF)	136	NR	NR	( 22)	NR	NR	NR
	Length of hospital stay	Arm 2 (Prophylactic group)	249	NR	NR	NR	NR	Mean: 33.8 Range: 1-181	NR
		Arm 3 (IVCF)	136	NR	NR	NR	NR	Mean: 38.5 days Range: 6-118	NR
	Length of ICU stay -days	Arm 2 (Prophylactic	249	NR	NR	NR	NR	Mean:14.1 Range:1-150	NR

Author, Year	Outcome	Arm	N for Analysis	Time Point	Definition	N(%) of Patients with Outcomes	N Events	Mean/Median /Range	Measures of Association
		group) (IVCF)							
		Arm 3 (IVCF)		NR	NR	NR	NR	Mean: 15.4 Range: 2-93	NR
Hermesen JL, 2008 <sup>10</sup>	Total Mortality	Arm 2 (R-IVC Filter)	92	NR	NR	4	NR	NR	NR
	Filter retrieval rate		NR	NR	Based on 39 patients with attempted removal	30 (77)	NR	NR	NR
Hoff WS, 2004 <sup>11</sup>	Filter retrieval rate	Arm 2 (IVC filter only)	35	Hospital discharge	NR	18 (51.4)	NR	NR	NR
Karmy-Jones R, 2007 <sup>12</sup>	Total Mortality	Arm 3(P-IVCF)	172	Hospital discharge	Deaths before discharge	18	NR	NR	NR
	Filter retrieval rate	Arm 2 (R-IVCF [all])	413	90 days	Number of filters retrieved	90 (22)	NR	NR	NR
	Total Mortality		446	Hospital discharge	Death before hospital discharge	33	NR	NR	NR
Keller IS, 2007 <sup>13</sup>	Filter retrieval rate	Arm 2 (Gunther Tulip)	92	NR	NR	46 (49)	NR	NR	NR
		Arm 3 (OptEase)	83	NR	NR	58 (70)	NR	NR	NR
Khansarinia S, 1995 <sup>14</sup>	Total Mortality	Arm 1 (control)	216	NR	NR	47 (22)	NR	NR	P value: 0.28 Ref group: Arm 2-PGF
		Arm 2 (PGF)	108	NR	NR	18 (16)	NR	NR	NR
	Fatal PE	Arm 1 (control)	216	NR	NR	9	NR	NR	P value: <0.03 Ref group: Arm 2-PGF
		Arm 2 (PGF)	108		NR	0	NR	NR	NR
Langan EM, 1999 <sup>15</sup>	Total Mortality	Arm 2 (IVCF)	187	NR	23 in hospital, 4 after discharge	27 (14.4)	NR	NR	NR
Leach TA, 1994 <sup>16</sup>	Total Mortality	Arm 2 (IVCF)	201	NR	IBE death without filter, despite two attempts to place filter procedure failed	1	NR	NR	NR
Lo CH, 2008 <sup>17</sup>	Total Mortality	Arm 2 (Gunther Tulip)	17	NR	NR	1	NR	NR	NR
	Filter retrieval rate		16	NR	NR	13	NR	NR	NR

Author, Year	Outcome	Arm	N for Analysis	Time Point	Definition	N(%) of Patients with Outcomes	N Events	Mean/Median /Range	Measures of Association
	Length of hospital stay		17	NR	NR	NR	NR	Mean: 36.4 Range: 9-100	NR
Mahrer A, 2008 <sup>18</sup>	Filter retrieval rate	Arm 2 (Gunther Tulip)	80	Filter retrieval 7-19 days after insertion	NR	29 (36)	NR	NR	NR
McMurtry AL, 1999 <sup>19</sup>	Total Mortality	Arm 4 (PVCF - all)	248	Period of study	Deaths in PVCF patients (none was due to PE)	31 (13)	NR	NR	NR
	Fatal PE	Arm 3 (PVCF during low VCF use)	22	Period of study	Deaths in patients diagnosed with PE	8 (0.06)	NR	NR	NS Ref group: Arm 2-PVCF during high VCF use
	Fatal PE	Arm 2 (PVCF during high VCF use)	NR	Period of study	Deaths in patients diagnosed with PE	11 (0.07)	NR	NR	NS Ref group: Arm 3-PVCF during low VCF use
McMurtry AL, 1999 <sup>19</sup>	Fatal PE	Arm 4 (PVCF - all)	248	Period of study	Deaths in patients diagnosed with PE	19	NR	NR	NR
	Fatal PE	Arm 3 (PVCF during low VCF use)	22	Period of study	deaths in patients diagnosed with PE	8	NR	NR	NR
Meier C, 2006 <sup>20</sup>	Total Mortality	Arm 2 (IVCF)	37	30 days	From severe brain injury	1	NR	NR	NR
	Filter retrieval rate		37	30 days	NR	32 (86)	NR	NR	NR
Meier C, 2006 <sup>21</sup>	Total Mortality	Arm 2 (IVCF)	95	NR	NR	( 7.4)	NR	NR	NR
	Length of hospital stay		95	Hospital discharge	NR	NR	NR	Median: 26 days Range: 6-159 days	NR
	Length of ICU stay -days		95	Hospital discharge	NR	NR	NR	Median: 11 days Range: 1-50 days	NR
	Filter retrieval rate		67	NR	NR	65 (97)	NR	NR	NR

Author, Year	Outcome	Arm	N for Analysis	Time Point	Definition	N(%) of Patients with Outcomes	N Events	Mean/Median /Range	Measures of Association
	Fatal PE		95	Hospital discharge	NR	0	NR	NR	NR
Millward SF, 1994 <sup>22</sup>	Total Mortality	Arm 2 (IVCF)	3	NR	NR	0	NR	NR	NR
Nunn CR, 1997 <sup>23</sup>	Cost of therapy	NR	49	Hospital discharge	Cost reduction of -\$1,481 and -\$2,432 per patient versus radiology and OR IVCF placement respectively	NR	NR	Mean: \$3508/patient	NR
O'Keeffe T, 2011 <sup>24</sup>	Filter retrieval rate	Arm 2 (Trauma group)	91	90 days	Filter retrieval rate at the 3 month check up after hospital discharge	( 47 )	NR	NR	p value: <0.001 Ref group: Arm 3-non trauma (control) group
		Arm 3 (Non-trauma group [control])	76	90 days	Filter retrieval rate at the 3 month check up after hospital discharge	( 8 )	NR	NR	p value: <0.001 Ref group: Arm 2-trauma group
Offner PJ, 2003 <sup>25</sup>	Total Mortality	Arm 2 (IVC filter)	44	NR	NR	0	NR	NR	NR
Patton JH Jr, 1996 <sup>26</sup>	Total Mortality	Arm 2 (IVCF – acute complications),	110	Hospital discharge	NR	22	NR	NR	NR
	Post-thrombotic syndrome	NR	30	4-42 months	Signs and symptoms of venous insufficiency	30	11	NR	NR
		Arm 2(IVCF – acute complications),	30	NR	NR	14	NR	NR	NR
Phelm HA, 2009 <sup>27</sup>	Total Mortality	Arm 2 (IVCF)	97	NR	NR	15	NR	NR	NR
	Fatal PE			NR	NR	1	NR	NR	NR
Rajasekhar	Total Mortality	Arm 1 (control -	18	6 month	Non VTE related	0(0)	NR	NR	NR

Author, Year	Outcome	Arm	N for Analysis	Time Point	Definition	N(%) of Patients with Outcomes	N Events	Mean/Median /Range	Measures of Association
A, 2011 <sup>28</sup>		no IVCF)		follow up	mortality				
		Arm 2(P-IVCF)	18	6 month follow up	Non VTE related mortality	1	NR	NR	NR
		Arm 1 (control - no IVCF)	18	6 month follow up	VTE related mortality	0 (0)	NR	NR	NR
		Arm 2 (P- IVCF)	18	6 month follow up	VTE related mortality	0 (0)	NR	NR	NR
Roberts A, 2010 <sup>29</sup>	Filter retrieval rate	Arm 2 (IVCF)	45	6-8 weeks post IVCF insertion	NR	17 ( 37)	NR	NR	NR
Rodriguez JL 1996 <sup>30</sup>	Fatal PE	Arm 1 (control - No VCF)	80	NR	NR	8	NR	NR	Odd ratio: 6.82 95% CI: 0.27-170.3 P value: 0.258 Ref group: Arm 2 VCF
		Arm 2 (VCF)	40	NR	NR	0	NR	NR	NR
	Total Mortality	Arm 1 (control - no VCF)	80	NR	NR	13	NR	NR	Odd ratio: 3.35 95% CI: 0.73-15.3 p value: 0.175
		Arm 2 (VCF)	40	NR	NR	2	NR	NR	NR
Rogers FB, 1993 <sup>33</sup>	Total Mortality	Arm 2 (IVCF)	NR	NR	2 patients died of their injury during the course of study	2	NR	NR	NR
Rogers FB, 1995 <sup>32</sup>	Fatal PE	Arm 2 (PVCF)	63	After discharge	NR	1	NR	NR	NR
	Total Mortality	Arm 2 (PVCF)	63	After discharge	NR	(4.8)	NR	NR	NR
		Arm 3 (all patients)	3088	After discharge		(2.9)	NR		
Rogers FB, 1997 <sup>31</sup>	Total Mortality	Arm 1 (control)	905	Hospital discharge	All-cause mortality	(5.1)	NR	NR	NR

Author, Year	Outcome	Arm	N for Analysis	Time Point	Definition	N(%) of Patients with Outcomes	N Events	Mean/Median /Range	Measures of Association
		Arm 2 (IVCF)	35	Hospital discharge	All-cause mortality	(11.4)	NR	NR	NR
Rogers FB, 1997 <sup>34</sup>	Fatal PE	Arm 1 (control), 132	Hospital discharge	Hospital discharge	Saddle embolus which was fatal	1	NR	NR	NR
	Total Mortality		NR	NR	NR	( 4.4)	NR	NR	NR
Rosenthal D, 2004 <sup>39</sup>	Filter retrieval rate	Arm 2 (IVC Filter)	94	19+/- 1 days	Filters successfully retrieved	31	NR	NR	NR
	Total Mortality			Hospital discharge	NR	19	NR	NR	NR
Rosenthal D, 2005 <sup>37</sup>	Filter retrieval rate	Arm 2 (IVCF only)	103	Hospital discharge	NR	44	NR	NR	NR
	Total Mortality		103	Hospital discharge	Died of their injuries	24	NR	NR	NR
Rosenthal D, 2006 <sup>38</sup>	Total Mortality	Arm 2 (IVCF)	127		39 patients died of their injuries after filter placement	39	NR	NR	NR
	Filter retrieval rate		NR	NR	NR	66	NR	NR	NR
Rosenthal D, 2007 <sup>36</sup>	Filter retrieval rate	Arm 2 (Filter dwell times <180days)	NR	NR	NR	60 (60)	NR	NR	P value: 0.367 Ref group: Arm 3
			64	NR	NR	60	NR	NR	Ref group: Arm 3
		Arm 3(Filter dwell times >180 days)	41	NR	NR	31 (76)	NR	NR	NR
Rosenthal D, 2009 <sup>35</sup>	Total Mortality	Arm 2 (Gunther Tulip)	97	90 days	Unrelated to VTE	29	NR	NR	NR
		Arm 3 (Celect)	90	NR	Unrelated to VTE	10	NR	NR	NR
	Filter retrieval rate	Arm 2(Gunther Tulip)	NR	End of study	NR	27	27/ 50 retrievals attempted were retrieved	NR	NR
	Filter retrieval	Arm 3(Celect)	NR	NR	NR	55	55/65	NR	NR

Author, Year	Outcome	Arm	N for Analysis	Time Point	Definition	N(%) of Patients with Outcomes	N Events	Mean/Median /Range	Measures of Association
	rate						attempted were retrieved		
Sekharan J, 2001 <sup>40</sup>	Total Mortality	Arm 2 (Follow up patients)	108 (Overall)	During study period	During the study period 18 out of 108 patients died	18 (17)	NR	NR	NR
	Fatal PE		108	During study period	Autopsies and medical records were available in 12 of these 18 (67%) patients, and these showed no evidence of PE. The remaining six patients did not clinically have signs or symptoms of a PE before their death, and other causes of their mortality were listed on their death certificates.	NR	NR	NR	NR
Shang EK, 2011 <sup>41</sup>	Total Mortality	Arm 2 (IVC Filter only)	1	5 years after IVCF placement	NR	0	NR	NR	NR
Sing RF, 2001 <sup>42</sup>	Total Mortality	Arm 2 (IVCF)	158		No deaths attributable to IVCF or venograms	18 (11)	NR	NR	NR
Sing RF <sup>43</sup>	Total Mortality	Arm 2 (IVCF)	8	3 weeks post IVCF insertion	Acute myocardial infarction unrelated to IVCF insertion	1	NR	NR	NR
Stefanidis D, 2006 <sup>44</sup>	Total Mortality	Arm 2 (IVCF)	83	Hospital discharge	Unrelated to VCF	3 (4)	NR	NR	NR
	Length of		NR	Hospital	NR		NR	Mean: 30	NR

Author, Year	Outcome	Arm	N for Analysis	Time Point	Definition	N(%) of Patients with Outcomes	N Events	Mean/Median /Range	Measures of Association
	hospital stay			discharge				days (SD 21 days)	
	Filter retrieval rate		NR	30 days post discharge	NR	47 (57)	NR	NR	NR
Tola JC, 1999 <sup>45</sup>	Cost of therapy	Arm 2 (IVC filter only)	25	Hospital discharge	Savings when IVC filter is placed at bedside/ICU compared to OR	NR	NR	Mean: \$1844	NR
	Total Mortality		25	Hospital discharge	four from the trauma group (all in the ICU)	4	NR	NR	NR
	Cost of therapy		25	Hospital discharge	Savings when IVC filter is placed at bedside/ICU compared to Radiology suite	NR	NR	Mean: \$2245	NR
	Total Mortality		25	Hospital discharge	NR	0 (0)	NR	NR	NR
Wilson JT, 1994 <sup>46</sup>	Fatal PE	Arm 1 (control)	111	NR	NR	3 (2.7)	NR	NR	NR
		Arm 2 (IVCF)	15	NR	NR	0	NR	NR	NR
Wojcik R, 2000 <sup>47</sup>	Total Mortality	Arm 2 (105 VCF Registry Patients)	191(total number of patients who had VCF placed during the study period)	NR	13/191 patients had in-hospital death	13 (6.8)	NR	NR	NR
	Length of hospital stay		105(Demographics of 105 VCF Registry patients Table 1 of article)	NR	NR	NR	NR	Mean: 36.5 days Range: 3-476	NR
Zakhary EM, 2008 <sup>48</sup>	Filter retrieval rate	Arm 2 (IVCF)	116	90-360	NR	47 (40.5)	NR	NR	NR
Zolfaghari D, 1995 <sup>49</sup>	Total Mortality	Arm 2 (no complications from filter placement)	45	NR	Declared brain dead 2 days after filter placement	1	NR	NR	NR



DVT= Deep Vein Thrombosis; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; NS= Not Significant; PE= Pulmonary Embolism; PGF= Prophylactic Greenfield Filter; P-IVCF= Prophylactic Inferior Vena Cava Filter; PVCF= Prophylactic Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; SCD= Sequential Compression Device; VCF= Vena Cava Filter; VTE= Venous Thromboembolism

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**Evidence Table 7. Adverse Events for KQ 1**

Author, Year	Outcome	Arm	N for analysis	Time point	Definition	n (%) of Patients with Outcomes	n Events
Bach JR, 1990 <sup>1</sup>	Filter complications-Filter misplacement	Arm 2 (IVCF)	1	NR	Filter discharged prematurely and migrated to near the SA node	1	NR
Benjamin ME, 1999 <sup>2</sup>	Bleeding-Other - IVC or insertion site thrombosis	Arm 2 (P-IVCF only)	23	Hospital discharge	NR	0 (0)	NR
			23	Hospital discharge	NR	0 (0)	NR
	Filter complications-Filter misplacement		23	Hospital discharge	Early filter complication (filter misplacement)	1	NR
			23	Hospital discharge	NR	1	NR
Binkert CA, 2006 <sup>3</sup>	Filter complications-Filter tilting	Arm 2 (IVCF)	13	>180 days post IVCF insertion	3-25 degree tilt	8 (61.5)	NR
	Filter complications-Migration		13	>180 days post IVCF insertion	NR	0 (0)	NR
	Filter complications-Filter parts malpositioned		13	>180 days post IVCF insertion	Filter arm and leg pointing outside the IVC	1	NR
	Filter complications- Mild IVC stenosis		13	>180 days post IVCF insertion	29% IVC diameter reduction	1	NR
	Filter complications-thrombosis - 0		13	>180 days post IVCF insertion	NR	0 (0)	NR
Bochicchio GV 2001 <sup>4</sup>	Bleeding-Major bleeding	Arm 2 (Case Report)	NR	NR	Coming from the IVC	1	NR
	Filter complications-Perforation		1	NR	Multiple perforations created by the struts of IVCF	NR	NR
	Infections		NR	NR	NR	NR	NR
Carlin AM, 2002 <sup>5</sup>	Infections	Arm 2	78	NR	Sepsis	2	NR
Cherry RA, 2008 <sup>6</sup>	Filter complications-Migration	Arm 2 (P-IVCF)	244	NR	NR	2	NR
	Filter complications-Filter tilt		244	NR	NR	1	NR
	Filter complications-Strut fracture		244	NR	NR	2	NR
	Filter complications-thrombosis IVC		244	NR	NR	3	NR
Connors MS, 2002 <sup>7</sup>	Bleeding-Non-serious bleeding	Arm 2 (IVCF)	284	NR	NR	1	NR
	Filter complications-Filter misplacement		284	NR	NR	6 (2)	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Definition	n (%) of Patients with Outcomes	n Events
	Filter complications-Migration		284	NR	NR	1	NR
	Filter complications-IVC occlusion		NR	NR	NR	3 (1)	NR
	Filter complications-thrombosis - Access site		284	NR	NR	1	NR
Doody O, 2009 <sup>8</sup>	Filter complications-Filter penetration	Arm 2 (IVCF), 115	61	2 months	Two patients had filter penetration	2	NR
	Filter complications- Rt IJ occlusion		61	2 months	NR	1	NR
	Filter complications-Strut fracture		61	2 months	Secondary strut fracture	1	NR
	Filter complications-thrombosis - Filter associated thrombosis		61	2 months	NR	15	NR
Duperier T, 2003 <sup>9</sup>	Filter complications-Thrombus within inserted GF	Arm 2 (IVCF)	133	68 days post insertion	NR	1	NR
	Filter complications-thrombosis - IVC occlusion		NR	NR	NR	0	NR
Gonzalez RP, 2006 <sup>10</sup>	Filter complications-Migration	Arm 2 (OR)	78	NR	Vertebra level migration of filter	1	NR
		Arm 3 (STICU)	56	NR	One-half vertebra level of filter migration after deployment	1	NR
	Filter complications-Incorrect deployment in OR	Arm 2 (OR)	78	NR	NR	1	NR
	Filter complications- SVT during filter insertion	Arm 3 (STICU)	NR	NR	NR	1	NR
Greenfield LJ, 2000 <sup>11</sup>	Bleeding-Non-serious bleeding	Arm 2	249	NR	None required intervention	2 (0.8)	NR
		Arm 3	136	NR	Not required intervention	1 (0.7)	NR
	Filter complications-Migration	Arm 2	197	NR	NR	2 (1.4)	NR
		Arm 3	96	NR	NR	4 (4.6)	NR
	Filter complications-filter occlusion	Arm 2	197	NR	NR	5 (3.5)	NR
		Arm 3	96	NR	NR	2 (2.3)	NR
	Filter complications-	Arm 2	197	NR	Caval penetration	0 (0)	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Definition	n (%) of Patients with Outcomes	n Events
	Perforation	Arm 3	96	NR	Caval penetration	2 (2.3)	NR
	Filter complications-thrombosis - insertion site thrombosis	Arm 2	197	NR	NR	3 (2)	NR
		Arm 3	96	NR	NR	5 (5.8)	NR
Hermesen JL, 2008 <sup>12</sup>	Filter complications-intractable abdominal pain due to strut penetrating duodenum	Arm 2	92	NR	NR	1	NR
Hoff WS, 2004 <sup>13</sup>	NR	Arm 2 (IVCF only)	35	Hospital discharge	No complications observed	NR	NR
Hughes GC, 1999 <sup>14</sup>	Filter complications	Arm 2 (Case 1)	1	Hospital discharge	NR	0	NR
		Arm 3 (Case 2)	1	Hospital discharge	NR	0 (0)	NR
Karmy-Jones R, 2007 <sup>15</sup>	Filter complications	Arm 2 (R-IVCF)			NR	NR	NR
	Filter complications-Migration	Arm 2 (R-IVCF)	413	90 days	NR	3	NR
		Arm 3 (P-IVCF)	172	90 days	NR	0 (0)	NR
	Filter complications-thrombosis - symptomatic caval occlusion	Arm 2 (R-IVCF)	413	90 days	NR	6	NR
		Arm 3 (P-IVCF)	172	90 days	NR	0 (0)	NR
Keller IS, 2007 <sup>16</sup>	Filter complications	Arm 2 (Gunther Tulip)	6282	NR	Study did not report complication	NR	NR
		Arm 3 (OptEase)	608,067	NR	study did not report complication	NR	NR
	Filter complications-Migration	Arm 2(Gunther Tulip)	93	NR	migration in a caudal direction by half a vertebra (15mm)	1	1
	Filter complications-Acute caval occlusion	Arm 2 (Gunther Tulip)	NR	NR	NR	(7)	NR
		Arm 3(OptEase)	NR	NR	NR	(3)	NR
	Filter complications-thrombosis – 1 delayed IVC thrombosis	Arm 2 (Gunther Tulip)	NR	NR	NR	1	1
	Filter complications-thrombosis - Delayed IVC thrombosis	Arm 3(OptEase)	83	NR	NR	1	1
Khansarinia S,	Filter complications-	Arm 2 (PGF)	108	NR	NR	1	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Definition	n (%) of Patients with Outcomes	n Events
1995 <sup>17</sup>	Migration						
	Filter complications-thrombosis - IJ thrombosis		NR	NR	NR	1	NR
	Infections	Arm 1 (control)	216	NR	NR	0	NR
		Arm 2 (PGF)	108	NR	0	NR	NR
Kurtoglu M, 2003 <sup>18</sup>	Filter complications	Arm 2 (IVCF)	11	17 months	NR	0	NR
Langan EM, 1999 <sup>19</sup>	Bleeding-Minor bleeding	Arm 2 (IVCF only)	187	Hospital discharge	Groin hematoma	1	NR
	Filter complications-Filter misplacement		187	Hospital discharge	Filter misplacement resulting in PE	1	NR
			187	Hospital discharge	Filter misplacement in the right common iliac vein resulting in PE.	1	NR
	Filter complications-arteriovenous fistula formation		187	1 months after discharge	NR	1	NR
	Filter complications-femoral arterial venous fistula formation		187	1 months after discharge	NR	1	NR
	Filter complications-Groin hematoma		187	Hospital discharge	Groin hematoma	1	NR
Leach TA, 1994 <sup>20</sup>	Filter complications-Migration	Arm 2 (Greenfield Stainless Steel Filter)	201 patients (205 IVCF inserted)	NR	One filter failed to flare when released in inferior vena cava, it migrated thru the right side of the heart , feet first, to lodge in the left inferior pulmonary artery where it flared the next day without any sequelae	1	1
	Filter complications-one filter was slightly angled across the right renal venous orifice		201 patients(2 05 filters)	NR	NR	1	NR
	Filter complications-premature release		201 patients (205 IVCF inserted)	NR	NR	1	NR



Author, Year	Outcome	Arm	N for analysis	Time point	Definition	n (%) of Patients with Outcomes	n Events
	Filter complications-thrombosis - no caval thrombosis		201 patients(205 filters)	NR	NR	0 (0)	NR
Mahrer A, 2008 <sup>21</sup>	Filter complications-thrombosis - thrombus within the filter	Arm 2 (IVCF)	80	NR	NR	8 (25)	NR
McMurtry AL, 1999 <sup>22</sup>	Bleeding	Arm 4 (PVCF [all])	248	Period of study	Hemorrhage	0 (0)	NR
		Arm 5 (all VCF [placed for prophylaxis and placed after 1 PE episode])	299	Period of study	Hemorrhage	2	NR
		Arm 4 (PVCF [all])	248	Period of study	Venous insufficiency	2	NR
	Filter complications-Filter misplacement	Arm 4 (PVCF [all])	248	Period of study	NR	2	NR
		Arm 5 (all VCF [placed for prophylaxis and placed after 1 PE episode])	299	Period of study	NR	3	NR
		Arm 4 (PVCF [all])	NR	NR	NR	2	NR
	Filter complications-venous insufficiency	Arm 5- all VCF (placed for prophylaxis and placed after 1 PE episode)	299	Period of study	Venous insufficiency	2	NR
		Arm 4 (PVCF [all])	NR	NR	NR	2	NR
	Filter complications-thrombosis - IVC thrombosis	Arm 4 (PVCF [all])	248	Period of study	NR	3	NR
		Arm 5 (all VCF [placed for prophylaxis and placed after 1 PE episode])	299	Period of study	NR	4	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Definition	n (%) of Patients with Outcomes	n Events
Meier C, 2006 <sup>23</sup>	Filter complications-Migration	Arm 2 (IVCF)	37	30 days	NR	1	NR
	Filter complications-thrombosis - Asymptomatic IVC occlusion		37	4 months post trauma	NR	1	NR
	Filter complications-thrombosis - Partial thrombosis		37	30 days	NR	4 (12)	NR
Meier C, 2006 <sup>24</sup>	Filter complications-Filter tilting	Arm 2 (IVCF)	67	NR	NR	2 (3)	NR
	Filter complications-Migration		95	NR	NR	1 (1.1)	NR
	Filter complications-thrombosis - Partial occlusion		95	NR	NR	5	NR
Millward SF, 1994 <sup>25</sup>	Bleeding-Other -bleeding from the site of a surgical incision while patient on anticoagulation therapy	Arm 2 (IVCF)	3	NR	NR	0	NR
	Filter complications-Migration		3	NR	NR	0	NR
	Filter complications-thrombosis - insertion vein thrombosis (asymptomatic)		3	NR	NR	1	NR
	Filter complications-thrombosis - occlusive thrombus in the IVC with filter		3	NR	NR	0	NR
Nunn CR, 1997 <sup>26</sup>	Filter complications-Filter tilting	Arm 2 (IVCF and Lovenox)	49	Hospital discharge	NR	1	NR
	Filter complications-Migration		49	NR	NR	1	NR
	Filter complications-IVC occlusion		49	NR	NR	1	NR
O'Keeffe T, 2011 <sup>27</sup>	Bleeding- renal vein thrombosis	Arm 4 (all arms)	167	90 days	NR	1	NR
	Filter complications-technical failure to remove IVCF	Arm 2 (trauma group)	91	90 days	Technical failure to remove IVCF	1	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Definition	n (%) of Patients with Outcomes	n Events
	Filter complications-Perforation	Arm 4 (all arms)	167	90 days	NR	1	NR
Offner PJ, 2003 <sup>28</sup>	Filter complications-Migration	Arm 2 (IVCF)	44	NR	NR	0	NR
	Filter complications-occlusion		44	NR	NR	0	NR
	Filter complications-Perforation		44	NR	NR	0	NR
	Filter complications-thrombosis -insertion or retrieval site thrombosis		44	NR	NR	0	NR
Patton JH Jr, 1996 <sup>29</sup>	Filter complications	Arm 2 (IVCF)	110	Hospital discharge	Bleeding due to filter placement	0	NR
	Filter complications-Filter misplacement	Arm 2 (IVCF)	110	Hospital discharge		3	NR
	Filter complications-Migration	Arm 2 (IVCF)	110	Hospital discharge	Significant migration of VCF	1	NR
	Filter complications-thrombosis	Arm 2 (patients who had DVT)	14	4-42 months	Insertion site thrombosis	14	4
	Filter complications-thrombosis - insertion site thrombosis	Arm 2 (IVCF)	110	Hospital discharge	NR	3	NR
Phelan HA, 2009 <sup>30</sup>	Filter complications-Migration	Arm 2 (Filter)	68	end of study	Migration above L1	0 (0)	NR
	Filter complications-Strut fracture	Arm 2 (Filter)	NR	End	NR	1 (1.5)	NR
Rodriguez JL, 1996 <sup>31</sup>	Bleeding-Bleeding requiring transfusion	Arm 1 (control - No VCF)	80	NR	Gastrointestinal bleeding requiring blood transfusion	4	NR
Rogers F, 2001 <sup>32</sup>	Filter complications-Migration	Arm 2 (Case Report)	NR	NR	NR	1	NR
	Filter complications-dislodgement		1	NR	NR	1	NR
Rogers FB 1993 <sup>35</sup>	Filter complications-thrombosis - at autopsy one of the two pts who died were found to have a thrombus in the struts of his filter	Arm 2 (IVCF and compression stockings)	34	NR	No complications related to VCF insertion	1	NR
Rogers FB, 1995 <sup>34</sup>	Filter complications-thrombosis - insertion-related DVT	Arm 2 (IVCF)	63	Within 48 hours of insertion	NR	2	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Definition	n (%) of Patients with Outcomes	n Events
	Filter complications-thrombosis - VCF thrombosis		63	NR	NR	2	NR
Rogers FB, 1997 <sup>33</sup>	Filter complications-Filter tilting	Arm 2	35	Hospital discharge	NR	1 (2.8)	NR
	Filter complications-Incomplete strut opening		NR		NR	0	NR
	Filter complications-thrombosis - Insertion site thrombosis		35	Hospital discharge	NR	2 (5.7)	NR
	Infections		35	Hospital discharge	NR	NR	NR
Rogers FB, 1997 <sup>36</sup>	Bleeding-Other - insertion related thrombosis	Arm 2 (IVCF only)	132	Hospital discharge	NR	4 (3)	NR
	Filter complications-Filter tilting		132	Hospital discharge	NR	(5.5)	NR
	Filter complications-strut malposition		132	Hospital discharge	NR	(38)	NR
Rosenthal D, 2004 <sup>40</sup>	Bleeding-Minor bleeding	Arm 2 (IVCF only)	94	Within 2 weeks of filter placement	Groin Hematomas	2 (2.1)	NR
	Filter complications-av fistulas		94	During procedure	NR	0	NR
	Filter complications-Misplacement		94	Within 2 weeks of filter placement	NR	3 (3.2)	NR
	Filter complications-Perforation		31	At time of retrieval	Contrast extravasation, penetration, impingement or caval occlusion	0	NR
	Filter complications-Strut fracture		31	At time of retrieval	Structural fracture or collapse	0	NR
	Filter complications-thrombosis		94	At time of retrieval	>25% thrombus trapped in filter	3	NR
	Infections		94	During procedure	NR	0	NR
Rosenthal D, 2005 <sup>38</sup>	Bleeding - groin	Arm 2 (IVCF only)	103	Hospital discharge	NR	3 (2.9)	NR
	Filter complications-Filter misplacement		103	Hospital discharge	NR	3 (2.9)	NR
	Filter complications-thrombosis - Femoral vein insertion site thrombosis		103	Hospital discharge	Insertion site thrombosis	2	NR
	Filter complications-Perforation	Arm 3 (Subset of patients that	44	Hospital discharge	Small (<1cm) IVC defects without contrast	3	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Definition	n (%) of Patients with Outcomes	n Events
		had uneventful filter removal)			extravasation		
	Filter complications-thrombosis -significant (>25%0 trapped thrombus within filter		44	Hospital discharge	NR	3	NR
Rosenthal D, 2006 <sup>39</sup>	Filter complications-thrombosis	Arm 2 (IVCF)	127	NR	At IVCF retrieval , vena-cavography identified 3 filters with significant(>25%) trapped thrombus		NR
Rosenthal D, 2009 <sup>37</sup>	Bleeding- Groin hematoma	Arm 2 (Gunther Tulip)	97	NR	NR	4	NR
	Filter complications-Filter misplacement at insertion		NR	NR	NR	6	NR
	Bleeding-Other - Groin hematoma	Arm 3 (Celect)	90	Time of placement	NR	1	NR
	Filter complications-Migration		90	NR	NR	1	NR
Sekharan J, 2001 <sup>41</sup>	Filter complications-Migration	Arm 2 (Follow up data available)	19	NR	Migration/Limb fracture of filter	0	NR
	Filter complications-thrombosis	Arm 2 (overall group)	108	NR	NR	1	NR
	Infections		108 (overall study group at baseline	NR	No PGF related wound infections	0	NR
Shang EK, 2011 <sup>42</sup>	Filter complications-Perforation	Arm 2 (IVCF only)	1	5 years after IVCF placement	Penetration through IVC wall into the right common iliac artery	1	NR
Sing RF 2001 <sup>43</sup>	Filter complications-filter dislodgement during catheter exchange over guide wire	Arm 2 (Case 1)	1	NR	NR	1	NR
		Arm 3 (Case 2)	1	NR	Guide wire became stuck	1	NR
	Filter complications-Guide wire incidents	Arm 3 (Case 2)	1	NR	Guide wire trapped in IVCF	1	NR
Sing RF <sup>45</sup>	one caval occlusion by thrombus trapping was	Arm 2 (IVCF)	8	NR	NR	NR	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Definition	n (%) of Patients with Outcomes	n Events
	reported						
Sing RF, 2001 <sup>44</sup>	Bleeding-Other - Insertion sheath hematomas	Arm 2 (IVCF only)	158	NR	Insertion sheath hematomas	2	NR
	Filter complications-Caval occlusion		158	NR	NR	1	NR
	Filter complications-Misplaced		158	NR	Misplaced greenfield R Gonadal	1	NR
	Filter complications-Tilting to 15		158	NR	Filter tilting to 15 degrees	2	NR
	Filter complications-Perforation		158	NR	1 right ventricular perforation from the internal jugular approach at insertion	1	NR
	Infections		158	NR	6 patients died of sepsis	6	NR
Smoot RL, 2010 <sup>46</sup>	Mechanical device complications	Arm 2 (Permanent)	86	NR	Clinically significant thrombus, ileofemoral thrombus, or IVC occlusion	3	NR
		Arm 3 (Retrievable)	140	NR	Clinically significant thrombus, ileofemoral thrombus, or IVC occlusion	12	NR
Stefanidis D, 2006 <sup>47</sup>	Filter complications-Filter tip endothelialization	Arm 2 (IVCF)	83	30 days post discharge	NR	4	NR
	Filter complications-Strut fracture		83	30 days post discharge	NR	1	NR
Tola JC, 1999 <sup>48</sup>	Bleeding-Other - hematoma	Arm 2 (IVCF only)	25	Hospital discharge	NR	0 (0)	NR
	Filter complications-Filter misplacement		25	Hospital discharge	NR	0 (0)	NR
	Filter complications		25	ICU stay	No complications were found related to IVC filters	0	NR
	Filter complications-Perforation		25	Hospital discharge	NR	0 (0)	NR
	Filter complications-thrombosis - embolus		25	Hospital discharge	NR	0 (0)	NR
Wojcik R, 2000 <sup>49</sup>	Filter complications-Migration	Arm 2 (105 VCF Registry Patients)	105	NR	Only 1 cm cephalad on abdominal radiograph	1 (0.95)	NR
	Filter complications-		105	NR	1 (0.95)	NR	NR

Author, Year	Outcome	Arm	N for analysis	Time point	Definition	n (%) of Patients with Outcomes	n Events
	Venacaval occlusion						
Zakhary EM, 2008 <sup>50</sup>	Filter complications	Arm 2 (All study populations)	116	NR	NR	NR	NR
	Filter complications- IVC occlusion		NR	90 - 360 days	NR	NR	4
	Filter complications- limb fractures		116	60 days	One limb was detected in the lung on plain X-ray	NR	1
Zolfaghari D, 1995 <sup>51</sup>	Filter complications	Arm 2 (Patients receiving an IVC filter)	45	NR	NR	NR	NR

DVT= Deep Vein Thrombosis; ICU= Intensive Care Unit; IPG= Impedance Phlebography; ISS= Injury Severity Score; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; PE= Pulmonary Embolism; OR= Operating Room; PGF= Prophylactic Greenfield Filter; P-IVCF= Prophylactic Inferior Vena Cava Filter; PVCf= Prophylactic Vena Cava Filter ;RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; SCD= Sequential Compression Device; SCI= Spinal Cord Injury; STICU=Surgical Trauma Intensive Care Unit; TBI= Traumatic Brain Injury; UFH= Unfractionated Heparin; USS= Ultrasound Scan; VCF= Vena Cava Filter; VTE= Venous Thromboembolism

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**Evidence Table 8. Study characteristics for KQ2a**

Author, year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Inclusion criteria	Exclusion criteria
<b>Pharmacological agent versus Pharmacological agent</b>							
Dudley, R.R., 2010, <sup>1</sup>	Cohort- retro	Single center- N.America	2004-2008	NR	Duplex ultrasonography of the limbs or neck	Type of trauma: TBI	The patient died within 72 h of admission, and therefore was never treated with VTE prophylaxis for any meaningful period of time, patients who survived but were never treated (many of these patients did well early and were mobilized early, thus avoiding prophylactic anticoagulation; others had persistent contraindications to the prophylactic use of LMWH), patients treated with UFH, patients treated with LMWH, but with an atypical dosing or timing schedule (e.g., enoxaparin 40mg once a day), patients that were initially (>24 h) treated abroad, but were eventually transferred to our hospital; and charts that were missing after multiple attempts to locate them.
Minshall, C.T., 2011, <sup>4</sup>	cohort-retro	Single center- N.America	2006-2009	duration hospitalized	clinical examination confirmed with duplex scan	NR	Age >16 years Length of stay - ICU >48 hours HAIS > 2
<b>Pharmacological agent versus Mechanical agent</b>							
Kurtoglu, M., 2004, <sup>3</sup>	RCT	Single center -Asia	2000 - 2003	till 1 week after hospital discharge	venous duplex color flow dopler ultrasonography, obtained on admission, each week of hospitalization, and one week after discharge	ICU admission: Study participants were patients being treated at the ICU	Age: <14 yrs INR: >1.5 Platelets: <100,000/uL Liver disease or Cirrhosis: hepatic dysfunction not defined History of VTE On anti-coagulants urinary dysfunction Type of Trauma: head/spinal trauma spinal cord injury patients with continuing hemorrhage on control scans within 24 hours of admission or who required

Author, year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Inclusion criteria	Exclusion criteria
							craniotomy
<b>Pharmacological agent versus Control</b>							
Phelan, H.A., 2012 <sup>5</sup>	RCT	Multiple, North America,	NR	48 hrs post injury	None	patients admitted with intracranial hemorrhage	Progression of ICH, spinal hematoma, pelvic fracture, GI injury, intracranial pressure >20 mmHg, INR>1.5, platelet <50,000, pregnancy, age <18 years, initial head CT performed >6 h after injury, heparin allergy
Sadeh, Y., 2012 <sup>6</sup>	cohort-retro	Single center: N. America	2009	NR	No	Type of trauma: TBI	Length of hospital stay: < 3 days Did not have a repeat or stable head CT
Salottolo, K., 2010 <sup>7</sup>	cohort-retro	Multiple center: N. America	2007-2008/2009	NR	Weekly ultrasounds for DVT surveillance	Age:>= 18 years Type of trauma: TBI	Length of stay-ICU: < 3 days Development of VTE within 1 day of admission. Progression on follow-up CT within 1 day of admission.
Scudday, T., 2011 <sup>8</sup>	cohort-retro	Single center- N.America	2006-2008	NR	Yes	Type of trauma: head injury + TBI, Body region: head AIS >=2 Trauma Center Trauma registry	Type of surgery- Craniotomy, Patients who died or were discharged before 72 hrs
<b>Mechanical agent vs. control</b>							
Gersin.K., 1992 <sup>2</sup>	Prospective cohort	Multiple center – N. America	1987-1991	One month	Technetium venous scans of the lower limbs and V/Q lung scans weekly for 1 month or till patient died, became ambulatory or developed VTE	Type of trauma: Head trauma, GCS: <= 8 Surgical ICU admission	Age : <18 years Death within a week of admission, hemodynamic instability preventing transport to radiology suite, depressed GCS due to narcotics or alcohol, family's request Inadvertent omission from the study 24 patients

AIS= Abbreviated Injury Scale; BMI= Body Mass Index; CAT= Computed Axial Tomography; CT= Computed Tomography; CTA= Computed Tomography Angiography; CUS= Compression Ultrasonography; DVT= Deep Vein Thrombosis; GCS= Glasgow Coma Scale; Hr(s)= Hour(s); ICU= Intensive Care Unit; INR= International Normalized Ratio; IPG= Impedance Phlebography; ISS= Injury Severity Score; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; LE= Lower Extremity; LMWH= Low Molecular Weight Heparin; mg= milligram; NIH= National Institutes of Health; NR= Not Reported; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; RYGB= Roux-en-Y gastric bypass; SCD= Sequential Compression Device; SCI= Spinal Cord Injury; SQ=Subcutaneous; TBI= Traumatic Brain Injury; UFH= Unfractionated Heparin; USS= Ultrasound Scan; U= units; VCF= Vena Cava Filter; V/Q Scan = Ventilation Perfusion Scan; VTE= Venous Thromboembolism

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**Evidence Table 9. Participant characteristics for KQ2a**

Author, Year	Intervention arm	Number of Patients in Each Arm, N	Mean Age	% of Males	Mean ISS	Mean GCS	Mean AIS head
Dudley RR, 2010 <sup>1</sup>	Dalteparin	159	45.9	72.3	35	6.9	NR
Dudley RR, 2010 <sup>1</sup>	Enoxaparin	128	47.4	77.3	31.1	8	
Gersin, K., 1994 <sup>2</sup>	No Intervention	18	36.1	77.8	32.1	6.8	NR
Gersin, K., 1994 <sup>2</sup>	SCD	14	38.3	71.4	30.5	7.1	NR
Kurtoglu M., 2004 <sup>3</sup>	IPC	60	NR	NR	18.3	NR	NR
Kurtoglu M., 2004 <sup>3</sup>	Enoxaparin	60	NR	NR	19.5	NR	NR
Minshall, 2011 <sup>4</sup>	Usual Care/ No Intervention	57	38.3	69	30.9	NR	4.3
Minshall, 2011 <sup>4</sup>	Enoxaparin	158	41.2	75	29	NR	3.8
Minshall, 2011 <sup>4</sup>	Heparin	171	42	78	33.8	NR	4.1
Phelan, H.A., 2012 <sup>5</sup>	Arm 1 Placebo	28	42.6	57	15.7	13.0	3.1
Phelan, H.A., 2012 <sup>5</sup>	Arm2 Enoxaparin	34	40.7	64	17.3	13.5	3.5
Salottolo K., 2011 <sup>7</sup>	No PTP	225	59.5 (med)	NR	16 (med)	NR	NR
Salottolo K., 2011 <sup>7</sup>	Enoxaparin/Heparin	255	48 (med)	NR	21 (med)	NR	NR
Scudday T., 2011 <sup>8</sup>	No Prophylaxis	410	51.5	69	16.6	28%≤9, 51%>9	3.4
Scudday T., 2011 <sup>8</sup>	Enoxaparin/Heparin	402	45.2	69	23.8	46%≤9, 49%>9	3.4
Sadeh, Y., 2012 <sup>6</sup>	Dalteparin	93	NR	NR	NR	NR	NR
Sadeh, Y., 2012 <sup>6</sup>	No prophylaxis	29	NR	NR	NR	NR	NR

NR = Not reported

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**Evidence Table 10. Intervention characteristics for KQ2a**

Author, Year	Arm	Intervention	Dose	Timing of first dose	Concurrent therapy
Dudley,R.R., 2010, <sup>1</sup>	Arm1	Dalteparin	5000 U, S.Q., OD	48-72 h post-trauma	No
Dudley,R.R., 2010, <sup>1</sup>	Arm2	Enoxaparin	30 mg, S.Q, BD	48-72 h post-trauma	No
Gersin.K., 1992, 2	Arm1	No intervention	NR	NR	No
Gersin.K., 1992, 2	Arm2	SCD	NR	NR	No
Kurtoglu,M., 2004, <sup>3</sup>	Arm1	IPC	NR	NR	NR
Kurtoglu,M., 2004, <sup>3</sup>	Arm2	Enoxaparin	40 mg daily	NR	NR
Minshall, C.T., 2011, <sup>4</sup>	Arm1	Usual care/ no intervention	NR	NR	SCD
Minshall, C.T., 2011, <sup>4</sup>	Arm2	Enoxaparin	30 mg, S.Q, BD	NR	SCD
Minshall, C.T., 2011, <sup>4</sup>	Arm3	UFH	5000 U, S.Q., TID	NR	SCD
Salottolo, K., 2010, <sup>7</sup>	Arm 1	No prophylaxis	NR	36 hours after admission	SCD
Phelan, H.A., 2012 <sup>5</sup>	Arm 1	Placebo	-	24 hrs after injury	None
Phelan, H.A., 2012 <sup>5</sup>	Arm2	Enoxaparin	30 mg s.c every 12 hours	24 hrs after injury	None
Sadeh, Y., 2012 <sup>6</sup>	Arm1	93	NR	49.5% received within 48hours and 50.5% % received within 72 hours	Yes- SCDs
Sadeh, Y., 2012 <sup>6</sup>	Arm2	29	--	--	Yes- SCDs
Salottolo, K., 2010, <sup>7</sup>	Arm 2	Enoxaparin	30 mg/ 5000 U. S.Q, BD	36 hours after admission	SCD
Scudday,T., 2011 <sup>8</sup>	Arm1	No prophylaxis	NR	24- 48 hrs after second CT or 48-72 hrs after intial injury	SCD
Scudday,T., 2010, <sup>8</sup>	Arm2	UFH	NR	24- 48 hrs after second CT or 48-72 hrs after intial injury	SCD

BD= Twice daily; BMI= Body Mass Index; DVT= Deep Vein Thrombosis; GCS= Glasgow Coma Scale; Hr(s)= Hour(s); ICU= Intensive Care Unit; INR= International Normalized Ratio; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; LE= Lower Extremity; LMWH= Low Molecular Weight Heparin; mg= milligram; OD= Once Daily; NR= Not Reported; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrieable Inferior Vena Cava Filter; SCD= Sequential Compression Device; TBI= Traumatic Brain Injury; TID=Three times daily; UFH= Unfractionated Heparin; USS= Ultrasound Scan; U= units; VCF= Vena Cava Filter; V/Q Scan = Ventilation Perfusion Scan; VTE= Venous Thromboembolism



## References

1. Dudley RR, Aziz I, Bonnici A, et al. Early venous thromboembolic event prophylaxis in traumatic brain injury with low-molecular-weight heparin: risks and benefits. *J Neurotrauma* 2010; 27(12):2165-72.
2. Gersin K, Grindlinger GA, Lee V, et al. The efficacy of sequential compression devices in multiple trauma patients with severe head injury. *J Trauma* 1994; 37(2):205-8.
3. Kurtoglu M, Yanar H, Bilsel Y et al. Venous thromboembolism prophylaxis after head and spinal trauma: intermittent pneumatic compression devices versus low molecular weight heparin. *World J Surg* 2004; 28(8):807-11.
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5. Phelan HA, Wolf SE, Norwood SH, et al. A randomized, double-blinded, placebo-controlled pilot trial of anticoagulation in low-risk traumatic brain injury: The Delayed Versus Early Enoxaparin Prophylaxis I (DEEP I) study. *J Trauma Acute Care Surg* 2012.
6. Saadeh Y, Gohil K., Bill C., et al. Chemical venous thromboembolic prophylaxis is safe and effective for patients with traumatic brain injury when started 24 hours after the absence of hemorrhage progression on head CT. *Journal of Trauma and Acute Care Surgery* 2012; Volume 73, Issue 2:Pages 426-30.
7. Salottolo K, Offner P, Levy AS, et al. Interrupted pharmacologic thromboprophylaxis increases venous thromboembolism in traumatic brain injury. *J Trauma* 2011; 70(1):19-24; discussion 25-6.
8. Scudday T, Brasel K, Webb T, et al. Safety and efficacy of prophylactic anticoagulation in patients with traumatic brain injury. *J Am Coll Surg* 2011; 213(1):148-53.

**Evidence Table 11. Patient-oriented Outcomes for KQ2a**

Author, Year	Intervention	Surveillance for VTE	Number of patients in each arm	Total VTE n(%)	Total DVT n(%)	Total PE n(%)	Upper extremity DVT n(%)
Dudley,R.R., 2010, <sup>1</sup>	Dalteparin	No	159	(7.5)	NR	1	1
Dudley,R.R., 2010, <sup>1</sup>	Enoxaparin	No	128	(7)	NR	NR	NR
Gersin.K., 1992, <sup>2</sup>	No intervention	Technetium venoscans, V/Q scans weekly or until patient was ambulatory	18	4 (22.2)	2 (11.1)	2 (11.11)	NR
Gersin.K., 1992, <sup>2</sup>	SCD	Technetium venoscans, V/Q scans weekly or until patient was ambulatory	14	4 (28.6)	0	4 (28.6)	NR
Kurtoglu,M., 2004, <sup>3</sup>	IPC	Non	60	NR	4 (6.6)	2 (3.3)	NR
Kurtoglu,M., 2004, <sup>3</sup>	Enoxaparin	No	60	NR	3 (5)	4 (6.6)	NR
Minshall, C.T., 2011, <sup>4</sup>	Usual care/ No Intervention	No	57	NR	1 (2)	1 (2)	NR
Minshall, C.T., 2011, <sup>4</sup>	Enoxaparin	No	158	NR	1 (1)	0	NR
Minshall, C.T., 2011, <sup>4</sup>	UFH	No	171	NR	2 (1)	7 (4)	NR
Phelan, H.A., 2012 <sup>5</sup>	Arm 1 Placebo	None	28	NR	1(3.6)	0	NR
Phelan, H.A., 2012 <sup>5</sup>	Arm2 Enoxaparin	None	34	NR	0	0	NR
Sadeh, Y., 2012 <sup>6</sup>	Dalteparin	No	93	0	NR	NR	NR
Sadeh, Y., 2012 <sup>6</sup>	No prophylaxis	No	29	0	NR	NR	NR
Salottolo, K., 2010, <sup>7</sup>	No prophylaxis	No	225	5 (2.2)	NR	NR	NR
Salottolo, K., 2010, <sup>7</sup>	Enoxaparin	No	225	10 (3.92)	NR	NR	NR
Scudday,T., 2011, <sup>8</sup>	No prophylaxis	Twice weekly USG	410	11 (3)	NR	NR	NR
Scudday,T., 2011, <sup>8</sup>	UFH	no	402	3 (1)	NR	NR	NR

## References

1. Dudley RR, Aziz I, Bonnici A, et al. Early venous thromboembolic event prophylaxis in traumatic brain injury with low-molecular-weight heparin: risks and benefits. *J Neurotrauma* 2010; 27(12):2165-72.
2. Gersin K, Grindlinger GA, Lee V, et al. The efficacy of sequential compression devices in multiple trauma patients with severe head injury. *J Trauma* 1994; 37(2):205-8.
3. Kurtoglu M, Yanar H, Bilsel Y, et al. Venous thromboembolism prophylaxis after head and spinal trauma: intermittent pneumatic compression devices versus low molecular weight heparin. *World J Surg* 2004; 28(8):807-11.
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8. Scudday T, Brasel K, Webb T, et al. Safety and efficacy of prophylactic anticoagulation in patients with traumatic brain injury. *J Am Coll Surg* 2011; 213(1):148-53.

**Evidence Table 12. Other Patient-oriented Outcomes for KQ2a**

Author, Year	Arms	Intervention	Number of patients in each arm	Fatal PE n(%)	Total Mortality n(%)	Length of hospital stay Mean/median (range)	Length of ICU stay Mean/median $\pm$ SD (range)
Dudley, R.R., 2010 <sup>1</sup>	Arm1	Dalteparin	159	NR	NR	NR	NR
Dudley, R.R., 2010 <sup>1</sup>	Arm2	Enoxaparin	128	NR	NR	NR	NR
Gersin, K., 1992 <sup>2</sup>	Arm1	No intervention	18	NR	NR	NR	18.4 (SD 2.8)
Gersin, K., 1992 <sup>2</sup>	Arm2	SCD	14	NR	NR	NR	21.2 (SD 2.3)
Kurtoglu, M., 2004 <sup>3</sup>	Arm1	IPC	60	2 (3.3)	7 (11.6)	NR	10.3 (4-39) mean
Kurtoglu, M., 2004 <sup>3</sup>	Arm2	Enoxaparin	60	4 (6.6)	8 (13.3)	NR	10.7 (3-75) mean
Minshall, C.T., 2011 <sup>4</sup>	Arm1	Usual care/ No Intervention	57	NR	27 (47)	4 (2-11) median	2 (2-11) median
Minshall, C.T., 2011 <sup>4</sup>	Arm2	Enoxaparin	158	NR	8 (5)	19 (2-100) median	8 (2-35) median
Minshall, C.T., 2011 <sup>4</sup>	Arm3	UFH	171	NR	27 (15.8)	17 (3-126) median	11 (2-126) median
Phelan, H.A., 2012 <sup>5</sup>	Arm 1	Placebo	28	NR	0	4.9	3.2 $\pm$ 3.3
Phelan, H.A., 2012 <sup>5</sup>	Arm2	Enoxaparin	34	NR	0	4.5	2.5 $\pm$ 2.9
Salottolo, K., 2010 <sup>6</sup>	Arm 1	No prophylaxis	225	NR	NR	NR	NR
Salottolo, K., 2010 <sup>6</sup>	Arm 2	Enoxaparin	225	NR	NR	NR	NR
Scudday, T., 2011 <sup>7</sup>	Arm1	No prophylaxis	410	NR	15 (3.66)	NR	NR
Scudday, T., 2011 <sup>7</sup>	Arm2	UFH	402	NR	3 (0.75)	NR	NR

## References

1. Dudley RR, Aziz I, Bonnici A, et al. Early venous thromboembolic event prophylaxis in traumatic brain injury with low-molecular-weight heparin: risks and benefits. *J Neurotrauma* 2010; 27(12):2165-72.
2. Gersin K, Grindlinger GA, Lee V, et al. The efficacy of sequential compression devices in multiple trauma patients with severe head injury. *J Trauma* 1994; 37(2):205-8.
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7. Scudday T, Brasel K, Webb T, et al. Safety and efficacy of prophylactic anticoagulation in patients with traumatic brain injury. *J Am Coll Surg* 2011; 213(1):148-53.

**Evidence Table 13. Adverse Events for KQ2a**

Author, Year	Arms	Intervention	Number of patients in each arm	Bleeding definition	Major bleeding n(%)	Minor bleeding n(%)	Hematoma at injection site n (%)	Bleeding from tracheostomy site (n%)	Infections n (%)
Dudley,R.R., 2010 <sup>1</sup>	arm1	Dalteparin	159	Bleeding symptomatic expansion of a pre-existing ICH	0	NR	NR	NR	NR
Dudley,R.R., 2010 <sup>1</sup>	arm2	enoxaparin	128	Bleeding symptomatic expansion of a pre-existing ICH	1 (0.08)	NR	NR	NR	NR
Kurtoglu,M., 2004 <sup>2</sup>	arm1	IPC	60	major bleeding: Exacerbation of epidural hematoma, minor bleeding:hematuria	1 (1.6)	4 (6.6)	0	0	10 (20)
Kurtoglu,M., 2004 <sup>2</sup>	arm2	enoxaparin	60	major bleeding: Exacerbation of epidural hematoma, minor bleeding:hematuria	1 (1.6)	5 (8.3)	2 (3.3)	1 (1.6)	14 (23.3)
Minshall, C.T., 2011 <sup>3</sup>	arm1	Usual care/ No Intervention	57	progression of ICH- Total /after initiation of chemoprophylaxis/ Bleeding requiring decompression (craniectomy post-CP)	14 (25)	NR	NR	NR	NR
Minshall, C.T., 2011 <sup>3</sup>	arm2	enoxaparin	158	progression of ICH- Total /after initiation of chemoprophylaxis/ Bleeding requiring decompression (craniectomy post-CP)	20 (13)/ 8 (5) / 0(0)	NR	NR	NR	NR
Minshall, C.T., 2011, <sup>3</sup>	arm3	UFH	171	progression of ICH- Total /after initiation of chemoprophylaxis/ Bleeding requiring	34 (20)/ 20 (12) / 2(1)	NR	NR	NR	NR

				decompression (craniectomy post-CP)					
Phelan, H.A., 2012 <sup>4</sup>	Arm 1	Placebo	28	Radiographic progression of ICH	3.6%	NR	NR	NR	NR
Phelan, H.A., 2012 <sup>4</sup>	Arm2	Enoxaparin	34	Radiographic progression of ICH	5.9%	NR	NR	NR	NR
Sadeh, Y., 2012 <sup>5</sup>	arm1	Dalteparin	93	Progression of ICH	0	NR	NR	NR	NR
Salottolo, K., 2010 <sup>6</sup>	Arm 1	no prophylaxis	225	TBI hemorrhage progression	(8.44)	NR	NR	NR	NR
Salottolo, K., 2010 <sup>6</sup>	Arm 2	enoxaparin	225	TBI hemorrhage progression	6.48% in <72 hours arm and 14.29% in >72 hours arm	NR	NR	NR	NR

UFH = Unfractionated heparin; IPC = Intermittent pneumatic compression devices; TBI = Traumatic brain injury; CP = Chemo prophylaxis; ICH = Intracranial hemorrhage

## References

1. Dudley RR, Aziz I, Bonnici A, et al. Early venous thromboembolic event prophylaxis in traumatic brain injury with low-molecular-weight heparin: risks and benefits. *J Neurotrauma* 2010; 27(12):2165-72.
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6. Salottolo K, Offner P, Levy AS, et al. Interrupted pharmacologic thromboprophylaxis increases venous thromboembolism in traumatic brain injury. *J Trauma* 2011; 70(1):19-24; discussion 25-6.



**Evidence Table 14. Study characteristics for KQ2b**

Author, Year	Study Design	Study Site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of Surveillance for VTE	Funding Source	Inclusion Criteria	Exclusion Criteria
<b>Pharmacological agent versus Pharmacological agent</b>								
Depew A.J., 2008 <sup>1</sup>	Retrospective Cohort	Single center-North America	2006-2006	NR	Weekly duplex ultrasound of the lower extremities	Industry	Age: ≥18 Length of stay-overall:>3 days Type of trauma: Intracranial hemorrhage from blunt head trauma ICD-9-CM codes for ICH from BHT (851–853) ISS: ≥ 9 Trauma Center: level 1 trauma center	Penetrating head trauma
Kim J., 2002 <sup>2</sup>	Retrospective Cohort	Single center-North America	2000-2000	NR	Weekly venous duplex Doppler sonograms of the Lower Extremities	NR	Presence of one or more of subdural hematoma, epidural hematoma, intraventricular hemorrhage, subarachnoid hemorrhage, contusion or diffuse axonal injury on CT  Trauma Center Admission to study trauma center	Platelets: <110,000  Receiving coumadin or LMWH for VTE prophylaxis  Prothrombin time>13 seconds, death within 72 hours of hospitalization  Receiving warfarin at time of accident; received LMWH for VTE proph
Koehler D.M., 2011 <sup>3</sup>	Retrospective Cohort	Multiple center-N. America	2004-2008	NR	No	NR	Age ≥ 16 years  Length of stay over all ≥ 72 hrs  Type of trauma: TBI Trauma Center	Pregnancy  INR >1.5  Platelets <100,000/ uL  History of VTE  On antiplatelet (Aspirin)

Author, Year	Study Design	Study Site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of Surveillance for VTE	Funding Source	Inclusion Criteria	Exclusion Criteria
Reiff D.A., 2009 <sup>4</sup>	Retrospective Cohort	Single center- North America	2000-2007	NR	Clinical surveillance during hospitalization with confirmation by Doppler ultrasound	NR	Type of trauma: all patients with blunt or penetrating injuries Trauma Center: all admitted patients with blunt or penetrating injuries	NR
Salotto K., 2011 <sup>5</sup>	Retrospective Cohort	Multiple center- North America	2007-2008/2009	NR	Weekly ultrasounds for DVT surveillance	NR	Age ≥ 18 years Type of trauma: TBI	Length of stay – ICU < 3 days  Development of VTE within 1 day of admission  Progression on follow-up CT

DVT=Deep Vein Thrombosis; ICH=Intracranial Hemorrhage; ISS=Injury Severity Score; LMWH=Low Molecular Weight Heparin; TBI=Traumatic Brain Injury; VTE=Venous Thromboembolism

## References

1. Depew AJ, Hu CK, Nguyen AC, et al. Thromboembolic prophylaxis in blunt traumatic intracranial hemorrhage: a retrospective review. *Am Surg* 2008; 74(10):906-11.
2. Kim J, Gearhart MM, Zurick A, et al. Preliminary report on the safety of heparin for deep venous thrombosis prophylaxis after severe head injury. *J Trauma* 2002; 53(1):38-42; discussion 43.
3. Koehler DM, Shipman J, Davidson MA, et al. Is early venous thromboembolism prophylaxis safe in trauma patients with intracranial hemorrhage. *J Trauma* 2011; 70(2):324-9.
4. Reiff DA, Haricharan RN, Bullington NM, Griffin RL, McGwin G Jr, Rue LW 3rd. Traumatic brain injury is associated with the development of deep vein thrombosis independent of pharmacological prophylaxis. *J Trauma* 2009; 66(5):1436-40.
5. Salottolo K, Offner P, Levy AS, et al. Interrupted pharmacologic thromboprophylaxis increases venous thromboembolism in traumatic brain injury. *J Trauma* 2011; 70(1):19-24; discussion 25-6.

**Evidence Table 15. Participant characteristics for KQ2b**

Author, Year	Intervention	Number of Patients in Each Arm, N	Mean Age	% of Males	Mean ISS	Mean GCS	Mean AIS head
Depew A.J., 2008 <sup>1</sup>	No prophylaxis	37	NR	NR	NR	NR	NR
Depew A.J., 2008 <sup>1</sup>	Any heparin <72 hrs	29	NR	NR	NR	NR	NR
Depew A.J., 2008 <sup>1</sup>	Any heparin >72 hrs	41	NR	NR	NR	NR	NR
Kim J., 2002 <sup>2</sup>	UFH early <72 hrs	47	37.7	NR	30.7	9.1	NR
Kim J., 2002 <sup>2</sup>	UFH late >72 hrs	17	44	NR	35.7	9.4	NR
Koehler D.M., 2011 <sup>3</sup>	Enoxaparin ≤72 hrs	268	39.8	69	27.8	NR	4
Koehler D.M., 2011 <sup>3</sup>	Enoxaparin >72 hrs	401	40.2	75	29.4	NR	NR
Reiff D.A., 2009 <sup>4</sup>	Any heparin 0 to <24 hrs	84	37.2	71.4	NR	NR	NR
Reiff D.A., 2009 <sup>4</sup>	Any heparin 24 to <48 hrs	177	39.8	62.7	NR	NR	NR
Reiff D.A., 2009 <sup>4</sup>	Any heparin >48 hrs	293	43	63.8	NR	NR	NR
Salotto K., 2011 <sup>5</sup>	Enoxaparin (<72 hr)	108	NR	NR	NR	NR	NR
Salotto K., 2011 <sup>5</sup>	Enoxaparin (≥ 72 hrs)	147	NR	NR	NR	NR	NR

AIS= Abbreviated Injury Scale; GCS= Glasgow Coma Scale; ISS= Injury Severity Score; UFH= Unfractionated Heparin

## References

1. Depew AJ, Hu CK, Nguyen AC, et al. Thromboembolic prophylaxis in blunt traumatic intracranial hemorrhage: a retrospective review. *Am Surg* 2008; 74(10):906-11.
2. Kim J, Gearhart MM, Zurick A, et al. Preliminary report on the safety of heparin for deep venous thrombosis prophylaxis after severe head injury. *J Trauma* 2002; 53(1):38-42; discussion 43.
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5. Salottolo K, Offner P, Levy AS, et al. Interrupted pharmacologic thromboprophylaxis increases venous thromboembolism in traumatic brain injury. *J Trauma* 2011; 70(1):19-24; discussion 25-6.

**Evidence Table 16. Intervention characteristics for KQ2b**

Author, Year	Intervention	Dose	Timing of first dose	Concurrent therapy
Depew A.J., 2008 <sup>1</sup>	No prophylaxis	NR	NR	SCD
Depew A.J., 2008 <sup>1</sup>	Any heparin <72 hrs	30 mg/ 5000 U. SC, BD	< 72 hrs post admission	SCD
Depew A.J., 2008 <sup>1</sup>	Any heparin >72 hrs	30 mg/ 5000 U. SC, BD	>72 hrs post admission	SCD
Kim J., 2002 <sup>2</sup>	UFH early <72 hrs	5000 IU SC, BD	≤ 72 hrs from admission	Pneumatic compression or arteriovenous foot pumps
Kim J., 2002 <sup>2</sup>	UFH late >72 hrs	5000 IU SC, BD	> 72 hrs from admission	Pneumatic compression or arteriovenous foot pumps
Koehler D.M., 2011 <sup>3</sup>	Enoxaparin ≤72 hrs	30 mg, SC, BD	≤ 72 hrs from admission	No
Koehler D.M., 2011 <sup>3</sup>	Enoxaparin >72 hrs	30 mg, SC, BD	> 72 hrs from admission	No
Reiff D.A., 2009 <sup>4</sup>	Any heparin 0 to <24 hrs	NR	<24 hours	SCD
Reiff D.A., 2009 <sup>4</sup>	Any heparin 24 to <48 hrs	NR	24-48 hours	SCD
Reiff D.A., 2009 <sup>4</sup>	Any heparin >48 hrs	NR	>48 hours	SCD
Salotto K., 2011 <sup>5</sup>	Enoxaparin (<72 hr)	30 mg/ 5000 IU	≤ 72 hrs from admission	SCD
Salotto K., 2011 <sup>5</sup>	Enoxaparin (≥ 72 hrs)	30 mg/ 5000 IU	> 72 hrs from admission	SCD

BD=Twice Daily; IU=International Units; SC=Subcutaneous; SCD= Sequential Compression Device; UFH= Unfractionated Heparin

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1. Depew AJ, Hu CK, Nguyen AC, et al. Thromboembolic prophylaxis in blunt traumatic intracranial hemorrhage: a retrospective review. *Am Surg* 2008; 74(10):906-11.
2. Kim J, Gearhart MM, Zurick A, et al. Preliminary report on the safety of heparin for deep venous thrombosis prophylaxis after severe head injury. *J Trauma* 2002; 53(1):38-42; discussion 43.
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5. Salottolo K, Offner P, Levy AS, et al. Interrupted pharmacologic thromboprophylaxis increases venous thromboembolism in traumatic brain injury. *J Trauma* 2011; 70(1):19-24; discussion 25-6.

**Evidence Table 17. Patient-oriented Outcomes for KQ2b**

Author, Year	Intervention	Number of Patients, N	Surveillance for VTE	Timing	Total VTE n(%)	Total DVT n(%)	Total PE n(%)	Upper extremity DVT, n(%)	Lower extremity DVT, n(%)	Proximal DVT n(%)	Distal DVT n(%)
Depew A.J.,2008 <sup>1</sup>	No prophylaxis	37	High risk patients only: weekly USG	Hospital discharge	NR	0	0	NR	NR	NR	NR
Depew A.J.,2008 <sup>1</sup>	Any heparin <72 hrs	29	No	Hospital discharge	NR	3 (10.4)	1 (3.5)	NR	NR	NR	NR
Depew A.J.,2008 <sup>1</sup>	Any heparin >72 hrs	41	No	Hospital discharge	NR	6 (14.6)	0	NR	NR	NR	NR
Kim J., 2002 <sup>2</sup>	UFH early <72 hrs	47	Weekly USG	Post injury days 7 and 19	NR	2 (4.3)	2 (4.3)	NR	NR	NR	NR
Kim J., 2002 <sup>2</sup>	UFH late >72 hrs	17	Weekly USG	30 days	NR	1 (5.9)	0	NR	NR	NR	NR
Koehler D.M., 2011 <sup>3</sup>	Enoxaparin >72 hrs	401	No	Hospital discharge	NR	NR	9 (2.2)	5 (1.3)	9 (2.2)	(3.5)	(6.7)
Koehler D.M.,2011 <sup>3</sup>	Enoxaparin ≤72 hrs	268	No	Hospital discharge	NR	NR	4 (1.5)	1 (0.4)	3 (1.1)	(1.5)	(3.7)
Reiff D.A.,2009 <sup>4</sup>	Any heparin 0 to <24 hrs	84	No	NR	NR	3.6 (DVT risk/100 patients)	NR	NR	NR	NR	NR
Reiff D.A.,2009 <sup>4</sup>	Any heparin 24 to <48 hrs	177	No	NR	NR	4.5 (DVT risk/100 patients)	NR	NR	NR	NR	NR
Reiff D.A.,2009 <sup>4</sup>	Any heparin >48 hrs	293	No	NR	NR	15.4 (DVT risk/100 patients)	NR	NR	NR	NR	NR
Salotto K.,2011 <sup>5</sup>	Enoxaparin (<72 hr)	108	No	Hospital discharge	6 (5.56)	NR	NR	NR	NR	NR	NR
Salotto K.,2011 <sup>5</sup>	Enoxaparin (≥ 72 hrs)	147	No	Hospital discharge	4 (2.72)	NR	NR	NR	NR	NR	NR

DVT= Deep Vein Thrombosis; PE= Pulmonary Embolism; UFH= Unfractionated Heparin; USG= Ultrasonography; VTE= Venous Thromboembolism



## References

1. Depew AJ, Hu CK, Nguyen AC, et al. Thromboembolic prophylaxis in blunt traumatic intracranial hemorrhage: a retrospective review. *Am Surg* 2008; 74(10):906-11.
2. Kim J, Gearhart MM, Zurick A, et al. Preliminary report on the safety of heparin for deep venous thrombosis prophylaxis after severe head injury. *J Trauma* 2002; 53(1):38-42; discussion 43.
3. Koehler DM, Shipman J, Davidson MA, et al. Is early venous thromboembolism prophylaxis safe in trauma patients with intracranial hemorrhage. *J Trauma* 2011; 70(2):324-9.
4. Reiff DA, Haricharan RN, Bullington NM, et al. Traumatic brain injury is associated with the development of deep vein thrombosis independent of pharmacological prophylaxis. *J Trauma* 2009; 66(5):1436-40.
5. Salottolo K, Offner P, Levy AS, et al. Interrupted pharmacologic thromboprophylaxis increases venous thromboembolism in traumatic brain injury. *J Trauma* 2011; 70(1):19-24; discussion 25-6.

**Evidence Table 18. Other Patient-oriented Outcomes for KQ2b**

Author, Year	Intervention	Number of Patients, N	Timing	Fatal PE n(%)	Total mortality n(%)	Mortality due to Bleeding n(%)
Kim J., 2002 <sup>1</sup>	UFH early <72 hrs	47	Post injury days 7 and 19	NR	4 (8.5)	NR
Kim J., 2002 <sup>1</sup>	UFH late >72 hrs	17	30 days	NR	1 (5.9)	NR
Koehler D.M., 2011 <sup>2</sup>	Enoxaparin ≤72 hrs	268	Hospital discharge	0	NR	0
Koehler D.M., 2011 <sup>2</sup>	Enoxaparin >72 hrs	401	Hospital discharge	1	NR	0

UFH= Unfractionated Heparin

## References

1. Kim J, Gearhart MM, Zurick A, et al. Preliminary report on the safety of heparin for deep venous thrombosis prophylaxis after severe head injury. J Trauma 2002; 53(1):38-42; discussion 43.
2. Koehler DM, Shipman J, Davidson MA, et al. Is early venous thromboembolism prophylaxis safe in trauma patients with intracranial hemorrhage. J Trauma 2011; 70(2):324-9.

**Evidence Table 19. Adverse Events for KQ2b**

Author, Year	Intervention	Number of Patients, N	Timing	Definition of Bleeding	Major Bleeding n(%)	Minor Bleeding n(%)
Depew A.J., 2008 <sup>1</sup>	No prophylaxis	37	Hospital discharge	Progression of ICH	0 (0)	NR
Depew A.J., 2008 <sup>1</sup>	Any heparin <72 hrs	29	Hospital discharge	Progression of ICH	1 (3.5)	NR
Depew A.J., 2008 <sup>1</sup>	Any heparin >72 hrs	41	Hospital discharge	Progression of ICH	2 (3.8)	NR
Kim J., 2002 <sup>2</sup>	UFH early <72 hrs	47	Post injury days 7 and 19	Hematuria- trauma from foley catheter insertion, bladder/parenchymal injuries	NR	3 (6)
Kim J., 2002 <sup>2</sup>	UFH late >72 hrs	17	30 days	Hematuria- trauma from foley catheter insertion, bladder/parenchymal injuries	NR	1 (6)
Koehler D.M., 2011 <sup>3</sup>	Enoxaparin ≤72 hrs	268	Hospital discharge	Major: ICH progression; minor: Non cranial bleeding complications	7 (1.46)	0
Koehler D.M., 2011 <sup>3</sup>	Enoxaparin >72 hrs	401	Hospital discharge	Major: ICH progression; minor: Non cranial bleeding complications	12 (1.54)	0
Salotto K., 2011 <sup>4</sup>	Enoxaparin (<72 hr)	108	Hospital discharge	Progression of ICH	(6.48)	NR
Salotto K., 2011 <sup>4</sup>	Enoxaparin (>72 hr)	147	Hospital discharge	Progression of ICH	(14.29)	NR

ICH=Intra Cranial Hemorrhage; UFH= Unfractionated Heparin

## References

1. Depew AJ, Hu CK, Nguyen AC, et al. Thromboembolic prophylaxis in blunt traumatic intracranial hemorrhage: a retrospective review. *Am Surg* 2008; 74(10):906-11.
2. Kim J, Gearhart MM, Zurick A, et al. Preliminary report on the safety of heparin for deep venous thrombosis prophylaxis after severe head injury. *J Trauma* 2002; 53(1):38-42; discussion 43.
3. Koehler DM, Shipman J, Davidson MA, et al. Is early venous thromboembolism prophylaxis safe in trauma patients with intracranial hemorrhage. *J Trauma* 2011; 70(2):324-9.
4. Salottolo K, Offner P, Levy AS, et al. Interrupted pharmacologic thromboprophylaxis increases venous thromboembolism in traumatic brain injury. *J Trauma* 2011; 70(1):19-24; discussion 25-6.

**Evidence Table 20. Study characteristics for KQ3**

Author, year	Study Design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding Source	Inclusion Criteria	Exclusion Criteria
Still, 2000 <sup>1</sup>	Case series	Single center- North America	NR	NR	NR	NR	Patients admitted with acute burns	NR

## References

1. Still J, Friedman B, Furman S et al. Experience with the insertion of vena caval filters in acutely burned patients. Am Surg 2000; 66(3):277-9.

**Evidence Table 21. Participant characteristics for KQ3**

Author, Year	Arm, n	Age (years) Mean, median, Range	Gender, n (%)	Race, n (%)	BMI	Weight	Prior History of VTE, n (%)	Trauma	ICU Duration	Burn
Still, 2000 <sup>1</sup>	Arm 2 (Patients received IVC filters strictly for prophylaxis of burns), 15	Mean:38.9 Range:22-69	Male, 9 (45)	NR	NR	Comment: 10 of 20 (i.e. 50%) patients in the overall group were morbidly obese. 6 of 15 patients who of IVC filters strictly for prophylaxis were morbidly obese	NR	NR	NR	Mean:37.8 Range:15-79

BMI= Body Mass Index; ICU= Intensive Care Unit; IVC= Inferior Vena Cava; VTE= Venous Thromboembolism

## References

1. Still J, Friedman B, Furman S et al. Experience with the insertion of vena caval filters in acutely burned patients. Am Surg 2000; 66(3):277-9.

**Evidence Table 22. Intervention characteristics for KQ3**

Author, Year	Arm Name	Filter Name	Filter type (temp or permanent)	Filter Placed by	Setting	Planned Duration of Filter	Concurrent Therapy
Still, 2000 <sup>1</sup>	Arm 2 (IVC filter for Prophylaxis Only)	NR	NR	NR	Unclear	NR	No

BMI= Body Mass Index; ICU= Intensive Care Unit; IVC= Inferior Vena Cava; VTE= Venous Thromboembolism

## References

1. Still J, Friedman B, Furman S et al. Experience with the insertion of vena caval filters in acutely burned patients. Am Surg 2000; 66(3):277-9.

**Evidence Table 23. Other Outcomes for KQ3**

Author, Year Refid	Arm	N for Analysis	Time Point	Outcome	Definition	n (%) of Patients with Outcomes	n Events	Mean/Med/Range	Other	Measure of Association
Still, 2000 <sup>1</sup>	Arm 2 (P-IVCF only)	20	Hospital discharge	Total mortality	9 out of 20 patients died in the overall study but don't report mortality data on the 15 burn patients	9	NR	NR	NR	NR

BMI= Body Mass Index; ICU= Intensive Care Unit; IVC= Inferior Vena Cava; P-IVCF=Prophylactic Inferior Vena Cava Filter; VTE= Venous Thromboembolism

## References

1. Still J, Friedman B, Furman S et al. Experience with the insertion of vena caval filters in acutely burned patients. Am Surg 2000; 66(3):277-9.

**Evidence Table 24. Adverse Events for KQ3**

Author, Year	Arm	N for analysis	Time Point	Outcome	Definition	n (%) of Patients with Outcomes	n Events
Still, 2000 <sup>1</sup>	Arm 2 (P-IVCF only)	15	Hospital discharge	Bleeding – IVC thromboses	NR	0 (0)	NR
Still, 2000 <sup>1</sup>	Arm 2 (P-IVCF only)	15	Hospital discharge	Infections	Site infections	0 (0)	NR
Still, 2000 <sup>1</sup>	Arm 2 (P-IVCF only)	15	Hospital discharge	Filter complications	Filter complications	0 (0)	NR

BMI= Body Mass Index; ICU= Intensive Care Unit; IVC= Inferior Vena Cava; P-IVCF=Prophylactic Inferior Vena Cava Filter; VTE= Venous Thromboembolism

## References

1. Still J, Friedman B, Furman S et al. Experience with the insertion of vena caval filters in acutely burned patients. Am Surg 2000; 66(3):277-9.

**Evidence Table 25. Study characteristics for KQ5**

Author, Year	Study Design	Study Site – Study Locations	Recruitment Date (start – end date)	Planned Length of Follow-up	Method of Surveillance for VTE	Funding Source	Inclusion Criteria	Exclusion Criteria
Eriksson B.I, 2012 <sup>1</sup>	Pooled data from 4 studies (Phase III clinical trials). These trials were randomized, double dummy design	NR	NR	NR	NR	NR	The data analyses and the definition of co-medications were pre specified in the RECORD1-4 (Regulation of Coagulation in Orthopedic surgery to prevent Deep Vein thrombosis and pulmonary embolism) pooled statistical analysis plan prior to un-blinding of any of the RECORD studies.	There was no limitation on the choice of a specific drug or dose of NSAIDs and PFIs or ASA in the study protocols.
Friedman,R.J, 2012 <sup>2</sup>	Pooled data from 3 trials (RE-MODEL, RE-NOVATE, RE-MOBILIZE)	Europe, North America	NR	NR	NR	Industry	RE-MODEL, RE-MOBILIZE - patients undergoing knee arthroplasty, RE-NOVATE- patients with total hip replacement,	NR

NR = Not reported

## References

1. Eriksson BI, Rosencher N, Friedman RJ, Homering M, Dahl OE. Concomitant use of medication with antiplatelet effects in patients receiving either rivaroxaban or enoxaparin after total hip or knee arthroplasty. Thromb Res 2012.
2. Friedman RJ, Kurth A, Clemens A, Noack H, Eriksson BI, Caprini JA. Dabigatran etexilate and concomitant use of non-steroidal anti-inflammatory drugs or acetylsalicylic acid in patients undergoing total hip and total knee arthroplasty: no increased risk of bleeding. Thromb Haemost 2012; 108(1):183-90.

**Evidence Table 26. Participant characteristics for KQ5**

Author, Year	Arm, n	Age (years) Mean,	Male (%)	Race, n (%)	BMI	Weight (kg) Mean,	Prior History of VTE, n (%)	Trauma, n(%)	ICU Duration	Number of patients with co-medication use* n (%)
Eriksson B.I, 2012 <sup>1</sup>	Arm 1 (Rivaroxaban), 6093	68	47	NR	NR	82	NR	NR	NR	563 (9)
	Arm 2 (Enoxaparin/placebo), 6107	68	47	NR	NR	83	NR	NR	NR	526 (9)
Friedman,R.J, 2012 <sup>2</sup>	Arm 1 (220 mg Dabigatran, no ASA), 1149	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Arm 2 (150 mg Dabigatran, no ASA), 1149	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Arm 3 (Enoxaparin, no ASA), 1167	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Arm 4 (220 mg Dabigatran + ASA), 126	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Arm 5 (150 mg Dabigatran + ASA), 128	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Arm 6 (Enoxaparin+ ASA), 132	NR	NR	NR	NR	NR	NR	NR	NR	NR

\*Co-medication use refers to use in the at-risk period, which starts on day 1 (day of surgery) and ends up to 2 days after the last intake of study medication.

NR = Not reported

## References

1. Eriksson BI, Rosencher N, Friedman RJ, Homering M, Dahl OE. Concomitant use of medication with antiplatelet effects in patients receiving either rivaroxaban or enoxaparin after total hip or knee arthroplasty. *Thromb Res* 2012.
2. Friedman RJ, Kurth A, Clemens A, Noack H, Eriksson BI, Caprini JA. Dabigatran etexilate and concomitant use of non-steroidal anti-inflammatory drugs or acetylsalicylic acid in patients undergoing total hip and total knee arthroplasty: no increased risk of bleeding. *Thromb Haemost* 2012; 108(1):183-90.



**Evidence Table 27. Intervention characteristics for KQ5**

Author, Year	Arm Name	Drug Name	Dose	Route	Frequency	Timing of First Dose	Planned Duration of Therapy (Other e.g. INR)	Concurrent Therapy
Eriksson B.I, 2012 <sup>1</sup>	Arm 1(Rivaroxaban)	Rivaroxaban	10mg	Oral	Once daily (od)	6-8 hours after surgery	NR	PFI or ASA
		Rivaroxaban	10mg	Oral	Once daily (od)	6-8 hours after surgery	31-39 days for patients undergoing THA	PFI or ASA
		Rivaroxaban	10mg	Oral	Once daily (od)	6-8 hours after surgery	10-14 days for patients undergoing TKA	PFI or ASA
	Arm 2 (Enoxaparin/placebo)	Enoxaparin/placebo	40mg	SC	Once daily (od)	12 hours before surgery	NR	PFI or ASA
		Enoxaparin/placebo	30mg	SC	Twice daily (bid)	12-24 hours after wound closure or after adequate hemostasis was obtained	NR	PFI or ASA
		Enoxaparin/placebo	40mg	SC	Once daily (od)	12 hours before surgery	31-39 days for patients undergoing THA	PFI or ASA
		Enoxaparin/placebo	40mg	SC	Once daily (od)	12 hours before surgery	10-14 days for patients undergoing TKA	PFI or ASA
		Enoxaparin/placebo	30mg	SC	Twice daily (bid)	12-24 hours after wound closure or after adequate hemostasis was obtained	31-39 days for patients undergoing THA	PFI or ASA
		Enoxaparin/placebo	30mg	SC	Twice daily (bid)	12-24 hours after wound closure or after adequate hemostasis was obtained	10-14 days for patients undergoing TKA	PFI or ASA
		Enoxaparin/placebo	30mg	SC	Twice daily (bid)	12-24 hours after wound closure or after adequate hemostasis was obtained	10-14 days for patients undergoing TKA	PFI or ASA

Author, Year	Arm Name	Drug Name	Dose	Route	Frequency	Timing of First Dose	Planned Duration of Therapy (Other e.g. INR)	Concurrent Therapy
Friedman,R.J, 2012 <sup>2</sup>	Arm 1 (220 mg Dabigatran, no ASA)	Dabigatran	220 mg	Oral	Daily	1-4/6-12 hrs after surgery	RE-MODEL- 6-10 days, RE-NOVATE- 28-35 days, RE-MOBILIZE- 12-15 days	None
	Arm 2 (150 mg Dabigatran, no ASA)	Dabigatran	150 mg	oral	Daily	1-4/6-12 hrs after surgery	RE-MODEL- 6-10 days, RE-NOVATE- 28-35 days, RE-MOBILIZE- 12-15 days	None
	Arm 3 (Enoxaparin, no ASA)	Enoxaparin	40 mg/ 30 mg	s.c	40 mg- once daily, 30 mg- twice daily	6-12 hrs after surgery	RE-MODEL- 6-10 days, RE-NOVATE- 28-35 days, RE-MOBILIZE- 12-15 days	None
	Arm 4 (220 mg Dabigatran + ASA)	Dabigatran	220 mg	Oral	Daily	1-4/6-12 hrs after surgery	RE-MODEL- 6-10 days, RE-NOVATE- 28-35 days, RE-MOBILIZE- 12-15 days	ASA
	Arm 5 (150 mg Dabigatran + ASA)	Dabigatran	150 mg	oral	Daily	1-4/6-12 hrs after surgery	RE-MODEL- 6-10 days, RE-NOVATE- 28-35 days, RE-MOBILIZE- 12-15 days	ASA
	Arm 6 (Enoxaparin+ ASA)	Enoxaparin	40 mg/ 30 mg	s.c	40 mg- once daily, 30 mg- twice daily	6-12 hrs after surgery	RE-MODEL- 6-10 days, RE-NOVATE- 28-35 days, RE-MOBILIZE- 12-15 days	ASA

\*SC=Subcutaneous; PFI=Platelet Function Inhibitors; ASA=Acetylsalicylic Acid; THA=Total Hip Arthroplasty; TKA=Total Knee Arthroplasty; NR = Not reported

## References

1. Eriksson BI, Rosencher N, Friedman RJ, Homering M, Dahl OE. Concomitant use of medication with antiplatelet effects in patients receiving either rivaroxaban or enoxaparin after total hip or knee arthroplasty. *Thromb Res* 2012.
2. Friedman RJ, Kurth A, Clemens A, Noack H, Eriksson BI, Caprini JA. Dabigatran etexilate and concomitant use of non-steroidal anti-inflammatory drugs or acetylsalicylic acid in patients undergoing total hip and total knee arthroplasty: no increased risk of bleeding. *Thromb Haemost* 2012; 108(1):183-90.

**Evidence Table 28. Patient-oriented Outcomes (any bleeding events + major and non-major clinically relevant bleeding) over three time windows in the at-risk period for KQ5**

Author, Year	Arm	N for Analysis	Time Points	Test to Confirm DVT/PE	Outcome	Rate ratio (per 100 patient weeks) for use versus non-use (95% CI)	Outcome	Rate ratio (per 100 patient weeks) for use versus non-use (95% CI)
Eriksson B.I, 2012 <sup>1</sup>	Arm 1 (Rivaroxaban)	6093	Day 1-3	NR	Any Bleeding	1.49 (0.75-2.93)	Major and non-major clinically relevant bleeding	0.91 (0.23-3.65)
			Day 4-7	NR		1.62 (0.81-3.26)		1.47 (0.46-4.68)
			After Day 7	NR		0.83 (0.31-2.25)		1.02 (0.32-3.25)
	Arm 2 (Enoxaparin/placebo)	6107	Day 1-3	NR	Any Bleeding	1.94 (0.94-4.02)	Major and non-major clinically relevant bleeding	1.34 (0.33-5.42)
			Day 4-7	NR		0.55 (0.18-1.70)		0.50 (0.07-3.55)
			After Day 7	NR		2.26 (1.04-4.88)		2.19 (0.52-9.28)

NR = Not reported

## References

1. Eriksson BI, Rosencher N, Friedman RJ, Homering M, Dahl OE. Concomitant use of medication with antiplatelet effects in patients receiving either rivaroxaban or enoxaparin after total hip or knee arthroplasty. Thromb Res 2012.

**Evidence Table 29. Patient-oriented Outcomes (Any Bleeding Events) over the total at risk period for KQ5**

Author, Year	Arm	N for Analysis	Time Points	Test to Confirm DVT/PE	Outcome	n (%) of Patients with Outcomes	Rate per 100 patient-weeks with co-medication	Rate per 100 patient-weeks without co-medication	Measures of Association, Rate ratio* for use versus non-use (95% CI)
Eriksson B.I, 2012 <sup>1</sup>	Arm 1 (Rivaroxaban)	6093	Day 1-3 Day 4-7 After Day 7	NR	Any Bleeding	20 (3.6)	2.04 (1.25-3.15)	1.76 (1.58-1.95)	1.32 (0.85-2.05)
	Arm 2 (Enoxaparin/placebo)	6107	Day 1-3 Day 4-7 After Day 7	NR	Any Bleeding	17 (3.2)	2.06 (1.20-3.29)	1.63 (1.46-1.81)	1.40 (0.87-2.25)

\*Stratified by time windows day 1-3, day 4-7 and after day 7

NR = Not reported

## References

1. Eriksson BI, Rosencher N, Friedman RJ, Homering M, Dahl OE. Concomitant use of medication with antiplatelet effects in patients receiving either rivaroxaban or enoxaparin after total hip or knee arthroplasty. Thromb Res 2012.

**Evidence Table 30. Patient-oriented Outcomes (Major and non-major clinically relevant bleeding events) over the total at risk period for KQ5**

Author, Year	Arm	N for Analysis	Time Points	Test to Confirm DVT/PE	Outcome	n (%) of Patients with Outcomes	Rate per 100 patient-weeks with co-medication	Rate per 100 patient-weeks without co-medication	Measures of Association, Rate ratio* for use versus non-use (95% CI)
Eriksson B.I, 2012 <sup>1</sup>	Arm 1 (Rivaroxaban)	6093	Day 1-3 Day 4-7 After Day 7	NR	Major and non-major clinically relevant bleeding	8 (1.4)	0.78 (0.34-1.54)	0.78 (0.67-0.91)	1.11 (0.55-2.55)
	Arm 2 (Enoxaparin/placebo)	6107	Day 1-3 Day 4-7 After Day 7	NR	Major and non-major clinically relevant bleeding	5 (1.0)	0.59 (0.19-1.38)	0.59 (0.49-0.70)	1.13 (0.47-2.75)

\*Stratified by time windows day 1-3, day 4-7 and after day 7

NR = Not reported

## References

1. Eriksson BI, Rosencher N, Friedman RJ, Homering M, Dahl OE. Concomitant use of medication with antiplatelet effects in patients receiving either rivaroxaban or enoxaparin after total hip or knee arthroplasty. Thromb Res 2012.

**Evidence Table 31. Adverse Events for KQ5**

Author, Year	Arm	N for analysis	Time point	Outcome	Definition	n Patients
Eriksson B.I., 2012 <sup>1</sup>	Arm 1 (Rivaroxaban)	6093	NR	NR	NR	NR
	Arm 2 (Enoxaparin/placebo)	6107	NR	NR	NR	NR
Friedman,R.J., 2012 <sup>2</sup>	Arm 1 (220 mg Dabigatran, no ASA)	1149	Hospital stay	Major bleeding	clinically overt bleeds associated with a $\geq 20$ g/l reduction in haemoglobin or leading to transfusion of two or more units of packed cells or whole blood; symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding requiring treatment cessation; bleeding leading to reoperation; and surgical site bleeds	16 (1.4%)
	Arm 2 (150 mg Dabigatran, no ASA)	1149	Hospital stay	Major bleeding	clinically overt bleeds associated with a $\geq 20$ g/l reduction in haemoglobin or leading to transfusion of two or more units of packed cells or whole blood; symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding requiring treatment cessation; bleeding leading to reoperation; and surgical site bleeds	11 (1.0%)
	Arm 3 (Enoxaparin, no ASA)	1167	Hospital stay	Major bleeding	clinically overt bleeds associated with a $\geq 20$ g/l reduction in haemoglobin or leading to transfusion of two or more units of packed cells or whole blood; symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding requiring treatment cessation; bleeding leading to reoperation; and surgical site bleeds	14 (1.2%)
	Arm 4 (220 mg Dabigatran + ASA)	126	Hospital stay	Major bleeding	clinically overt bleeds associated with a $\geq 20$ g/l reduction in haemoglobin or leading to transfusion of two or more units of packed cells or whole blood; symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding requiring treatment cessation; bleeding leading to reoperation; and surgical site bleeds	2 (1.6%)

Author, Year	Arm	N for analysis	Time point	Outcome	Definition	n Patients
	Arm 5 (150 mg Dabigatran + ASA)	128	Hospital stay	Major bleeding	clinically overt bleeds associated with a $\geq 20$ g/l reduction in haemoglobin or leading to transfusion of two or more units of packed cells or whole blood; symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding requiring treatment cessation; bleeding leading to reoperation; and surgical site bleeds	2 (1.6%)
	Arm 6 (Enoxaparin+ ASA)	132	Hospital stay	Major bleeding	clinically overt bleeds associated with a $\geq 20$ g/l reduction in haemoglobin or leading to transfusion of two or more units of packed cells or whole blood; symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding requiring treatment cessation; bleeding leading to reoperation; and surgical site bleeds	4 (3.0%)

NR = Not reported

## References

1. Eriksson BI, Rosencher N, Friedman RJ, Homering M, Dahl OE. Concomitant use of medication with antiplatelet effects in patients receiving either rivaroxaban or enoxaparin after total hip or knee arthroplasty. *Thromb Res* 2012.
2. Friedman RJ, Kurth A, Clemens A, Noack H, Eriksson BI, Caprini JA. Dabigatran etexilate and concomitant use of non-steroidal anti-inflammatory drugs or acetylsalicylic acid in patients undergoing total hip and total knee arthroplasty: no increased risk of bleeding. *Thromb Haemost* 2012; 108(1):183-90.



**Evidence Table 32. Study characteristics KQ6**

Author, Year	Study Design	Study Site – Study Locations	Recruitment Date (start date – end date)	Planned Length of Follow-up	Method of Surveillance for VTE	Funding Source	Inclusion Criteria	Exclusion Criteria
<b>IVCF versus IVCF</b>								
Van Ha, TG, 2011 <sup>1</sup>	Retrospective Cohort	Single center-North America	2005-2008	10 weeks (4 weeks post placement + 6 weeks post retrieval)	All patients underwent venous color-flow duplex ultrasound of the lower extremities 1 week before filter removal to rule out lower extremity DVT.	NR	BMI- >50 kg/m2 One patient undergoing removal of a retroperitoneal primitive neuroectodermal tumor received bilateral iliac filter placement not because of megacava, but to prevent potential surgical field disruption caused by IVC placement. All patients underwent full assessment and informed consent for retrievable filter placement and subsequent retrieval.	NR
<b>IVCF versus Control</b>								
Birkmeyer, N. J. <sup>2</sup>	Retrospective Cohort	Multi-center-North America	2006-2008	NR	NR	Longitudinal	Open or laparoscopic gastric bypass procedure	Revisional surgery, laparoscopic gastric banding, biliopancreatic diversion, sleeve gastrectomy procedures
<b>IVCF versus Control</b>								
Gargiulo, N.J., 2006 <sup>3</sup>	Ambidirectional-Retrospective-Pro prospective Cohort	Single center-North America	1999-2005	NR	DVT: All patients had routine pre and post-operative lower extremity venous duplex examination. PE: For patients with clinical sequelae suggestive of a PE, PEs were documented by spiral CT, V/Q scan or autopsy	NR	NR	NR

Author, Year	Study Design	Study Site – Study Locations	Recruitment Date (start date – end date)	Planned Length of Follow-up	Method of Surveillance for VTE	Funding Source	Inclusion Criteria	Exclusion Criteria
					within the perioperative period (30 days after surgery)			
Li, W., 2012 <sup>4</sup>	Retrospective Cohort	Multi-center-North America	2007-2009	90 day post operative follow-up visit information was collected	NR	Surgical Review Corporation	Patients undergoing Roux-en-Y gastric bypass and adjustable gastric banding surgeries.	NR
Obeid, F. N., 2007 <sup>5</sup>	Retrospective Cohort	Single center-North America	2000-2006	NR	NR	NR	NR	NR
Overby, D. W., 2009 <sup>6</sup>	Retrospective Cohort	Single center-North America	2001-2008	NR	CT venography or lower extremity venous duplex ultrasonography prior to filter removal only (no surveillance immediately post-op)	NR	Elevation above the normal range of any of the variables associated with thrombophilia (antithrombin III deficiency, protein C deficiency, protein S deficiency, homocysteine elevation, factor V Leiden mutation, presence of anticardiolipin antibodies (immunoglobulins G and M), presence of lupus anticoagulant, those who had strong clinical indicators of high VTE risk including: poor ambulation, history of severe venous stasis disease, pulmonary hypertension, severe sleep apnea with obesity hypoventilation syndrome, BMI over 60, prior VTE	Revisional surgery
<b>IVCF alone</b>								
Kardys, C. M. 2008 <sup>7</sup>	Retrospective Cohort	Single center-North America	2004-2006	NR	NR	NR	Review of all bariatric patients who underwent IVUS-guided IVCF placement at Roux-en-Y	NR

Author, Year	Study Design	Study Site – Study Locations	Recruitment Date (start date – end date)	Planned Length of Follow-up	Method of Surveillance for VTE	Funding Source	Inclusion Criteria	Exclusion Criteria
							gastric bypass was performed. Patients with a history of VTE, profound immobility, venous insufficiency, hypercoagulable disorder were considered for IVC placement.	
Piano, G., 2007 <sup>8</sup>	Prospective Cohort	Single center-North America	2004-2005	NR	One week before filter retrieval, all patients were re-evaluated by the vascular surgeon (G. P.) and underwent venous color-flow duplex ultrasound scanning of the lower extremities to rule out lower extremity DVT	NR	BMI $\geq 55$ kg/m <sup>2</sup> , previous history of deep venous thrombosis (DVT) or pulmonary embolus, candidates for bariatric surgery, severe immobility, hypercoagulable state, venous stasis	NR
Schuster, R., 2007 <sup>9</sup>	Retrospective Cohort	Single center-North America	2003-2006	Follow up was $16 \pm 7.6$ months (range 8-33)	No	NR	All patients underwent laparoscopic gastric bypass surgery. Indications for IVC filter insertion were history of DVT or PE, severe venous stasis disease, long-standing sleep apnea and/or weight >400 pounds	NR
Schweitzer, M., 2006 <sup>10</sup>	Case Report	Single center-North America	NR	NR	NR	NR	NR	NR
Vaziri, K., 2010 <sup>11</sup>	Retrospective Cohort	Single site-North America	2007-2009	NR	NR	NR	BMI $\geq 55$ kg/m <sup>2</sup> , bariatric surgery, severe immobility, prior history of VTE, preexisting hypercoagulable	NR

Author, Year	Study Design	Study Site – Study Locations	Recruitment Date (start date – end date)	Planned Length of Follow-up	Method of Surveillance for VTE	Funding Source	Inclusion Criteria	Exclusion Criteria
							disorder	
Veerapong, J., 2008 <sup>12</sup>	Case report	Single center-North America	NR	NR	NR	NR	NR	NR
<b>Pharmacological versus Pharmacological</b>								
Borkgren-Okonek, M. 2008 <sup>13</sup>	Non randomized prospective open trial	Single center-North America	2004-2006	3 months post surgery	Lower extremity venous USS, Computed Chest Tomography	Study was an investigator-initiated trial funded in part by a pharmaceutical company	Age≥18 years, patients meeting eligibility criteria established by the NIH and underwent first time RYGB	Creatinine >1.6 mg/dL, previous VTE or known hypercoagulable state, chronic warfarin use, contraindication/hypersensitivity to UFH or LMWH (including a history of heparin-induced thrombocytopenia)
Hamad, G.G., 2005 <sup>14</sup>	Retrospective Cohort	Multi center-North America	January 2002-December 2002	NR	Doppler USS, V/Q scan, Chest CT	Funded by an unrestricted educational grant from a pharmaceutical company	All patients satisfied the NIH criteria for bariatric surgery and had undergone a primary bariatric surgical procedure (RYGB, VBG or laparoscopic RYGB)	NR
Kothari, S. 2007 <sup>15</sup>	Prospective Cohort	Single center-North America	NR	30 days	NR	NR	Laparoscopic Gastric Bypass patients	NR
Ojo, P., 2008 <sup>16</sup>	Retrospective Cohort	Single center-North America	2004-2005	Post-op till 2 weeks after discharge from hospital	NR	NR	Previous history of PE or DVT; BMI≥60; or BMI≥50 with any of these 3 risk factors: venous stasis disease; obstructive sleep apnea or severe ambulation limitation	Patients with previous history of bleeding and those discharged on therapeutic LMWH dosages or warfarin
Raftopoulos, I., 2008 <sup>17</sup>	Non randomized trial	Single center-North America	2003-2007	>1month	Pre-hospital discharge bilateral lower extremities	NR	Patients who underwent bariatric surgery with more than 1 month follow-up	NR

Author, Year	Study Design	Study Site – Study Locations	Recruitment Date (start date – end date)	Planned Length of Follow-up	Method of Surveillance for VTE	Funding Source	Inclusion Criteria	Exclusion Criteria
					venous doppler studies			
Rowan, B. O. 2008 <sup>18</sup>	Prospective Cohort	Single center-North America	2005-2006	NR	NR	NR	Any patient undergoing laparoscopic banding or laparoscopic gastric bypass surgery	All anti-Xa levels drawn earlier than 3hr postdose or later than 5hr postdose
Scholten, D. J., 2002 <sup>19</sup>	Retrospective Cohort	Single center-North America	1997-2000	6 months	DVT by USS or venogram PE by spiral CAT scan	NR	Primary bariatric surgical patients and revisional bariatric surgical patients.	Inpatient death (not due to PE), patients with previous VTE or hypercoagulable state who opted for outpatient prophylactic treatment following hospital discharge
Simone, E. 2008 <sup>20</sup>	Prospective Cohort	Single center-North America	2006-2007	Duration of hospital stay	NR	NR	Laparoscopic gastric bypass or laparoscopic adjustable gastric band placement, admission between November 2006-March 2007	Anti-Xa levels were not drawn correctly, withheld enoxaparin because of bleeding concerns
Singh, K., 2011 <sup>21</sup>	Retrospective Cohort	Single center-North America	2004-2007	2 years	Venous color Doppler flow, CTA	NR	Patients who underwent Roux-en-Y gastric bypass surgery	NR

AIS= Abbreviated Injury Scale; BMI= Body Mass Index; CAT= Computed Axial Tomography; CT= Computed Tomography; CTA= Computed Tomography Angiography; CUS= Compression Ultrasonography; DVT= Deep Vein Thrombosis; GCS= Glasgow Coma Scale; ICU= Intensive Care Unit; IPG= Impedance Phlebography; ISS= Injury Severity Score; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; LE= Lower Extremity; LMWH= Low Molecular Weight Heparin; NIH= National Institutes of Health; NR= Not Reported; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrieval Inferior Vena Cava Filter; RYGB= Roux-en-Y gastric bypass; SCD= Sequential Compression Device; SCI= Spinal Cord Injury; TBI= Traumatic Brain Injury; UFH= Unfractionated Heparin; USS= Ultrasound Scan; VCF= Vena Cava Filter; V/Q Scan = Ventilation Perfusion Scan; VTE= Venous Thromboembolism; VBG=Vertical Banded Gastroplasty

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thromboembolic and bleeding events following laparoscopic gastric bypass in patients treated with prophylactic regimens of unfractionated heparin or enoxaparin. 2007; 194:709-11.

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**Evidence Table 33. Participant characteristics for KQ6**

Author, Year	Arm, n	Age (Years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI (kg/m <sup>2</sup> )	Weight (lbs)	Prior History of VTE, n (%)	Trauma, n(%)	ICU duration
Birkmeyer, N. J., 1*	Arm 1 (Filter), 542	Mean: 48	Male (30)	NR	>50 in 72%	NR	(35)	NR	NR
Birkmeyer, N. J., 1*	Arm 2 (No filter), 5834	Mean: 48	Male (19)	NR	>50 in 34%	NR	(2)	NR	NR
Borkgren- Okonek, M. 2008 <sup>2</sup>	Arm 2 (Enoxaparin 40 mg), 124	Mean: 44.7 Range: 18-67	Male, 28	NR	Mean: 44.9 Range: 36-50	Mean: 125.5 Range: 87-175	NR	NR	NR
Borkgren- Okonek, M. 2008 <sup>2</sup>	Arm 3 (Enoxaparin 60 mg), 99	Mean: 44.3 Range: 19-65	Male, 27	NR	Mean: 57.4 Range: 51-82	Mean: 161.4 Range: 116-249	NR	NR	NR
Gargiulo, N.J., 2006 <sup>3</sup>	Arm 1 (Filter), 58	NR	NR	NR	>55: 100%	NR	NR	NR	NR
Gargiulo, N.J., 2006 <sup>3</sup>	Arm 2 (No filter), 351	NR	NR	NR	>55: 12%	NR	NR	NR	NR
Hamad, G.G., 2005 <sup>4</sup>	Arm 1 (Enoxaparin 30mg pre-op), 100	Mean: 39.5	Male, (25)	NR	Mean: 47.0	NR	0 (0)	NR	NR
Hamad, G.G., 2005 <sup>4</sup>	Arm 2 (Enoxaparin 30 mg post- discharge q24h), 124	Mean: 42.1	Male, (18)	NR	Mean: 51.5	NR	2 (1.6)	NR	NR
Hamad, G.G., 2005 <sup>4</sup>	Arm 3 (Enoxaparin 40mg post-op q24h: 12 to 120 hours), 84	Mean: 47.5	Male, (29)	NR	Mean: 56.8	NR	6 (7.1)	NR	NR
Hamad, G.G., 2005 <sup>4</sup>	Arm 4 (Enoxaparin 40mg post-op q24h: 12-24	Mean: 41.9	Male, (10)	NR	Mean: 49.9	NR	0 (0)	NR	NR



Author, Year	Arm, n	Age (Years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI (kg/m <sup>2</sup> )	Weight (lbs)	Prior History of VTE, n (%)	Trauma, n(%)	ICU duration
	hours), 180								
Hamad, G.G., 2005 <sup>4</sup>	Arm 5 (Enoxaparin 40mg post-op q24h: 12-36 hours), 180	Mean: 39.7	Male, (3)	NR	Mean: 46.0	NR	3 (1.6)	NR	NR
Kardys, C. M. 2008 <sup>5</sup>	Arm 1(Control), 563	NR	NR	NR	NR	NR	NR	NR	NR
Kardys, C. M. 2008 <sup>5</sup>	Arm 2 (Filter), 31	Mean: 43	Male, 12	NR	Mean: 71.2	NR	5	NR	NR
Kothari, S. 2007 <sup>6</sup>	Arm 2 (Enoxaparin), 238	Mean: 42	NR	NR	Mean: 48.7	Mean: 302 lb	NR	NR	NR
Kothari, S. 2007 <sup>6</sup>	Arm 3 (UFH), 238	Mean: 44	NR	NR	Mean: 47.0	Mean: 296 lb	NR	NR	NR
Li, W., 2012 <sup>7</sup>	Arm 1 (Filter), 322	Mean: 47	Male (31.4)	AA (18)	Mean: 45.3	NR	(21.4)	NR	NR
Li, W., 2012 <sup>7</sup>	Arm 2 (No filter), 96,806	Mean: 46	Male (21.1)	AA (10.5)	Mean: 44.5	NR	(3.1)	NR	NR
Obeid, F. N., 2007 <sup>8</sup>	Arm 2 (Filter), 246	Mean: 46.6	Male (23.6)	NR	Mean: 60	NR	NR	NR	NR

Author, Year	Arm, n	Age (Years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI (kg/m <sup>2</sup> )	Weight (lbs)	Prior History of VTE, n (%)	Trauma, n(%)	ICU duration
Obeid, F. N., 2007 <sup>8</sup>	Arm 1 (No filter), 1847	Mean: 44.7	Male (14)	NR	Mean: 48.8	NR	NR	NR	NR
Ojo, P., 2008 <sup>9</sup>	Arm 2 (Enoxaparin 40 mg), 59	Mean: 48	Male, 20	NR	Mean: 57	NR	NR	NR	NR
Ojo, P., 2008 <sup>9</sup>	Arm 3 (Enoxaparin 60 mg), 68	Mean: 46	Male, 42	NR	Mean: 58	NR	NR	NR	NR
Overby, D. W., 2009 <sup>10</sup>	Arm 2 (Filter), 160	NR	Overall Male, 48 (14.55)	NR	Overall Mean: 51.42	NR	NR	NR	NR
Overby, D. W., 2009 <sup>10</sup>	Arm 1 (No filter), 170	NR		NR		NR	NR	NR	NR
Piano, G., 2007 <sup>11</sup>	Arm 2 (Filter), 59	Mean: 43	Male, 10 (17)	NR	Mean: 61	NR	6 (10)	NR	NR
Raftopoulos, I., 2008 <sup>12</sup>	Arm 2 (Enoxaparin 30mg), 132	Mean: 42.6	Male, 20 (15.2)	NR	Mean: 47.8	NR	3 (2.3)	NR	NR
Raftopoulos, I., 2008 <sup>12</sup>	Arm 3 (Enoxaparin 30mg, extended duration), 176	Mean: 44.1	Male, 33 (18.75)	NR	Mean: 46.1	NR	7 (4.0)	NR	NR
Rowan, B. O. 2008 <sup>13</sup>	Arm 2 (Enoxaparin 30mg), 19	Mean: 41.7	Male (26)	NR	Mean: 48.4	Mean: 141.6	NR	NR	NR

Author, Year	Arm, n	Age (Years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI (kg/m <sup>2</sup> )	Weight (lbs)	Prior History of VTE, n (%)	Trauma, n(%)	ICU duration
Rowan, B. O. 2008 <sup>13</sup>	Arm 3 (Enoxaparin 40mg), 33	Mean: 40.8	Male (18)	NR	Mean: 48.5	Mean: 135.6	NR	NR	NR
Scholten, D. J.,2002 <sup>14</sup>	Arm 2 (Enoxaparin 30mg), 92	Mean: 43.7	Male, 19 (20.2)	NR	Mean: 51.7	NR	NR	NR	NR
Scholten, D. J.,2002 <sup>14</sup>	Arm 3 (Enoxaparin 40mg), 389	Mean: 44.3	Male, 62 (15.8)	NR	Mean: 50.4	NR	NR	NR	NR
Schuster, R., 2007 <sup>15</sup>	Arm 2 (Filter), 24	Mean: 49.8	Male, 14	NR	Mean: 57.2	NR	NR	NR	NR
Schweitzer, M., 2006 <sup>16</sup>	Overall, 1	63 year old	Female, 1	NR	Mean: 45	Mean: 284 lb	NR	NR	NR
Simone, E. 2008 <sup>17</sup>	Arm 2 (Enoxaparin 40mg), 24	Mean: 40.0	Male (12.5)	NR	Mean: 48.8	Mean: 135	NR	NR	NR
Simone, E. 2008 <sup>17</sup>	Arm 3 (Enoxaparin 60mg), 16	Mean: 41.0	Male (6.3)	NR	Mean: 47.3	Mean: 127	NR	NR	NR
Singh, K., 2011 <sup>18</sup>	Group 1 (Enoxaparin 30mg), 11	Overall Mean: 43	Overall Male, 91 (53)	NR	Mean: 39	Mean: 108	NR	NR	NR
Singh, K., 2011 <sup>18</sup>	Group 2 (Enoxaparin 40mg), 145				Mean: 48	Mean: 134	NR	NR	NR

Author, Year	Arm, n	Age (Years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI (kg/m <sup>2</sup> )	Weight (lbs)	Prior History of VTE, n (%)	Trauma, n(%)	ICU duration
Singh, K., 2011 <sup>18</sup>	Group 3 (Enoxaparin 50mg), 9				Mean: 51	Mean: 149	NR	NR	NR
Singh, K., 2011 <sup>18</sup>	Group 4 (Enoxaparin 60mg), 5				Mean: 65	Mean: 169	NR	NR	NR
Van Ha, TG, 2011 <sup>19</sup>	Arm 2 (Filter), 9	Mean: 45	Male: 6	NR	Mean: >50	NR	NR	NR	NR
Vaziri, K., 2010 <sup>20</sup>	Arm 2 (Filter), 41	Mean: 48	Male, 12	NR	Mean: 58.4	NR	1	NR	NR
Veerapong, J., 2008 <sup>21</sup>	Overall, 1	31 year old	Male, 1	NR	74	526	NR	NR	NR

AA=African American; AIS= Abbreviated Injury Scale; BMI= Body Mass Index; CAT= Computed Axial Tomography; CT= Computed Tomography; CTA= Computed Tomography Angiography; CUS= Compression Ultrasonography; DVT= Deep Vein Thrombosis; GCS= Glasgow Coma Scale; ICU= Intensive Care Unit; IPG= Impedance Phlebography; ISS= Injury Severity Score; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; LE= Lower Extremity; LMWH= Low Molecular Weight Heparin; NIH= National Institutes of Health; NR= Not Reported; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; RYGB= Roux-en-Y gastric bypass; SCD= Sequential Compression Device; SCI= Spinal Cord Injury; TBI= Traumatic Brain Injury; UFH= Unfractionated Heparin; USS= Ultrasound Scan; VCF= Vena Cava Filter; V/Q Scan = Ventilation Perfusion Scan; VTE= Venous Thromboembolism

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Record Number: 523
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**Evidence Table 34. Filter Interventions for KQ 6**

Author, Year	Arm Name	Filter Name	Filter Type (temp or permanent)	Filter Placed by	Setting	Planned Duration of Filter	Concurrent Therapy	Comparator Arm
<b>IVCF versus IVCF</b>								
Van Ha, TG, 2011 <sup>1</sup>	(Bilateral Iliac Vein Filter)	Celect <sup>®</sup> 1patient Gunther Tulip <sup>®</sup> 9 patients	Temporary	NR	Operating room	4 weeks	All patients received IV heparin infusion at the beginning of procedure. At discharge, patients were on twice daily enoxaparin which continued until time of filter retrieval	None
<b>IVCF versus Control Cohort- Retrospective</b>								
Birkmeyer, N. J., <sup>2</sup>	IVCF	NR	NR	NR	NR	NR	None	No Filter Arm
Gargiulo, N.J., 2006 <sup>3</sup>	IVCF	Greenfield Stainless Steel <sup>®</sup> , Simon Nitinol <sup>®</sup> , TRAPEASE <sup>®</sup> , Bard Recovery	NR	NR	NR	NR	NR	No Filter Arm
Li, W., 2012 <sup>4</sup>	IVCF	NR	NR	NR	NR	NR	Intraoperative anticoagulation: 89.8% Foot pump: 15.5%	No Filter Arm
Obeid, F. N., 2007 <sup>5</sup>	IVCF	NR	Temporary	NR	NR	NR	Sequential compression devices, Ambulation, prophylactic enoxaparin for all patients and warfarin for IVCF group only	No Filter Arm
Overby, D. W., 2009 <sup>6</sup>	IVCF	Celect <sup>®</sup> , Gunther Tulip <sup>®</sup> , OPTEASE <sup>®</sup> , Bard Recovery, Bard G2.	Temporary	Interventional radiologist or vascular surgeon	Interventional radiology suite	6 weeks post-op	Sequential calf compression devices, SQ heparin 5000-7500U 8hourly from before surgery to hospital discharge	NR
<b>IVCF Alone Cohort- Prospective</b>								
Piano, G., 2007 <sup>7</sup>	IVC Filter	Gunther Tulip <sup>®</sup>	Temporary	NR	NR	4weeks post-op	Sequential compression devices,	NR

Author, Year	Arm Name	Filter Name	Filter Type (temp or permanent)	Filter Placed by	Setting	Planned Duration of Filter	Concurrent Therapy	Comparator Arm
							heparin 500U/hr pre-op, enoxaparin 40mg 12hrly post op	
<i>Cohort-Retrospective</i>								
Kardys, C. M. 2008 <sup>8</sup>	IVC Filter	Greenfield Stainless Steel <sup>®</sup>	NR	NR	NR	NR	Sequential compression devices or foot pumps. Ambulated day of surgery if not in ICU, 5000u heparin SQ pre-op and enoxaparin 40mg bid post-op	NR
Schuster, R., 2007 <sup>9</sup>	IVC Filter	Gunther Tulip <sup>®</sup>	Temporary	Interventional radiologist		2weeks	NR	NR
<i>Cohort-Retrospective</i>								
Vaziri, K., 2010 <sup>10</sup>	IVC Filter	Gunther Tulip <sup>®</sup> , G2 <sup>®</sup> filters	Temporary	NR	NR	NR	SQ Heparin 5000 8hourly	NR
<i>Case report</i>								
Schweitzer, M., 2006 <sup>11</sup>	The patient had an IVCF placed	OPTEASE	Temporary	NR	NR	NR	Antiembolism stockings, sequential compression devices, op-day ambulation, SQ enoxaparin 40 mg 12 hourly	NR
Veerapong, J., 2008 <sup>12</sup>	The patient had an IVCF placed	Gunther Tulip <sup>®</sup>	Temporary	NR	Operating room	NR	NR	NR

AIS= Abbreviated Injury Scale; BMI= Body Mass Index; CAT= Computed Axial Tomography; CT= Computed Tomography; CTA= Computed Tomography Angiography; CUS= Compression Ultrasonography; DVT= Deep Vein Thrombosis; GCS= Glasgow Coma Scale; Hr(s)= Hour(s); ICU= Intensive Care Unit; IPG= Impedance Phlebography; ISS= Injury Severity Score; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; LE= Lower Extremity; LMWH= Low Molecular Weight Heparin; mg= milligram; NIH= National Institutes of Health; NR= Not Reported; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrieval Inferior Vena Cava Filter; RYGB= Roux-en-Y gastric bypass; SCD= Sequential Compression Device; SCI= Spinal Cord Injury; SQ=Subcutaneous; TBI= Traumatic Brain Injury; UFH= Unfractionated Heparin; USS= Ultrasound Scan; U= units; VCF= Vena Cava Filter; V/Q Scan = Ventilation Perfusion Scan; VTE= Venous Thromboembolism



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**Evidence Table 35. Drug Interventions for KQ 6**

Author, Year	Arm Name	Drug name	Dose	Route	Frequency	Timing of first dose	Planned duration of therapy (Other e.g.INR)	Concurrent Therapy
<b>Pharmacological versus Pharmacological Cohort-Pro prospective</b>								
Kothari, S. 2007 <sup>1</sup>	Enoxaparin	Enoxaparin	40mg	SQ	Twice daily	Pre-op	Hospital stay	Sequential compression devices, early ambulation
Kothari, S. 2007 <sup>1</sup>	Heparin	Heparin	5000U	SQ	Thrice daily	Pre-op	Hospital stay	Sequential compression devices, early ambulation
Rowan, B. O. 2008 <sup>2</sup>	Group1	Enoxaparin	30mg	SQ	12 hourly	11pm on op-day	NR	Pneumatic compression devices before anesthesia, early ambulation was encouraged on day of surgery
Rowan, B. O. 2008 <sup>2</sup>	Group2	Enoxaparin	40mg	SQ	12 hourly	11pm on op-day	NR	Pneumatic compression devices before anesthesia, early ambulation was encouraged on day of surgery
Simone, E. 2008 <sup>3</sup>	40mg arm	Enoxaparin	40mg	SQ	12 hourly	11pm on op day	Hospital stay	None
Simone, E. 2008 <sup>3</sup>	60mg arm	Enoxaparin	60mg	SQ	12 hourly	11pm on op day	Hospital stay	None
<b>Cohort-retrospective</b>								
Hamad, G.G., 2005 <sup>4</sup>	Center A	Enoxaparin	30mg	SC	NR	NR	Duration not available,	No
Hamad, G.G., 2005 <sup>4</sup>	Center B	Enoxaparin	30 mg	SC	Q24h	not reported	10days	No
Hamad, G.G., 2005 <sup>4</sup>	Center C	Enoxaparin	40 mg	SC	Q24h	not reported	12-120hrs	No
Hamad, G.G.,	Center D	Enoxaparin	40 mg	SC	Q24h	not reported	12-24hrs	No

Author, Year	Arm Name	Drug name	Dose	Route	Frequency	Timing of first dose	Planned duration of therapy (Other e.g.INR)	Concurrent Therapy
2005 <sup>4</sup>								
Hamad, G.G., 2005 <sup>4</sup>	Center E	Enoxaparin	40 mg	SC	Q12h	not reported	12-36hours	No
Ojo, P., 2008 <sup>5</sup>	40mg	Enoxaparin	40mg	SQ	12 hourly	12 hours post-op	2 weeks post-op	None
Ojo, P., 2008 <sup>5</sup>	60mg	Enoxaparin	60mg	SQ	12 hourly	12 hours post-op	2 weeks post-op	None
<i>Cohort-retrospective</i>								
Scholten, D. J.,2002 <sup>6</sup>	Group 1	Enoxaparin	30mg	SQ	12 hourly	2 hours pre-op	Till fully ambulatory or hospital discharge	Graded compression stockings, intermittent pneumatic compression devices or sequential compression devices and early ambulation
Scholten, D. J.,2002 <sup>6</sup>	Group 2	Enoxaparin	40mg	SQ	12 hourly	2 hours pre-op	Till fully ambulatory or hospital discharge	Graded compression stockings, intermittent pneumatic compression devices or sequential compression devices and early ambulation
<i>Non-randomized Trials</i>								
Borkgren-Okonek, M. 2008 <sup>7</sup>	40mg	Enoxaparin	40mg	SQ	12hourly till hospital discharge then once daily	12 hours post-op	Till 10 days after hospital discharge	Calf-length intermittent pneumatic compression devices, Post-op day or next day mobilization,

Author, Year	Arm Name	Drug name	Dose	Route	Frequency	Timing of first dose	Planned duration of therapy (Other e.g.INR)	Concurrent Therapy
								UFH 5000U within 2hrs before surgery
<i>Non-randomized Trials</i>								
Borkgren-Okonek, M. 2008 <sup>7</sup>	60mg	Enoxaparin	60mg	SQ	12hourly till hospital discharge then once daily	12 hours post-op	Till 10 days after hospital discharge	Calf-length intermittent pneumatic compression devices, Post-op day or next day mobilization, UFH 5000U within 2hrs before surgery
Raftopoulos, I., 2008 <sup>8</sup>	Group A	Enoxaparin	30mg	SQ	12 hourly	1 hour pre-op	Hospital stay	Calf-length pneumatic compression devices
Raftopoulos, I., 2008 <sup>8</sup>	Group B	Enoxaparin	30mg	SQ	12hourly	1 hour pre-op	Hospital stay and 10 days post hospital discharge	Calf-length pneumatic compression devices
<b>Pharmacological Alone Cohort-retrospective</b>								
Singh, K., 2011 <sup>9</sup>	NR	Enoxaparin	BMI <40: 30mg	SQ	12 hourly	1 hour before incision	NR	Pneumatic compression device
Singh, K., 2011 <sup>9</sup>	NR	Enoxaparin	BMI 40-49: 40mg	SQ	12 hourly	1 hour before incision	NR	Pneumatic compression device
Singh, K., 2011 <sup>9</sup>	NR	Enoxaparin	BMI 50-59: 50mg	SQ	12 hourly	1 hour before incision	NR	Pneumatic compression device
Singh, K., 2011 <sup>9</sup>	NR	Enoxaparin	BMI >50: 60mg	SQ	12 hourly	1 hour before incision	NR	Pneumatic compression device

AIS= Abbreviated Injury Scale; BMI= Body Mass Index; CAT= Computed Axial Tomography; CT= Computed Tomography; CTA= Computed Tomography Angiography; CUS= Compression Ultrasonography; DVT= Deep Vein Thrombosis; GCS= Glasgow Coma Scale; Hr(s)= Hour(s); ICU= Intensive Care Unit; IPG= Impedance Phlebography; ISS=

Injury Severity Score; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; LE= Lower Extremity; LMWH= Low Molecular Weight Heparin; mg= milligram; NIH= National Institutes of Health; NR= Not Reported; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrievable

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**Evidence Table 36. Patient-oriented Outcomes for KQ 6**

Author, Year	Arm	N for analysis	Time point	Test to confirm DVT/PE	Outcome	n (%) of Patients with Outcomes	n(%) of Events	Point Estimate	Measures of Association, Odds Ratio (95%CI)
<b>IVCF versus control Cohort- retrospective</b>									
Birkmeyer, N. J. <sub>1</sub>	Filter	542	30 days post surgery	NR	Composite VTE outcomes	11 (2.03)	NR	NR	1.40 (0.91-2.16) Reference group: No Filter) p-value:< 0.0001
Birkmeyer, N. J. <sub>1</sub>	No Filter	5834	30 days post surgery	NR	Composite VTE outcomes	31 (0.53)	NR	NR	NA
Gargiulo, N.J., 2006 <sup>2</sup>	Filter	58	Average follow up: 2.5 years, Range: 1-42 months	DVT: Ultrasonography. PE: For patients with clinical sequelae suggestive of a PE, spiral CT, V/Q scan or autopsy within the perioperative period (30 days after surgery)	DVT	2(3.0)	NR	NR	NR
Gargiulo, N.J., 2006 <sup>2</sup>	Filter	58	Average follow up: 2.5 years, Range: 1-42 months	DVT: Ultrasonography. PE: For patients with clinical sequelae suggestive of a PE, spiral CT, V/Q scan or autopsy within the perioperative period (30 days after surgery)	PE	0(0)	NR	NR	NR
Gargiulo, N.J., 2006 <sup>2</sup>	No Filter	351	Average follow up: 2.5 years, Range: 1-42 months	DVT: Ultrasonography. PE: For patients with clinical sequelae suggestive of a PE, spiral CT, V/Q scan or autopsy within the perioperative period (30 days after surgery)	DVT	NR	NR	NR	NR
Gargiulo, N.J., 2006{#3261	No Filter	351	Average follow up: 2.5 years, Range: 1-42 months	DVT: Ultrasonography. PE: For patients with clinical sequelae suggestive of a PE, spiral CT, V/Q scan or	PE	9(2.56)	NR	NR	NR

Author, Year	Arm	N for analysis	Time point	Test to confirm DVT/PE	Outcome	n (%) of Patients with Outcomes	n(%) of Events	Point Estimate	Measures of Association, Odds Ratio (95%CI)
				autopsy within the perioperative period (30 days after surgery)					
Li, W., 2012 <sup>3</sup>	Filter	322	NR	NR	DVT	3(0.93)	NR	NR	p-value: <0.001
Li, W., 2012 <sup>3</sup>	Filter	322	NR	NR	PE	1(0.31)	NR	NR	p-value: 0.33
Li, W., 2012 <sup>3</sup>	No Filter	96806	NR	NR	DVT	116(0.12)	NR	NR	NA
Li, W., 2012 <sup>3</sup>	No Filter	96806	NR	NR	PE	116(0.12)	NR	NR	NA
Obeid, F.N., 2007 <sup>4</sup>	Filter	246	30 days	DVT: Ultrasonography	DVT	3(1.2)	NR	NR	1.87 (0.53 - 6.70) p-value:0.56 (reference group: filter group)
Obeid, F.N., 2007 <sup>4</sup>	Filter	246	30 days	DVT: Ultrasonography	PE	2(0.8)	NR	NR	1.36 (0.30 - 6.19) p-value:0.69 (reference group: filter group)
Obeid, F.N., 2007 <sup>4</sup>	No Filter	1847	30 days	DVT: Ultrasonography	DVT	12 (0.65)	NR	NR	NA
Obeid, F.N., 2007 <sup>4</sup>	No Filter	1847	30 days	DVT: Ultrasonography	PE	11 (0.59)	NR	NR	NA
Overby, D.W., 2009 <sup>5</sup>	Filter	160	NR	DVT: Venography Ultrasonography	Total DVT only (Similarly this is for unspecified DVT)	5 (3.13)	NR	NR	NR
Overby, D.W., 2009 <sup>5</sup>	Filter	160	NR	DVT: Venography Ultrasonography	Total PE only (Unspecified PE)	1 (0.63)	NR	NR	NR
Overby, D.W., 2009 <sup>5</sup>	No Filter	170	NR	DVT: Venography Ultrasonography	Total DVT only (Similarly this is for unspecified DVT)	4 (2.35)	NR	NR	NR
Overby, D.W., 2009 <sup>5</sup>	No Filter	170	NR	DVT: Venography Ultrasonography	Total PE only (Unspecified PE)	5 (2.94)	NR	NR	NR
<b>IVCF Alone Cohort-retrospective</b>									
Kardys, C.M. 2008 <sup>6</sup>	Filter	31	262 ± 38 days	DVT: Other	Upper extremity DVT	1 (3.1)	NR	NR	NR
Kardys, C.M. 2008 <sup>6</sup>	Filter	31	262 ± 38 days	DVT: Other	Total PE only (Unspecified PE)	2 (6.4)	NR	NR	NR
Kardys, C.M. 2008 <sup>6</sup>	Filter	31	262 ± 38 days	DVT: Other	Total VTE only (only if VTE	3 (9.5)	NR	NR	NR

Author, Year	Arm	N for analysis	Time point	Test to confirm DVT/PE	Outcome	n (%) of Patients with Outcomes	n(%) of Events	Point Estimate	Measures of Association, Odds Ratio (95%CI)
					events are unspecified, you should choose this option)				
Piano, G., 2007 <sup>7</sup>	Filter	59	NR	DVT: Ultrasonography	Total DVT only (Similarly this is for unspecified DVT)	0	NR	NR	NR
Piano, G., 2007 <sup>7</sup>	Filter	59	NR	NR	Total PE only (Unspecified PE)	1 (1.69)	NR	NR	NR
Schuster, R., 2007 <sup>8</sup>	Filter	24	16 ± 7.6 months	DVT: Ultrasonography	DVT	5 (21)	NR	NR	NR
Schuster, R., 2007 <sup>8</sup>	Filter	24	16 ± 7.6 months	NR	PE	1 (4.2)	NR	NR	NR
Van Ha, T.G, 2011 <sup>9</sup>	Filter	10	4-6 weeks post IVC filter retrieval	NR	Total VTE	0	NR	NR	NR
Vaziri, K., 2010 <sup>10</sup>	Filter	41	NR	DVT: Ultrasonography	Total DVT only (Similarly this is for unspecified DVT)	2 (4.9)	NR	NR	NR
Vaziri, K., 2010 <sup>10</sup>	Filter	41	NR	DVT: Ultrasonography	PE	0	NR	NR	NR
<i>Case report</i>									
Schweitzer, M., 2006 <sup>11</sup>	NA	1	2 weeks post-operative	DVT: Autopsy PE: Autopsy	DVT	1 (100)	NR	NR	NR
Schweitzer, M., 2006 <sup>11</sup>	NA	1	2 weeks post-operative	DVT: Autopsy PE: Autopsy	PE	1 (100)	NR	NR	NR
<b>Pharmacological versus Pharmacological Cohort-Pro prospective</b>									
Kothari, S., 2007 <sup>12</sup>	Enoxaparin Arm	238	30 days	NR	DVT	0 (0)	NR	NR	p-value: 0.999
Kothari, S., 2007 <sup>12</sup>	Enoxaparin Arm	238	30 days	NR	PE	0 (0)	NR	NR	p-value: 0.999
Kothari, S., 2007 <sup>12</sup>	Heparin Arm	238	30 days	NR	DVT	0 (0)	NR	NR	p-value: 0.999
Kothari, S.,	Heparin Arm	238	30 days	NR	PE	1 (0.42)	NR	NR	p-value: 0.999



Author, Year	Arm	N for analysis	Time point	Test to confirm DVT/PE	Outcome	n (%) of Patients with Outcomes	n(%) of Events	Point Estimate	Measures of Association, Odds Ratio (95%CI)
2007 <sup>12</sup>									
<i>Cohort-retrospective</i>									
Scholten, D. J., 2002 <sup>13</sup>	Enoxaparin 40mg Arm	389	NR	NR	DVT	2 (0.5)	NR	NR	p-value: <0.01
Scholten, D. J., 2002 <sup>13</sup>	Enoxaparin 40mg Arm	389	NR	NR	PE	0 (0)	NR	NR	NR
Scholten, D. J., 2002 <sup>13</sup>	Enoxaparin 30mg Arm	92	NR	NR	DVT	1 (1.1)	NR	NR	NR
Scholten, D. J., 2002 <sup>13</sup>	Enoxaparin 30mg Arm	92	NR	NR	PE	4 (4.3)	NR	NR	NR
<i>Non-randomized trials</i>									
Borkgren-Okonek, M., 2008 <sup>14</sup>	Enoxaparin 40mg Arm	124	Day 37 post op	DVT: Ultrasonography PE: CT scan	DVT	1 (0.45)	NR	NR	NR
Borkgren-Okonek, M., 2008 <sup>14</sup>	Enoxaparin 40mg Arm	124	Day 37 post op	DVT: Ultrasonography PE: CT scan	PE	1 (0.45)	NR	NR	NR
Borkgren-Okonek, M., 2008 <sup>14</sup>	Enoxaparin 60mg Arm	99	Day 37 post op	DVT: Ultrasonography PE: CT scan	DVT	NR	NR	NR	NR
Borkgren-Okonek, M., 2008 <sup>14</sup>	Enoxaparin 60mg Arm	99	Day 37 post op	DVT: Ultrasonography PE: CT scan	PE	NR	NR	NR	NR
Raftopoulos, I., 2008 <sup>15</sup>	Enoxaparin Extended Dose Arm	176	30 days	DVT: Ultrasonography PE: CT scan	Total VTE only	0	NR	NR	NR
Raftopoulos, I., 2008 <sup>15</sup>	Enoxaparin Short Term Dose Arm	132	30 days	DVT: Ultrasonography PE: CT scan	DVT	3 (2.3)	NR	NR	p-value: 0.006 reference group-extended dose arm
Raftopoulos, I., 2008 <sup>15</sup>	Enoxaparin Short Term Dose Arm	132	30 days	DVT: Ultrasonography PE: CT scan	PE	3 (2.3)	NR	NR	NR
<b>Pharmacological alone</b> <i>Cohort-retrospective</i>									
Singh, K., 2011 <sup>16</sup>	Enoxaparin at different doses	170	Immediate post op period to 2 years follow up	DVT: Ultrasonography PE: CT scan	Total VTE only	0 (0)	NR	NR	NR

Author, Year	Arm	N for analysis	Time point	Test to confirm DVT/PE	Outcome	n (%) of Patients with Outcomes	n(%) of Events	Point Estimate	Measures of Association, Odds Ratio (95%CI)
Hamad, G.G., 2005 <sup>17</sup>	Enoxaparin 40mg q12h	180	10.5 ± 7.1 months	DVT: Ultrasonography, PE: V/Q scan /chest CT	PE	1 (0.6)	NR	NR	NR
Hamad, G.G., 2005 <sup>17</sup>	Enoxaparin 40mg q12h	180	10.5 ± 7.1 months	DVT: Ultrasonography, PE: V/Q scan /chest CT	DVT	0 (0)	NR	NR	NR
Hamad, G.G., 2005 <sup>17</sup>	Enoxaparin 40mg qd post op for 12-120 hours	84	10.5 ± 7.1 months	DVT: Ultrasonography, PE: V/Q scan /chest CT	PE	1 (1)	NR	NR	NR
Hamad, G.G., 2005 <sup>17</sup>	Enoxaparin 40mg qd post op for 12-120 hours	84	10.5 ± 7.1 months	DVT: Ultrasonography, PE: V/Q scan /chest CT	DVT	0 (0)	NR	NR	NR
Hamad, G.G., 2005 <sup>17</sup>	Enoxaparin 40mg qd post op for 12-24 hours	180	10.5 ± 7.1 months	DVT: Ultrasonography, PE: V/Q scan /chest CT	PE	0 (0)	NR	NR	NR
Hamad, G.G., 2005 <sup>17</sup>	Enoxaparin 40mg qd post op for 12-24 hours	180	10.5 ± 7.1 months	DVT: Ultrasonography, PE: V/Q scan /chest CT	DVT	0 (0)	NR	NR	NR
Hamad, G.G., 2005 <sup>17</sup>	Enoxaparin 30mg qd pre op	100	10.5 ± 7.1 months	DVT: Ultrasonography, PE: V/Q scan /chest CT	PE	2 (2)	NR	NR	NR
Hamad, G.G., 2005 <sup>17</sup>	Enoxaparin 30mg qd pre op	100	10.5 ± 7.1 months	DVT: Ultrasonography, PE: V/Q scan /chest CT	DVT	0 (0)	NR	NR	NR
Hamad, G.G., 2005 <sup>17</sup>	Enoxaparin 30mg qd post discharge	124	10.5 ± 7.1 months	DVT: Ultrasonography, PE: V/Q scan /chest CT	PE	2 (1.6)	NR	NR	NR
Hamad, G.G., 2005 <sup>17</sup>	Enoxaparin 30mg qd post discharge	124	10.5 ± 7.1 months	DVT: Ultrasonography, PE: V/Q scan /chest CT	DVT	1 (0.8)	NR	NR	NR

BMI= Body Mass Index; CAT= Computed Axial Tomography; CT= Computed Tomography; CTA= Computed Tomography Angiography; CUS= Compression Ultrasonography; DVT= Deep Vein Thrombosis; GCS= Glasgow Coma Scale; Hr(s)= Hour(s); ICU= Intensive Care Unit; IPG= Impedance Phlebography; ISS= Injury Severity Score; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; LMWH= Low Molecular Weight Heparin; mg= milligram; NIH= National Institutes of Health; NR= Not Reported; NA=Not Applicable PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; SCD= Sequential Compression Device; SQ=Subcutaneous; UFH= Unfractionated Heparin; USS= Ultrasound Scan; U= units; VCF= Vena Cava Filter; V/Q Scan = Ventilation Perfusion Scan; VTE= Venous Thromboembolism

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**Evidence Table 37. Other Patient-oriented Outcomes for KQ6**

Author, Year	Arm	N for analysis	Time point	Outcome	Definition	n (%) of patients with outcomes	n events	Mean/Med/Range	Other	Measures of Association
<b>IVCF versus control Cohort- retrospective</b>										
Birkmeyer, N. J. <sup>1</sup>	Filter	542	30 days post surgery	Death/Permanent Disability	Death/Permanent Disability	10 (1.85)	NR	NR	NR	2.49 (0.99-6.26) p-value:<0.0001 (Reference Group: No Filter Group)
Birkmeyer, N. J. <sup>1</sup>	No Filter	5834	30 days post surgery	Death/Permanent Disability	Death/Permanent Disability	30 (0.51)	NR	NR	NR	NA
Birkmeyer, N. J. <sup>1</sup>	Filter	542	30 days post surgery	Serious complication	NR	(3.62)	NR	NR	NR	1.40(0.91-2.16) p-value:<0.0001 (Reference Group: No Filter Group)
Birkmeyer, N. J. <sup>1</sup>	No Filter	5834	30 days post surgery	Serious complication	NR	(7.56)	NR	NR	NR	NA
Gargiulo, N.J., 2006 <sup>2</sup>	Filter	58	30 days	Total Mortality	PE related mortality	0 (0)	NR	NR	NR	NR
Gargiulo, N.J., 2006 <sup>2</sup>	No Filter	351	30 days	Total Mortality	PE related mortality	5 (1.42)	NR	NR	NR	NR
Gargiulo, N.J., 2006 <sup>2</sup>	Filter	58	30 days	Filter Retrieval Rate	NR	NR	NR	NR	NR	NR
Li, W., 2012 <sup>3</sup>	Filter	322	NR	Total Mortality	Deaths from PE or indeterminate causes	1 (0.31)	NR	NR	NR	NA
Li, W., 2012 <sup>3</sup>	No Filter	96806	NR	Total Mortality	Deaths from PE or indeterminate causes	29 (0.03)	NR	NR	NR	Comparing deaths in No Filter group to Filter group, the p-value is 0.003
Li, W., 2012 <sup>3</sup>	Filter	322	NR	Filter Retrieval Rate	NR	NR	NR	NR	NR	NR
Obeid, F. N., 2007 <sup>4</sup>	Filter	246	30 days	Total Mortality	NR	2 (0.81)	NR	NR	NR	NR
Obeid, F. N., 2007 <sup>4</sup>	No Filter	1847	30 days	Total Mortality	NR	4 (0.22)	NR	NR	NR	NR

Author, Year	Arm	N for analysis	Time point	Outcome	Definition	n (%) of patients with outcomes	n events	Mean/Med/Range	Other	Measures of Association
Obeid, F. N., 2007 <sup>4</sup>	Filter	246	30 days	Filter Retrieval Rate	NR	NR	NR	NR	NR	NR
Overby, D. W., 2009 <sup>5</sup>	Filter + No Filter Arms	330	NR	Total Mortality	Death	3 (0.9)	NR	NR	NR	NR
Overby, D. W., 2009 <sup>5</sup>	Filter	160	NR	Filter Retrieval Rate	Successful removal	147 (92)	NR	NR	NR	NR
<b>IVCF Alone Cohort-prospective</b>										
Piano, G., 2007 <sup>6</sup>	Filter	59	NR	Total Mortality	NR	0 (0)	NR	NR	NR	NR
Piano, G., 2007 <sup>6</sup>	Filter	59	NR	Filter Retrieval Rate	NR	52 (88)	NR	NR	NR	NR
<b>Cohort-retrospective</b>										
Kardys, C.M., 2008 <sup>7</sup>	Filter	31	NR	Total Mortality	NR	2 (6.4)	NR	NR	NR	NR
Kardys, C.M., 2008 <sup>7</sup>	Filter	31	NR	Filter Retrieval Rate	NR	NR	NR	NR	NR	NR
Schuster, R., 2007 <sup>8</sup>	Filter	NR	16 ± 7.6 months	Total Mortality	NR	0 (0)	NR	NR	NR	NR
Schuster, R., 2007 <sup>8</sup>	Filter	NR	16 ± 7.6 months	Filter Retrieval Rate	NR	20 (83)	NR	NR	NR	NR
Van Ha, T.G., 2011 <sup>9</sup>	Filter	10	4-6 weeks post IVC filter retrieval	Total Mortality	NR	0 (0)	NR	NR	NR	NR
Van Ha, T.G., 2011 <sup>9</sup>	Filter	10	4-6 weeks post IVC filter retrieval	Filter Retrieval Rate	NR	10 (100)	NR	NR	NR	NR
Vaziri, K., 2010 <sup>10</sup>	Filter	41	NR	Total Mortality	Mortality occurred secondary to a postoperative myocardial	1 (2.4)	NR	NR	NR	NR

Author, Year	Arm	N for analysis	Time point	Outcome	Definition	n (%) of patients with outcomes	n events	Mean/Med/Range	Other	Measures of Association
					infarction					
Vaziri, K., 2010 <sup>10</sup>	Filter	41	NR	Filter Retrieval Rate	Successful filter retrieval	28 (68)	NR	NR	NR	NR
<i>Case report</i>										
Schweitzer, M., 2006 <sup>11</sup>	NA	1	2 weeks post-operative	Total Mortality	NR	1 (100)	NR	NR	NR	NR
<b>Pharmacological versus Pharmacological Cohort-Pro prospective</b>										
Kothari, S. 2007 <sup>12</sup>	Enoxaparin Arm	238	30 days	Total Mortality	NR	0 (0)	NR	NR	NR	NR
Kothari, S. 2007 <sup>12</sup>	Heparin Arm	238	30 days	Total Mortality	NR	0 (0)	NR	NR	NR	NR
Rowan, B.O. 2008 <sup>13</sup>	Enoxaparin 30mg q12 (Group 1)	19 (first dose anti-Xa level were included)	Anti-Xa level drawn 4 hours after the first dose	Factor Xa level	NR	19	NR	0.06 units/mL	NR	NR
Rowan, B.O. 2008 <sup>13</sup>	Enoxaparin 30mg q12 (Group 1)	11 (third dose anti-Xa levels were included)	Anti-Xa levels drawn 4 hours after the third dose	Factor Xa level	NR	11	NR	0.08 units/mL	NR	NR
Rowan, B.O. 2008 <sup>13</sup>	Enoxaparin 40mg q12 (Group 2)	12 (third dose anti-Xa levels were included)	Anti-Xa levels drawn after 4 hours after the third dose	Factor Xa level	NR	12	NR	0.15 units/mL	NR	NR
Rowan, B. O. 2008 <sup>13</sup>	Enoxaparin 40mg q12 (Group 2)	26 (first dose anti-Xa levels were included)	Anti-Xa levels drawn 4 hours after the first dose	Factor Xa level	NR	26	NR	0.14 units/mL	NR	NR

Author, Year	Arm	N for analysis	Time point	Outcome	Definition	n (%) of patients with outcomes	n events	Mean/Med/Range	Other	Measures of Association
Simone, E. 2008 <sup>14</sup>	Enoxaparin 40mg	24	1st dose (day of surgery)	Factor Xa level	Mean heparin antifactor Xa (anti-Xa) concentrations (U/ml)	NR	NR	0.173 units/mL	NR	NR
Simone, E. 2008 <sup>14</sup>	Enoxaparin 40mg	24	3rd dose	Factor Xa level	Mean heparin antifactor Xa (anti-Xa) concentrations (U/ml)	NR	NR	0.212 units/mL	NR	NR
Simone, E. 2008 <sup>14</sup>	Enoxaparin 40mg	24	1st dose (day of surgery)	NR	% of supratherapeutic heparin antifactor xa concentration	NR	NR	20%	NR	NR
Simone, E. 2008 <sup>14</sup>	Enoxaparin 40mg	24	3rd dose	NR	% of supratherapeutic heparin antifactor Xa concentration	NR	NR	0%	NR	NR
Simone, E. 2008 <sup>14</sup>	Enoxaparin 60mg	16	1st dose (day of surgery)	Factor Xa level	Mean heparin antifactor Xa (anti-Xa) concentrations (U/ml)	NR	NR	0.261 units/mL	NR	NR
Simone, E. 2008 <sup>14</sup>	Enoxaparin 60mg	16	3rd dose	NR	Mean heparin antifactor Xa (anti-Xa) concentrations (U/mL)	NR	NR	0.433 units/mL	NR	NR
Simone, E. 2008 <sup>14</sup>	Enoxaparin 60mg	16	1st dose (day of surgery)	NR	% of supratherapeutic heparin antifactor Xa concentration	NR	NR	55%	NR	NR
Simone, E. 2008 <sup>14</sup>	Enoxaparin 60mg	16	3rd dose	NR	% of supratherapeutic heparin antifactor Xa concentration	NR	NR	44%	NR	NR
Cohort-retrospective										



Author, Year	Arm	N for analysis	Time point	Outcome	Definition	n (%) of patients with outcomes	n events	Mean/Med/Range	Other	Measures of Association
Scholten, D. J., 2002 <sup>15</sup>	Enoxaparin 30mg Arm	92	NR	Length of hospital stay	NR	NR	5.67 days	NR	NR	p-value:<0.05
Scholten, D. J., 2002 <sup>15</sup>	Enoxaparin 40mg Arm	389	NR	Length of hospital stay	NR	NR	3.81 days	NR	NR	NA
<i>Non-randomized trials</i>										
Borkgren-Okonek, M. 2008 <sup>16</sup>	Enoxaparin 40mg Arm	124	4 hours after 3 <sup>rd</sup> Enoxapar in dose	Factor Xa level	Within target limit (0.18-0.44 IU/ml)	86 (78.9)	NR	NR	NR	NR
Borkgren-Okonek, M. 2008 <sup>16</sup>	Enoxaparin 40mg Arm	99	4 hours after 3 <sup>rd</sup> Enoxapar in dose	Factor Xa level	Within target limit (0.18-0.44 IU/ml)	67 (69.1)	NR	NR	NR	NR
Borkgren-Okonek, M. 2008 <sup>16</sup>	Enoxaparin 60mg Arm	99	Day 15 post-op	Total Mortality	NR	1 (0.8)	NR	NR	NR	NR
Raftopoulos, I., 2008 <sup>17</sup>	Enoxaparin Extended Dose Arm	176	30 days	Total Mortality	NR	0 (0)	NR	NR	NR	NR
Raftopoulos, I., 2008 <sup>17</sup>	Enoxaparin Short Term Dose Arm	132	30 days	Total Mortality	NR	0 (0)	NR	NR	NR	NR
Raftopoulos, I., 2008 <sup>17</sup>	Enoxaparin Extended Dose Arm	176	Hospital discharge	Length of hospital stay	NR	NR	NR	Mean: 2.2 days	NR	p-value :<0.0001 Reference Group: Short Term Dose Arm
Raftopoulos, I., 2008 <sup>17</sup>	Enoxaparin Short Term Dose Arm	132	Hospital discharge	Length of hospital stay	NR	NR	NR	Mean: 3 days	NR	p-value: <0.0001 Reference Group: Extended Dose Arm
<i>Cohort -retrospective</i>										
Hamad, G.G., 2005 <sup>18</sup>	Enoxaparin 30mg qd post discharge	124	Variable	Total Mortality	2 patients died. 1 died due to bleeding complications (20 days after surgery) and one died from sepsis.	2 (1.6)	NR	NR	NR	NR

Author, Year	Arm	N for analysis	Time point	Outcome	Definition	n (%) of patients with outcomes	n events	Mean/Med/Range	Other	Measures of Association
Hamad, G.G., 2005 <sup>18</sup>	Enoxaparin 40mg q12h	180	NR	Length of hospital stay	NR	NR	NR	Mean: 2.5 days	NR	NR
Hamad, G.G., 2005 <sup>18</sup>	Enoxaparin 40mg qd post op for 12-120 hours	84	NR	Length of hospital stay	NR	NR	NR	Mean: 4.8 days	NR	NR
Hamad, G.G., 2005 <sup>18</sup>	Enoxaparin 40mg qd post op for 12-24 hours	180	NR	Length of hospital stay	NR	NR	NR	Mean: 2.9 days	NR	NR
Hamad, G.G., 2005 <sup>18</sup>	Enoxaparin 30mg qd pre op	100	NR	Length of hospital stay	NR	NR	NR	Mean: 2.3 days	NR	NR
Hamad, G.G., 2005 <sup>18</sup>	Enoxaparin 30mg qd post discharge	124	NR	Length of hospital stay	NR	NR	NR	Mean: 4.3 days	NR	NR

BMI= Body Mass Index; CAT= Computed Axial Tomography; CT= Computed Tomography; CTA= Computed Tomography Angiography; CUS= Compression Ultrasonography; DVT= Deep Vein Thrombosis; GCS= Glasgow Coma Scale; Hr(s)= Hour(s); ICU= Intensive Care Unit; IPG= Impedance Phlebography; ISS= Injury Severity Score; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; LMWH= Low Molecular Weight Heparin; mg= milligram; NIH= National Institutes of Health; NR= Not Reported; NA=Not Applicable; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; SCD= Sequential Compression Device; SQ=Subcutaneous; UFH= Unfractionated Heparin; USS= Ultrasound Scan; U= units; VCF= Vena Cava Filter; V/Q Scan = Ventilation Perfusion Scan; VTE= Venous Thromboembolism

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**Evidence Table 38. Adverse Events for KQ6**

Author, Year	Arm	N for Analysis	Time Point	Outcome	Definition	n of Patients with Outcomes	% of Patients with Outcomes
Birkmeyer, N. J. 1	Filter	542	NR	IVC filter specific complications	Of the 10 IVC filter patients suffering death/permanent disability, 3 experienced pulmonary embolism and 2 had complications directly related to the filter itself including fatal IVC thrombosis and IVC filter migration to the heart.	2	0.37
Borkgren-Okonek, M. 2008 <sup>2</sup>	Enoxaparin 40mg Arm	124	Follow up period: mean 77.7 ± 23 days	Major Bleeding	Bleeding requiring transfusion	4	3.2
Borkgren-Okonek, M. 2008 <sup>2</sup>	Enoxaparin 40mg Arm	124	Follow up period: mean 77.7 ± 23 days	Major Bleeding	Bleeding requiring surgery	1	0.8
Borkgren-Okonek, M. 2008 <sup>2</sup>	Enoxaparin 60mg Arm	99	Follow up period: mean 77.7 ± 23 days	Major Bleeding	Bleeding requiring transfusion	1	1
Borkgren-Okonek, M. 2008 <sup>2</sup>	Enoxaparin 60mg Arm	99	Follow up period: mean 77.7 ± 23 days	Minor Bleeding	2 patients had rectal bleeding and 1 patient had bloody drain output	3	3.03
Gargiulo, N.J., 2006 <sup>3</sup>	Filter	58	NR	IVC filter specific complications	1 postoperative IVC thrombosis occurred 4 months after Trapease IVC filter placement while 2 postoperative localized, insertion-site DVTs occurred 3	3	5.17

Author, Year	Arm	N for Analysis	Time Point	Outcome	Definition	n of Patients with Outcomes	% of Patients with Outcomes
					months after filter placement.		
Hamad, G.G., 2005 <sup>4</sup>	Enoxaparin 40mg q12	180	NR	Major Bleeding	3 severe bleeding complications (1 due to haematemesis and 2 due to vaginal bleeding)	3	1.7
Hamad, G.G., 2005 <sup>4</sup>	Enoxaparin 40mg qd post op for 12-120 hours	84	NR	Major Bleeding	NA	0	0
Hamad, G.G., 2005 <sup>4</sup>	Enoxaparin 40mg qd post op for 12-24 hours	180	NR	Major Bleeding	3 severe bleeding complications (1 due to haematemesis and 2 due to GIT bleeding)	3	1.7
Hamad, G.G., 2005 <sup>4</sup>	Enoxaparin 30mg qd pre op	100	NR	Major Bleeding	NA	0	0
Hamad, G.G., 2005 <sup>4</sup>	Enoxaparin 30mg qd post discharge	124	NR	Major Bleeding	This patient died due to bleeding complications (20 days after surgery)	1	0.8
Kothari, S., 2007 <sup>5</sup>	Enoxaparin Arm	238	30 days	Bleeding requiring transfusion	Number of patients requiring post operative transfusion	14	5.9
Kothari, S., 2007 <sup>5</sup>	Heparin Arm	238	30 days	Bleeding requiring transfusion	Number of patients requiring post operative transfusion	3	1.3
Kothari, S., 2007 <sup>5</sup>	Enoxaparin Arm	238	30 days	Bleeding	Bleeding requiring re-exploration	4	1.7
Kothari, S., 2007 <sup>5</sup>	Heparin Arm	238	30 days	Bleeding	Bleeding requiring re-exploration	0	0
Li, W., 2012 <sup>6</sup>	Filter	322	NR	IVC filter specific complications	NR	NR	NR
Obeid, F.N., 2007 <sup>7</sup>	Filter	246	NR	IVC filter specific complications	NR	NR	NR
Ojo, P., 2008 <sup>8</sup>	Enoxaparin 40mg	59	2 weeks post hospital discharge	Major Bleeding	Bleeding occurring during the period of the LMWH use associated with symptomatic decrease in hematocrit necessitating stopping	0	NR

Author, Year	Arm	N for Analysis	Time Point	Outcome	Definition	n of Patients with Outcomes	% of Patients with Outcomes
					of the LMWH administration before the end of the study period, bleeding-related readmission, blood transfusion, or intervention to stop the bleeding		
Ojo, P., 2008 <sup>8</sup>	Enoxaparin 60mg	68	2 weeks post hospital discharge	Major Bleeding	Bleeding occurring during the period of the LMWH use associated with symptomatic decrease in hematocrit necessitating stopping of the LMWH administration before the end of the study period, bleeding-related readmission, blood transfusion, or intervention to stop the bleeding	0	NR
Overby, D.W., 2009 <sup>9</sup>	Filter	160	NR	IVC filter specific complications	The complications were due to insertion (pneumothorax), early removal (hemopericardium, pulmonary embolism) and delayed removal (unable to perform transvenous accessory pathway ablation) of the IVC filter.	4	2.5
Piano, G., 2007 <sup>10</sup>	Filter	59	NR	Filter complications	Pneumothorax, hematoma, or pulmonary embolus, or cardiopulmonary events during filter placement or retrieval	0	NR
Raftopoulos, I.,	Enoxaparin Extended Dose	176	Hospital	Bleeding	Bleeding requiring	0	0

Author, Year	Arm	N for Analysis	Time Point	Outcome	Definition	n of Patients with Outcomes	% of Patients with Outcomes
2008 <sup>11</sup>	Arm		discharge		transfusion		
Raftopoulos, I., 2008 <sup>11</sup>	Enoxaparin Extended Dose Arm	176	Hospital discharge	Bleeding	Bleeding requiring surgery	1	0.56
Raftopoulos, I., 2008 <sup>11</sup>	Enoxaparin Short Term Dose Arm	132	Hospital discharge	Bleeding	Bleeding requiring transfusion	6	4.5
Raftopoulos, I., 2008 <sup>11</sup>	Enoxaparin Short Term Dose Arm	132	Hospital discharge	Bleeding	Bleeding requiring surgery	1	0.75
Scholten, D. J., 2002 <sup>12</sup>	Enoxaparin 30mg Arm	92	NR	Bleeding	Bleeding requiring transfusion	1	1.1
Scholten, D. J., 2002 <sup>12</sup>	Enoxaparin 40mg Arm	389	NR	Surgical site bleeding	Bleeding requiring transfusion	1	0.26
Schuster, R., 2007 <sup>13</sup>	Filter	24	NR	Filter complications	Complications from IVC filter placement or retrieval. IVC thrombus noted on the venogram after filter was removed	1	4
Schweitzer, M., 2006 <sup>14</sup>	NA	1	16 days post-op	Bleeding	Retroperitoneal hemorrhage	1	100
Schweitzer, M., 2006 <sup>14</sup>	NA	1	16 days post-op	Filter complications	Perforation: 1 leg of IVC filter extended 1mm through the wall of the IVC	1	100
Schweitzer, M., 2006 <sup>14</sup>	NA	1	16 days post-op	Filter complications	Thrombosis: Complete IVC filter occlusion by thrombus	1	100
Simone, E., 2008 <sup>15</sup>	Enoxaparin 40mg	24	NR	Significant Bleeding Event	Bleeding requiring transfusion	1	4.2
Simone, E., 2008 <sup>15</sup>	Enoxaparin 60mg	16	NR	Significant Bleeding Event	Bleeding requiring transfusion	NR	NR
Singh, K., 2011 <sup>16</sup>	Enoxaparin of varying doses	170	Hospital discharge	Bleeding: Major bleeding	Post operative bleeding	5	2.9
Vaziri, K., 2010 <sup>17</sup>	Filter	41	NR	Filter complications	1 patient had self-limiting pain at the insertion site of the IVC filter for 5 days while the other patient had a filter deployed in the right common iliac vein.	2	4.87



Author, Year	Arm	N for Analysis	Time Point	Outcome	Definition	n of Patients with Outcomes	% of Patients with Outcomes
Veerapong, J., 2008 <sup>18</sup>	Filter	1	In hospital	Filter complications	Migration: IVC filter migration to right ventricle	1	100

BMI= Body Mass Index; CAT= Computed Axial Tomography; CT= Computed Tomography; CTA= Computed Tomography Angiography; CUS= Compression Ultrasonography; DVT= Deep Vein Thrombosis; GCS= Glasgow Coma Scale; Hr(s)= Hour(s); GIT= Gastrointestinal; ICU= Intensive Care Unit; IPG= Impedance Phlebography; ISS= Injury Severity Score; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; LMWH= Low Molecular Weight Heparin; mg= milligram; NIH= National Institutes of Health; NR= Not Reported; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; SCD= Sequential Compression Device; SQ=Subcutaneous; UFH= Unfractionated Heparin; USS= Ultrasound Scan; U= units; VCF= Vena Cava Filter; V/Q Scan = Ventilation Perfusion Scan; VTE= Venous Thromboembolism

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**Evidence Table 39. Study characteristics for KQ7**

Author, Year	Study Design	Study Site – Study Locations	Recruitment Date (start date – end date)	Planned Length of Follow-up	Method of Surveillance for VTE	Funding Source	Inclusion Criteria	Exclusion Criteria
<b>Pharmacological Therapy versus Placebo</b>								
Freeman A, 2012 <sup>1</sup>	Prospective cohort study with sequentially assigned study arms	Hospitalized medically ill patients at risk for VTE at the Department of Internal Medicine, University of Utah, Salt Lake City, UT	NR	Median length of hospital stay for these patients was 3 days	Clinical assessment for VTE	NIH	Hospitalized, medically ill patients ≥18 years of age with extreme obesity (WHO Class Obesity: BMI ≥40 kg/m <sup>2</sup> ) and having ≥1 major VTE risk factor, including age >70, heart failure, acute respiratory failure, previous VTE, cancer, stroke, sepsis, and immobility (defined as ≥3 days of bed-rest)	Patients who were pregnant, on therapeutic anticoagulation, had a bleeding disorder, platelet count of less than 100,000/mL, coagulopathy, active bleeding, estimated creatinine clearance <30 mL/min, or stroke, surgery or trauma within 14 days
Kucher, N., 2005 <sup>2</sup>	Randomized Controlled Trial	Multiple center: N. America	NR	90 days	Compression ultrasound at day 21	Industry	BMI≥30 for males; ≥28.6 for women	NR

BMI= Body Mass Index; VTE= Venous Thromboembolism; NR = Not Reported

## References

- Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. 2012; 87(7):740-3.
- Kucher N, Leizorovicz A, Vaitkus PT et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. Arch Intern Med 2005; 165(3):341-5.

**Evidence Table 40. Participant characteristics for KQ7**

Author, Year	Arm, n	Age (years) Mean, median, Range	Gender, n (%)	Race, n (%)	BMI	Weight	Prior History of VTE, n (%)	ICU duration
Freeman A, 2012 <sup>1</sup>	Arm 1 (Fixed-dose (FD) Enoxaparin), 11	45.5 ± 7.2	2 (18.2)	NR	63.4 ± 11.6	175.0 ± 39.9	NR	3
	Arm 2 (Lower-dose (LD) Enoxaparin), 9	43.8 ± 15.7	6 (66.7)	NR	60.7 ± 12.4	171.2 ± 42.8	NR	3
	Arm 3 (Higher-dose (HD) Enoxaparin), 11	42.7 ± 12.3	3 (27.3)	NR	61.3 ± 12.2	179.6 ± 30.3	NR	3
Kucher, N., 2005 <sup>2</sup>	Arm 2 (Obese patients), 1118	NR	Male, 396 (35.4)	White: 1025 (91.7) Black: 17 (1.5) Other: 70, (6.3)	Median:32.9	Mean:90.8 Median:89.5	2 (1.6)	NR
	Arm 3 (Non-obese patients), 2563	NR	Male, 1376 (53.7)	White: 2366 (92.3) Black: 35, (1.4) Other: 151, (5.9)	Median:24.7	Mean:68.4 Median:68	6 (7.1)	NR
	Arm 4 (Obese patients-Dalteparin)	NR	NR	NR	NR	NR	0 (0)	NR
	Arm 5 (Obese Patient – Placebo)	NR	NR	NR	NR	NR	3 (1.6)	NR

BMI= Body Mass Index; VTE= Venous Thromboembolism; NR = Not Reported

## References

- Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. 2012; 87(7):740-3.
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**Evidence Table 41. Interventions for KQ7**

Author, Year	Arm Name	Drug Name	Dose	Route	Frequency	Timing of First Dose	Planned Duration of Therapy (Other e.g.INR)	Concurrent Therapy
<b>Pharmacological versus Pharmacological</b> <i>Randomized Controlled Trial</i>								
Freeman A, 2012 <sup>1</sup>	Arm 1 (Fixed-dose (FD) Enoxaparin)	Enoxaparin	Enoxaparin 40mg once daily, 11	SC	Once daily	NR	NR	NR
	Arm 2 (Lower-dose (LD) Enoxaparin)	Enoxaparin	Enoxaparin 0.4 mg/kg once daily, 9	SC	Once daily	NR	NR	NR
	Arm 3 (Higher-dose (HD) Enoxaparin)	Enoxaparin	Enoxaparin 0.5mg/kg once daily, 11	SC	Once daily	NR	NR	NR
Kucher, N., 2005 <sup>2</sup>	Arm 2(Obese Patients)	Dalteparin (Fragmin)	5000U	NR	Daily	NR	NR	No
	Arm 3(Non Obese Patients)	Dalteparin (Fragmin)	5000U	NR	Daily	NR	NR	No
	Arm 4(Obese patients-Dalteparin)	Dalteparin (Fragmin)	5000U	NR	Daily	NR	NR	No
	Arm 5(Obese patient-Placebo)	Placebo	NR	NR	NR	NR	NR	No

BMI= Body Mass Index; INR= International Normalized Ratio; NR= Not Reported; U= units

## References

- Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. 2012; 87(7):740-3.
- Kucher N, Leizorovicz A, Vaitkus PT et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. Arch Intern Med 2005; 165(3):341-5.

**Evidence Table 42. Patient-oriented Outcomes for KQ7**

Author, Year	Arm	N for Analysis	Time Point	Test to Confirm DVT/PE	Outcome	n (%) of Patients with Outcomes	n(%) of Events	Point Estimate	Measures of Association
Kucher, N., 2005 <sup>1</sup>	Arm 2 (Obese patients)	1118	21 days	DVT: Ultrasonography	Total PE (unspecified PE)	3 (0.28) symptomatic PE	NR	NR	NR
	Arm 3 (Non-obese patients)	2563	21 days	DVT: Ultrasonography	Total PE only (unspecified PE)	2 (0.08) fatal PE	NR	NR	NR
	Arm 4 (Obese patients - dalteparin)	NR	21 days	DVT: Ultrasonography	Total VTE only	(2.8) composite of symptomatic VTE, fatal pulmonary embolism, sudden death, or asymptomatic proximal deep venous thrombosis	NR	Relative hazard (RR, 0.64; 95% CI, 0.32-1.28)	Ref. group: Arm 4 Placebo- Obese patients <i>Comments:</i> n non-obese dalteparin group, total VTE was reported in 2.8% and 5.2% of dalteparin (n=558) and placebo (n=560) groups respectively. (RR, 0.53; 95% CI 0.34-0.82)
	Arm 5 (Obese patients - placebo)	NR	21 days	DVT: Ultrasonography	Total VTE only	(4.3)	NR	NR	NR
	Arm 2 (Obese patients)	1118	21 days	DVT: Ultrasonography	Total PE only (unspecified PE), symptomatic	0 (0) fatal PE	NR	NR	NR
	Arm 3 (Non-obese patients)	2563	21 days	DVT: Ultrasonography	Total PE only (unspecified PE), symptomatic	8 (0.33) Other - symptomatic PE	NR	NR	NR
	Arm 2 (Obese patients)	1118	NR	DVT: Ultrasonography	Distal symptomatic	NR	NR	NR	NR
	Arm 3 (Non-obese patients)	2563	NR	DVT: Ultrasonography	Proximal asymptomatic	NR	NR	NR	NR
	Arm 2 (Obese patients)	1118	21 days	DVT: Ultrasonography	Lower extremity	3 (0.28)	NR	NR	NR

Author, Year	Arm	N for Analysis	Time Point	Test to Confirm DVT/PE	Outcome	n (%) of Patients with Outcomes	n(%) of Events	Point Estimate	Measures of Association
					DVT proximal				
	Arm 3 (Non-obese patients)	2563	21 days	DVT: Ultrasonography	Lower extremity DVT proximal	66 (3.19)	NR	NR	NR
	Arm 2 (Obese patients)	1118	21 days	DVT: Ultrasonography	Lower extremity DVT	23 (2.49)	NR	NR	NR
	Arm 3 (Non-obese patients)	2563	21 days	DVT: Ultrasonography	Lower extremity DVT	58 (2.84)	NR	NR	NR
	Arm 2 (Obese patients)	1118	21 days	DVT: Ultrasonography	Lower extremity DVT proximal asymptomatic	22 (2.40)	NR	NR	NR
	Arm 3 (Non-obese patients)	2563	21 days	DVT: Ultrasonography	Lower extremity DVT distal symptomatic	4 (0.17)	NR	NR	NR

BMI= Body Mass Index; DVT= Deep Vein Thrombosis; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; NR= Not Reported; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; U= units; VCF= Vena Cava Filter; VTE= Venous Thromboembolism

## References

1. Kucher N, Leizorovicz A, Vaitkus PT et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. Arch Intern Med 2005; 165(3):341-5.



**Evidence Table 43. Other Patient-oriented Outcomes for KQ7**

Author, Year	Arm	N for analysis	Time point	Outcome	Definition	n of Patients with Outcomes	% of Patients with Outcomes	n events	Mean/Med/Range	Measures of Association
Freeman A, 2012 <sup>1</sup>	Arm 1 (Fixed-dose (FD) Enoxaparin)	11	4-6 hours after Enoxaparin	Peak anti-Factor Xa level	Between 0.20 and 0.50 IU/mL	11	100	NA	~19	The differences in percentage of patients who achieved the target Anti-Xa levels was significant across all study arms (p<0.001)
	Arm 2 (Lower-dose (LD) Enoxaparin)	9	4-6 hours after Enoxaparin	Peak anti-Factor Xa level	Between 0.20 and 0.50 IU/mL	9	100	NA	~32	
	Arm 3 (Higher-dose (HD) Enoxaparin)	11	4-6 hours after Enoxaparin	Peak anti-Factor Xa level	Between 0.20 and 0.50 IU/mL	11	100	NA	~86	
Kucher, N., 2005 <sup>2</sup>	Arm 4 (Obese patients-dalteparin)	558	21 days	Total Mortality	NR	NR	4.6	NR	NR	NR
	Arm 5 (Obese patients-placebo)	560	21 days	Total Mortality	NR	NR	2.7	NR	NR	NR
	Arm 4 (Obese patients)	558	90 days	Total Mortality	NR	NR	9.9	NR	NR	NR
	Arm 5 (Obese patients-placebo)	560	90 days	Total Mortality	NR	NR	8.6	NR	NR	NR

NR = Not Reported

## References

- Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. 2012; 87(7):740-3.
- Kucher N, Leizorovicz A, Vaitkus PT et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. Arch Intern Med 2005; 165(3):341-5.

**Evidence Table 44. Adverse Events for KQ7**

Author,Year	Arm	N for analysis	Time point	Outcome	Definition	n Patients	% Patients	n Events	Other
Kucher, N., 2005 <sup>1</sup>	Arm 4 (Obese patients-dalteparin)	558	NR	Bleeding: Major bleeding	Major bleeding by day 21	NR	0	NR	NR
	Arm 5 (Obese patients-placebo)	560	NR	Bleeding: Major bleeding	NR	NR	0.7	NR	NR
	Arm 5 (Non-obese dalteparin group)	1290	NR	Bleeding: Major bleeding	NR	NR	1.6	NR	NR
	Arm 4 (Obese patients-Dalteparin)	558	NR	Bleeding: Minor bleeding	Major bleeding by day 21	NR	1.4	NR	NR
	Arm 5 (Obese patients-placebo)	560	NR	Bleeding: Minor bleeding	NR	NR	0.7	NR	In non-obese placebo group (n=1273) % of hemorrhage on day 21: Major= 0.3% and minor=0.31% and thrombocytopenia on day 21 = 1.0%
	Arm 5 (Non-obese dalteparin group)	1290	NR	Bleeding: Minor bleeding	NR	NR	2.5	NR	NR
	Arm 4 (Obese patients-Dalteparin)	558	NR	Heparin-induced thrombocytopenia	NR	NR	0.9	NR	NR
	Arm 5 (Obese patients-placebo)	560	NR	Heparin-induced thrombocytopenia	NR	NR	0.9	NR	NR
	Arm 5 (Non-obese dalteparin group)	1290	NR	Heparin-induced thrombocytopenia	NR	NR	1.5	NR	NR

There were no bleeding events, thrombosis, symptomatic DVT or PE, or episodes of heparin-induced thrombocytopenia (HIT) in any of the 3 arms of the study.

NR = Not Reported

## References

1. Kucher N, Leizorovicz A, Vaitkus PT et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. Arch Intern Med 2005; 165(3):341-5.

**Evidence Table 45. Study characteristics for KQ8**

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
Pharmacologic Agent versus Pharmacological								
Bauersachs, 2011 <sup>1</sup>	RCT	Europe	NR	Multiple center-Europe	CUS	Industry	Age ≥70 years	Severe liver disease; creatinine clearance severe renal disease; High risk of GI bleeding type of surgery: expected major surgical or invasive procedure within three weeks following randomization immobilization longer than three days prior to randomisation immobilization due to cast or fracture, patient with severe sepsis or need for mechanical ventilation; acute endocarditis, hemorrhagic stroke or intracranial bleeding <12 months acute or ongoing intracranial disease spinal or epidural anesthesia lumbar puncture within last 12 hr uncontrolled hypertension active retinopathy intravitreal or other intraocular bleeding
Dahl, 2011 <sup>2</sup>	RCT	Europe	NR	Multiple center-Europe; patients followed for three	Composite of proximal DVT (bilateral venography), any symptomatic	Boehringer Ingelheim funded writing and editorial assistance.	Age ≥75 years or with moderate renal impairment	Patients with a baseline creatinine clearance <30 ml/min were excluded.

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
				months after study end for late stage side effects	DVT or PE, and deaths in which VTE could not be excluded as the cause (independent adjudication committee)			
Elsaid, A.K., 2012 <sup>3</sup>	Retro-spective cohort study (we have abstracted data only for the before intervention group)	United States	January 1 and June 30, 2008.	NR	NR	NR	Age >40 years, hospitalization >6 days, treatment with enoxaparin or unfractionated heparin (UFH) and acute or chronic renal insufficiency.	Patients receiving long-term anticoagulation at admission or being treated for DVT or pulmonary embolism.
Mahe, 2007 <sup>4</sup>	RCT	Multiple center-Europe	NR		No		Age >75 years, creatinine clearance between 20-50ml/min Immobility : bed bound with an acute medical illness Renal impairment (Creatinine clearance between 20-50ml/min) Hospitalized patients in the Department of internal Medicine of the 2 study hospitals Indication for thromboprophylaxis written informed consent	wt->65kg Platelets : <100,000/mm <sup>3</sup> Contraindication to anticoagulation treatment Current bleeding Prothrombin time <50% at day 0 or within 7 days prior to inclusion Hemoglobin <9g/dl at day 0 or within 7 days prior to inclusion Life expectancy less than 1 month History of heparin induced thrombocytopenia Known Hypersensitivity reaction to any

Author, Year	Study design	Study site – study locations	Recruitment date (start date – end date)	Planned length of follow-up	Method of surveillance for VTE	Funding source	Inclusion criteria	Exclusion criteria
								component of investigational products Heparin or LMWH within 48Hours prior to the first injection of investigational products Oral anticoagulant within 4 days prior to inclusion
Shor,A.F., 2012 <sup>5</sup>	RCT- post hoc subgroup analysis	Europe	NR	Multiple center- Europe	Mandatory venograms at end of study, ventilation- perfusion scan for PE if clinical suspected	Industry	Age ≥18 years, Weight ≥ 50 kg, undergoing primary total hip replacement	Child bearing potential, bilateral hip operation, other major surgery in past month, history of hemorrhagic stroke, cerebroischemic events, uncontrolled hypertension, renal impairment, nephrectomy, renal transplantation, allergy to heparin or hirudin or contrast media.

AIS= Abbreviated Injury Scale; BMI= Body Mass Index; CAT= Computed Axial Tomography; CT= Computed Tomography; CTA= Computed Tomography Angiography; CUS= Compression Ultrasonography; DVT= Deep Vein Thrombosis; GCS= Glasgow Coma Scale; Hr(s)= Hour(s); ICU= Intensive Care Unit; INR= International Normalized Ratio; IPG= Impedance Phlebography; ISS= Injury Severity Score; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; LE= Lower Extremity; LMWH= Low Molecular Weight Heparin; mg= milligram; NIH= National Institutes of Health; NR= Not Reported; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; SCD= Sequential Compression Device; SCI= Spinal Cord Injury; SQ=Subcutaneous; TBI= Traumatic Brain Injury; UFH= Unfractionated Heparin; USS= Ultrasound Scan; U= units; VCF= Vena Cava Filter; V/Q Scan = Ventilation Perfusion Scan; VTE= Venous Thromboembolism

## References

1. Bauersachs R, Schellong SM, Haas S et al. CERTIFY: prophylaxis of venous thromboembolism in patients with severe renal insufficiency. *Thromb Haemost* 2011; 105(6):981-8.
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**Evidence Table 46. Participant characteristics for KQ8**

Author, Year	Arm, n	Age (years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI	Weight	Prior History of VTE, n (%)	Trauma, n(%)	ICU Duration
Bauersachs, 2011 <sup>1</sup>	Arm 2 (GFR<30), 92	Mean: 85.3	Male (20.7)	NR	Mean: 23.5	NR	NR	NR	NR
Dahl, 2011 <sup>2</sup>	Arm 1 (Enoxaparin), 332	Mean ± standard deviation: 78.0±3.9	Female, 242 (72.9)	NR	Mean ± standard deviation: 26.8±4.2	NR	NR	NR	NR
Dahl, 2011 <sup>2</sup>	Arm 2 (Dabigatran), 300	Mean ± standard deviation: 78.4±3.7	Female, 221 (73.7)	NR	Mean ± standard deviation: 27.3±4.2	NR	NR	NR	NR
Elsaid, A.K., 2012 <sup>3</sup>	Arm 1 (Enoxaparin, CLCr ≥60 mL/min), 17	NR	NR	NR	NR	NR	NR	NR	NR
Elsaid, A.K., 2012 <sup>3</sup>	Arm 2 (Enoxaparin, CLCr 30-59 mL/min), 86	NR	NR	NR	NR	NR	NR	NR	NR
Elsaid, A.K., 2012 <sup>3</sup>	Arm 3 (Enoxaparin, CLCr <30 mL/min), 53	NR	NR	NR	NR	NR	NR	NR	NR
Elsaid, A.K., 2012 <sup>3</sup>	Arm 4 (UFH, CLCr ≥60 mL/min), 19	NR	NR	NR	NR	NR	NR	NR	NR
Elsaid, A.K., 2012 <sup>3</sup>	Arm 5 (UFH, CLCr 30-59 mL/min), 99	NR	NR	NR	NR	NR	NR	NR	NR
Elsaid, A.K., 2012 <sup>3</sup>	Arm 6 (UFH, CLCr <30 mL/min), 49	NR	NR	NR	NR	NR	NR	NR	NR
Mahe, 2007 <sup>4</sup>	Arm 2 (Tinzaparin), 27	Mean: 87.7	NR	NR	NR	Mean: 52.3	NR	NR	NR
Mahe, 2007 <sup>4</sup>	Arm 3 (Enoxaparin), 28	Mean: 88.0		NR	NR	Mean: 51.7	NR	NR	NR
Shor, A.F., 2012 <sup>5</sup>	Arm 1 (Stage 1	Median: 60	NR	NR	NR	Median: 82 kg	NR	NR	NR

Author, Year	Arm, n	Age (years) Mean, Median, Range	Gender, n (%)	Race, n (%)	BMI	Weight	Prior History of VTE, n (%)	Trauma, n(%)	ICU Duration
	and 2- Enoxaparin), 353	Range: 18-82							
Shor,A.F., 2012 <sup>b</sup>	Arm 2 (Stage 1 and 2- Desirudin), 353	Median: 59 Range: 51- 120	NR	NR	NR	Median: 81	NR	NR	NR
Shor,A.F., 2012 <sup>b</sup>	Arm 3 (Stage 3a- enoxaparin), 369	Median: 66 Range: 36- 83	NR	NR	NR	Median: 72	NR	NR	NR
Shor,A.F., 2012 <sup>b</sup>	Arm 4 (Stage 3a- desirudin), 395	Median: 66 Range: 45-86	NR	NR	NR	Median: 72	NR	NR	NR
Shor,A.F., 2012 <sup>b</sup>	Arm 5 (Stage 3b- enoxaparin), 298	Median: 74 Range: 47-87	NR	NR	NR	Median: 65	NR	NR	NR
Shor,A.F., 2012 <sup>b</sup>	Arm 6 (Stage 3b- desirudin), 279	Median: 65 Range: 42-98	NR	NR	NR	Median: 65	NR	NR	NR

BMI= Body Mass Index; DVT= Deep Vein Thrombosis; ICU= Intensive Care Unit; INR= International Normalized Ratio; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; NR= Not Reported; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; VTE= Venous Thromboembolism



## References

1. Bauersachs R, Schellong SM, Haas S et al. CERTIFY: prophylaxis of venous thromboembolism in patients with severe renal insufficiency. *Thromb Haemost* 2011; 105(6):981-8.
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**Evidence Table 47. Interventions for KQ8**

Author, year	Arm Name	Drug name	Dose	Route	Frequency	Timing of first dose	Planned duration of therapy	Other (e.g. INR)	Concurrent therapy
<b>Pharmacologic agent versus pharmacological</b> <i>Randomized Controlled Trial</i>									
Bauersachs, 2011 <sup>1</sup>	Arm 2(GFR<30)	Heparin	5000 IU	SQ	t.i.d	NR	NR	NR	No
	Arm 3(GFR>30)	Heparin	5000 IU	SQ	t.i.d	NR	NR	NR	No
Dahl,2011 <sup>2</sup>	Arm 1 (Enoxaparin)	enoxaparin	40 mg qd	Injection	NR	12 hours before surgery	Ranged from six to ten up to 28-35 days	NR	Aspirin ( $\leq$ 160 mg), selective cyclo-oxygenase-2 inhibitors, and elastic compression stockings permitted.
	Arm 2 (Dabigatran)	dabigatran	150 mg qd	Orally	NR	Half dose one to four hours after surgery	Ranged from six to ten up to 28-35 days	NR	Aspirin ( $\leq$ 160 mg), selective cyclo-oxygenase-2 inhibitors, and elastic compression stockings permitted.
Mahe, 2007 <sup>4</sup>	Arm 2 (Tinzaparin)	Tinzaparin (Innohep)	10,000 IU/ml	SQ	Daily	8am	Until ICU discharge or a maximum of 30 days, whichever came first	NR	No
	Arm 3 (Enoxaparin)	Enoxaparin (Lovenox)	4000 IU/ml	SQ	Daily	8am	At least 8 days	NR	No
Shor,A.F., 2012 <sup>5</sup>	Arm 1 (Stage 1 and 2- Enoxaparin)	Enoxaparin	40 mg	SC	OD	Evening prior to surgery	NR	NR	NR
	Arm 2 (Stage 1 and 2- Desirudin)	Desirudin	15 MG	SC	BD	30 mins prior to surgery	NR	NR	NR
	Arm 3(Stage	Enoxaparin	40 mg	SC	OD	Evening prior	NR	NR	NR

Author, year	Arm Name	Drug name	Dose	Route	Frequency	Timing of first dose	Planned duration of therapy	Other (e.g. INR)	Concurrent therapy
	3a-enoxaparin)					to surgery			
	Arm 4(Stage 3a- desirudin)	Desirudin	SC	BD	30 mins prior to surgery	NR	NR	NR	SC
	Arm 5(Stage 3b- enoxaparin)	Enoxaparin	40 mg	SC	OD	Evening prior to surgery	NR	NR	NR
	Arm 6(Stage 3b- desirudin)	Desirudin	SC	BD	30 mins prior to surgery	NR	NR	NR	SC
<b>Pharmacologic agent versus pharmacological</b>									
Elsaid,A.K., 2012 <sup>3</sup>	Arm 1(Enoxaparin, CLCr $\geq$ 60 mL/min)	Enoxaparin	30 mg	S.C	Twice daily	NR	NR	NR	NR
	Arm 2 (Enoxaparin, CLCr 30-59 mL/min)	Enoxaparin	30 mg	S.C	Twice daily	NR	NR	NR	NR
	Arm 3 (Enoxaparin, CLCr $\leq$ 30 mL/min)	Enoxaparin	30 mg	S.C	empirical dose adjustments to once daily	NR	NR	NR	NR
	Arm 4 (UFH, CLCr $\geq$ 60 mL/min)	UFH	5000 units	S.C	Two to three times daily	NR	NR	NR	NR
	Arm 5 (UFH, CLCr 30-59 mL/min)	UFH	5000 units	S.C	Two to three times daily	NR	NR	NR	NR
	Arm 6 (UFH, CLCr $\leq$ 30 mL/min)	UFH	5000 units	S.C	Two to three times daily	NR	NR	NR	NR

BMI= Body Mass Index; DVT= Deep Vein Thrombosis; GFR = Glomerular Filtration rate; ICU= Intensive Care Unit; INR= International Normalized Ratio; IV= Intravenous; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; NR= Not Reported; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; t.i.d.= Three times daily; VTE= Venous Thromboembolism

## References

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5. Shorr AF, Eriksson BI, Jaffer A, Smith J. Impact of Stage 3B chronic kidney disease on thrombosis and bleeding outcomes after orthopedic surgery in patients treated with desirudin or enoxaparin: Insights from a randomized trial. *J Thromb Haemost* 2012.

**Evidence Table 48. Patient-oriented Outcomes for KQ8**

Author, Year	DVT Confirmed	PE	Arm name	N for analysis	Time point	Outcomes	n Patient	% Patient	Comments
<b>Pharmacological Agent versus Pharmacological Agent RCT</b>									
Bauersachs, 2011 <sup>1</sup>	DVT-compression USS	NR	Arm 2 (GFR<30)	92	NR	Total DVT only (unspecified DVT)	NR	11.11	NR
	DVT-compression USS	NR	Arm 3 (GFR>30)	1523	NR	Total DVT only (unspecified DVT)	NR	10.28	NR
	DVT-compression USS	NR	Arm 2 (GFR<30)		NR	PE	NR	0.0	NR
	DVT-compression USS	NR	Arm 3 (GFR>30)		NR	PE	NR	0.21	NR
Dahl,2011 <sup>2</sup>	DVT-mandatory bilateral venography or VTE-related death	Patients with PE included	Arm 1 (enoxaparin)	89	NR	Major VTE	8	9.0	NR
	DVT-mandatory bilateral venography or VTE-related death	Patients with PE included	Arm 2 (dabigatran)	70	NR	Major VTE	3	4.3	OR: 0.48 (0.13-1.73); p=0.271
Shor,A.F., 2012 <sup>3</sup>	venogram	V/Q scan	Arm 1 (Stage 1 and 2- Enoxaparin)	275	discharge	Total VTE	NR	6.2	
	venogram	V/Q scan	Arm 2 (Stage 1 and 2- Desirudin)	284	discharge	Total VTE	NR	4.6	
	venogram	V/Q scan	Arm 3 (Stage 3a- enoxaparin)	282	discharge	Total VTE	NR	6.4	
	venogram	V/Q scan	Arm 4 (Stage 3a- desirudin)	303	discharge	Total VTE	NR	5.6	
	venogram	V/Q scan	Arm 5 (Stage 3b-	216	discharge	Total VTE	NR	11.1	

Author, Year	DVT Confirmed	PE	Arm name	N for analysis	Time point	Outcomes	n Patient	% Patient	Comments
			enoxaparin)						
	venogram	V/Q scan	Arm 6 (Stage 3b-desirudin)	205	discharge	Total VTE	NR	3.4	

BMI= Body Mass Index; DVT= Deep Vein Thrombosis; GFR = Glomerular Filtration rate; ICU= Intensive Care Unit; INR= International Normalized Ratio; IV= Intravenous; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; NR= Not Reported; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; t.i.d.= Three times daily; VTE= Venous Thromboembolism

## References

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**Evidence Table 49. Other Patient-oriented Outcomes**

Author, Year	Arm	N for analysis	Time Point	Outcomes	Definition	n (%)	Mean, Median	Reference Group
<b>Pharmacological Agent versus Pharmacological Agent <i>Randomized Controlled Trial</i></b>								
Bauersachs, 2011 <sup>1</sup>	Arm 2 (GFR<30)	92	NR	Total Mortality	Death from any cause	(5.81)	NR	NR
	Arm 3 (GFR>30)	1523	NR	Total Mortality	NR	(1.1)	NR	NR
Dahl, 2011 <sup>2</sup>	Arm 1 (enoxaparin)	332	NR	Infections and infestations	NR	25 (7.5)	NR	NR
	Arm 2 (dabigatran)	300	NR	Infections and infestations	NR	21 (7.0)	NR	NR
	Arm 1 (enoxaparin)	332	NR	Wound infection	NR	4 (1.2)	NR	NR
	Arm 2 (dabigatran)	300	NR	Wound infection	NR	3 (1.0)	NR	NR
Mahe, 2007 <sup>3</sup>	Arm 2 (Tinzaparin)	27	NR	Factor Xa level	Anti-Xa accumulation factor evaluation was based on cmax, calculated as the ratio on day 8 to day 1	NR	Accumulation factor CmaxD8/Cmax D1 = 1.05	NR
	Arm 3 (Enoxaparin)	28	NR	Factor Xa level	Area under curve on day 8 vs day 1	NR	Accumulation factor Cmax D8/Cmax D1 = 1.22	NR
Shor, A.F., 2012 <sup>4</sup>	All arms	2047	NR	All other outcomes		NR	NR	NR

BMI= Body Mass Index; DVT= Deep Vein Thrombosis; GFR = Glomerular Filtration rate; ICU= Intensive Care Unit; INR= International Normalized Ratio; IV= Intravenous; IVC= Inferior Vena Cava; IVCF= Inferior Vena Cava Filter; NR= Not Reported; PE= Pulmonary Embolism; P-IVCF= Prophylactic Inferior Vena Cava Filter; RCT= Randomized Controlled Trial; R-IVCF= Retrievable Inferior Vena Cava Filter; t.i.d.= Three times daily; VTE= Venous Thromboembolism

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**Evidence Table 50. Adverse Events for KQ8**

Author, Year	Arm	N for analysis	Time Point	Outcomes	Definition	n (%)
<b>Pharmacologic agent versus pharmacological RCTs</b>						
Bauersachs, 2011 <sup>1</sup>	Arm 2 (GFR<30)	92	NR	Bleeding - Major bleeding	Major bleeding was defined as fatal bleeding, clinically overt bleeding associated with a fall of the hemoglobin concentration greater than 2 g/l compared to the baseline hemoglobin concentration, clinically overt bleeding that required transfusion of two or more units of packed red cells or whole blood, symptomatic bleeding in a critical area or organ (intracranial, intraspinal, retroperitoneal, and pericardial).	4 (4.35)
	Arm 3 (GFR>30)	1523	NR	Bleeding - Major bleeding	Major bleeding was defined as fatal bleeding, clinically overt bleeding associated with a fall of the hemoglobin concentration greater than 2 g/l compared to the baseline hemoglobin concentration, clinically overt bleeding that required transfusion of two or more units of packed red cells or whole blood, symptomatic bleeding in a critical area or organ (intracranial, intraspinal, retroperitoneal, and pericardial).	6 (0.39)
	Arm 2 (GFR<30)	92	NR	Bleeding - Minor bleeding	NR	9 (9.78)
	Arm 3 (GFR>30)	1523	NR	Bleeding - Minor bleeding	NR	56 (3.58)
Dahl, 2011 <sup>2</sup>	Arm 1 (enoxaparin)	128	NR	Major bleeding	Major bleeding events were defined as fatal bleeds; clinically overt bleeds associated with a greater than 20 g/l fall in haemoglobin or leading to transfusion of more than two units of packed cells or whole blood; bleeding into a critical organ (retroperitoneal, intracranial, intraocular or central nervous system); bleeding requiring	6 (4.7)

Author, Year	Arm	N for analysis	Time Point	Outcomes	Definition	n (%)
					treatment cessation; bleeding leading to reoperation.	
	Arm 2 (dabigatran)	96	NR	Major bleeding	Major bleeding events were defined as fatal bleeds; clinically overt bleeds associated with a greater than 20 g/l fall in haemoglobin or leading to transfusion of more than two units of packed cells or whole blood; bleeding into a critical organ (retroperitoneal, intracranial, intraocular or central nervous system); bleeding requiring treatment cessation; bleeding leading to reoperation.	0 (0.0)
	Arm 1 (enoxaparin)	326	NR	Clinically relevant non-major bleeding events (CRBE)	Comprised the following: spontaneous skin haematoma >25 cm <sup>2</sup> , wound haematomas >100 cm <sup>2</sup> , spontaneous nose bleed lasting form over five minutes, macroscopic haematuria (spontaneous or lasting >24 hours if associated with an intervention), spontaneous rectal bleeding, gingival bleeding for more than five minutes and any other bleeding event considered clinically relevant by the investigator.  <i>Note: data for CRBE is for patients aged &gt;75 years <b>or</b> with moderate renal impairment. In contrast, previous outcome (Major Bleeding) was reported for moderate renal impairment subpopulation only.</i>	21 (6.3)
	Arm 2 (dabigatran)	299	NR	Clinically relevant non-major bleeding events (CRBE)	Comprised the following: spontaneous skin haematoma >25 cm <sup>2</sup> , wound haematomas >100 cm <sup>2</sup> , spontaneous nose bleed lasting form over five minutes, macroscopic haematuria (spontaneous or lasting >24 hours if associated with an intervention), spontaneous rectal bleeding, gingival bleeding for more	21 (7.0)

Author, Year	Arm	N for analysis	Time Point	Outcomes	Definition	n (%)
					than five minutes and any other bleeding event considered clinically relevant by the investigator.  <i>Note: data for CRBE is for patients aged &gt;75 years <b>or</b> with moderate renal impairment. In contrast, previous outcome (Major Bleeding) was reported for moderate renal impairment subpopulation only.</i>	
Mahe, 2007 <sup>4</sup>	Arm 2 (Tinzaparin)	27	NR	Bleeding - Major bleeding	NR	2
	Arm 3 (Enoxaparin)	28	NR	Bleeding - Major bleeding	NR	1
	Arm 2 (Tinzaparin)	NR	NR	Bleeding - Minor bleeding	NR	3
	Arm 3 (Enoxaparin)	NR	NR	Bleeding - Minor bleeding	NR	3
Shor,A.F., 2012 <sup>5</sup>	Arm 1 (Stage 1 and 2- Enoxaparin)	351	NR	Bleeding - Major bleeding	If hemorrhage produced fall in hemoglobin of 2g/dl or transfusion of 2 or more units of packed cells post operatively, retroperitoneal, intracranial, intraocular, intraspinal.	0
	Arm 2 (Stage 1 and 2- Desirudin)	349	NR	Bleeding - Major bleeding	If hemorrhage produced fall in hemoglobin of 2g/dl or transfusion of 2 or more units of packed cells post operatively, retroperitoneal, intracranial, intraocular, intraspinal.	2 (0.27)
	Arm 3 (Stage 3a- enoxaparin)	365	NR	Bleeding - Major bleeding	If hemorrhage produced fall in hemoglobin of 2g/dl or transfusion of 2 or more units of packed cells post operatively, retroperitoneal, intracranial, intraocular, intraspinal.	1 (0.27)
	Arm 4 (Stage 3a- desirudin)	393	NR	Bleeding - Major bleeding	If hemorrhage produced fall in hemoglobin of 2g/dl or transfusion of 2 or more units of packed cells post operatively, retroperitoneal, intracranial, intraocular, intraspinal.	1 (0.25)
	Arm 5 (Stage 3b- enoxaparin)	294	NR	Bleeding - Major bleeding	If hemorrhage produced fall in hemoglobin of 2g/dl or transfusion of 2 or more units of packed cells post operatively, retroperitoneal,	1 (0.34)

Author, Year	Arm	N for analysis	Time Point	Outcomes	Definition	n (%)
					intracranial, intraocular, intraspinal.	
	Arm 6 (Stage 3b-desirudin)	275	NR	Bleeding - Major bleeding	If hemorrhage produced fall in hemoglobin of 2g/dl or transfusion of 2 or more units of packed cells post operatively, retroperitoneal, intracranial, intraocular, intraspinal.	5 (1.82)
<b>Pharmacologic agent versus pharmacological</b>						
Elsaid,A.K., 2012 <sup>3</sup>	Arm 1 (Enoxaparin, CLCr $\geq 60$ mL/min)	17	NR	Bleeding –Major bleeding	Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ (e.g., intracranial, intraspinal, or pericardial bleeding requiring hemodynamic support; bleeding causing a $\geq 2$ -g/dL decrease in hemoglobin concentration). Or bleeding leading to the transfusion of $\geq 2$ units of packed red blood cells.	2 (11.8)
	Arm 2 (Enoxaparin, CLCr <u>30-59</u> mL/min)	86	NR	Bleeding –Major bleeding	Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ (e.g., intracranial, intraspinal, or pericardial bleeding requiring hemodynamic support; bleeding causing a $\geq 2$ -g/dL decrease in hemoglobin concentration). Or bleeding leading to the transfusion of $\geq 2$ units of packed red blood cells.	9 (10.5)
	Arm 3 (Enoxaparin, CLCr $\leq 30$ mL/min)	53	NR	Bleeding –Major bleeding	Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ (e.g., intracranial, intraspinal, or pericardial bleeding requiring hemodynamic support; bleeding causing a $\geq 2$ -g/dL decrease in hemoglobin concentration). Or bleeding leading to the transfusion of $\geq 2$ units of packed red blood cells.	10 (18.9)
	Arm 4(UFH, CLCr $\geq 60$ mL/min)	19	NR	Bleeding –Major bleeding	Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ (e.g., intracranial, intraspinal, or pericardial bleeding requiring	2 (10.5)

Author, Year	Arm	N for analysis	Time Point	Outcomes	Definition	n (%)
					hemodynamic support; bleeding causing a $\geq 2$ -g/dL decrease in hemoglobin concentration). Or bleeding leading to the transfusion of $\geq 2$ units of packed red blood cells.	
	Arm 5 (UFH, CLCr <u>30-59</u> mL/min)	99	NR	Bleeding –Major bleeding	Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ (e.g., intracranial, intraspinal, or pericardial bleeding requiring hemodynamic support; bleeding causing a $\geq 2$ -g/dL decrease in hemoglobin concentration). Or bleeding leading to the transfusion of $\geq 2$ units of packed red blood cells.	3 (3)
	Arm 6 (UFH, CLCr $\leq 30$ mL/min)	49	NR	Bleeding –Major bleeding	Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ (e.g., intracranial, intraspinal, or pericardial bleeding requiring hemodynamic support; bleeding causing a $\geq 2$ -g/dL decrease in hemoglobin concentration). Or bleeding leading to the transfusion of $\geq 2$ units of packed red blood cells.	2 (4)

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**Evidence Table 51. Between Group Comparisons for KQ8**

Author, year	Comparison	Outcome	Comments
Elsaid,A.K., 2012 <sup>1</sup>	Enoxaparin, CLCr $\leq 30$ mL/min (vs) UFH, CLCr $\leq 30$ mL/min	Major bleeding	Relative risk= 4.68 (95% CI. 1.06-20.59)
	Total population enoxaparin vs UFH	Major bleeding	Relative risk= 3.21 (95% CI. 1.40-7.34) p=0.005

## References

1. Elsaid KA, Collins CM. Initiative to improve thromboprophylactic enoxaparin exposure in hospitalized patients with renal impairment. Am J Health Syst Pharm 2012; 69(5):390-6.

## Appendix F. Scientific Information Packet Tables

**Table 1. SIP Submission - Statement Indicating No Relevant Studies Have been Conducted**

Company	Product	Description of Submission	Number of Published Studies	Number of Unpublished Studies	Number of Clinical Trials
APP Pharmaceuticals	Heparin Sodium Injection	Letter stating that no relevant studies had been conducted with this drug	0	0	0
Bayer	Refludan (Lepirudin)		0	0	0
The Medicines Company	Bivalirudin		0	0	0

**Table 2. SIP Submission - Potentially Relevant Studies**

Company	Product	Description of Submission	Number of Published Studies	Number of Unpublished Studies	Number of Clinical Trials	Citations not previously included in database
Boehringer Ingelheim	Pradaxa (Dabigatran)	Prescribing information and relevant study citations	7	0	9	Of the 36 citations submitted, six were found to be missing from the previously created database. These six studies were then reviewed for eligibility.
Sanofi-Aventis	Lovenox (Enoxaparin)	Prescribing information and relevant study citations	14	0	6	
Covidien	Kendall SCD™ Sequential Compression and A-V Impulse	Journal articles	12	0	0	
GlaxoSmithKline	Arixtra (Fondaparinux)	Prescribing information, relevant citations, and study data	3	1	6	

**Table 3. SIP Submission – Chemoprophylaxis Protocol**

Organization	Description of Submission	Additional Study Information
American Association of Neurological Surgeons	Chemoprophylaxis Protocol Following Traumatic Brain Injury	<p>Safety of a DVT Chemoprophylaxis Protocol Following Traumatic Brain Injury: A Single Center Quality Improvement Initiative. (Publication Pending)  Christopher M Nickele MD<sup>1</sup>, Timothy K Kamps<sup>2</sup>, Joshua E Medow MD<sup>1</sup></p> <p><sup>1</sup> Department of Neurologic Surgery, University of Wisconsin, Madison, Wisconsin, United States of America</p> <p><sup>2</sup> Department of Quality Resources, University of Wisconsin, Madison, Wisconsin, United States of America</p>



## Appendix G. Sensitivity Analysis for IVC Filters in Trauma on PE, Fatal PE, and Mortality in Controlled Studies

**Table 1. Sensitivity analysis for IVC filters in trauma on PE, fatal PE and mortality in controlled studies**

	RR ( 95% CI)	Statistical inconsistency I <sup>2</sup> %
<b>PE</b>		
All Studies	0.55 ( 0.10-2.96)	61
Wilson excluded	0.62 ( 0.10-3.68)	66.3
Rogers 1995 excluded	0.44 (0.06-3.09)	62
Khansarina excluded	0.76 ( 0.13-4.34)	60.7
Rodriguez excluded	0.70 ( 0.10-5.05)	63.6
Rogers 1997 excluded	0.33( 0.09-1.33)	30
Gosin excluded	0.72( 0.12-4.25)	62.7
Gorman excluded	0.43 (0.07-2.75)	64.6
Rajashekhar excluded	0.58(0.08-4.05)	67.2
Rogers 1995; Rogers 1997 excluded	0.20 (0.06-0.70)	0
<b>FATAL PE</b>		
All Studies	0.35 ( 0.01-8.16)	70
Wilson excluded	0.37 (0.01to 17.31)	80
Rogers 1995 excluded	0.09(0.01 to 0.81)	0
Khansarina excluded	0.59 (0.01 to 30.79)	73.4
Rodriguez excluded	0.57 ( 0.01 to 32.80)	74.9
<b>MORTALITY</b>		
All Studies	1.33 (0.53 to 3.32)	69.8
Rogers 1995 excluded	0.95(0.41 to 2.22)	55
Khansarina excluded	1.66 ( 0.46-5.97)	68.5
Rodriguez excluded	1.82 (90.68 to 4.85)	69.7

<b>Rogers 1997 excluded</b>	1.14 ( 0.36 to 3.62)	70.8
<b>Rajashekhar 2011 excluded</b>	1.26 (0.47 to 3.37)	76.8
<b>DVT</b>		
<b>All studies</b>	1.76 (0.49-6.18)	56.8
<b>Rodriguez excluded</b>	3.78 ( 1.21 to 11.8)	Not estimable
<b>Gorman excluded</b>	0.87 ( 0.38 to 2.02)	Not estimable
<b>Rajasekhar excluded</b>	1.67 (0.35 to 8.04)	Not estimable

## Appendix H. Sensitivity Analysis for KQ 1 and KQ 6

Table 1. Sensitivity analysis for KQ 1

Outcome	Meta-analysis	Continuity correction	Effect estimate and 95% CI	Effect estimate and 95% CI (Stata)	Statistical heterogeneity, %	Statistical heterogeneity (Stata)
<b>PE</b> <sup>1-6</sup>	RR Random effects	0.1	0.13 (95% CI = 0.02 to 0.92) *	0.13 (95% CI = 0.02 to 0.92) *	0 %	0%
	RR Random effects	0.5	0.23 (95% CI = 0.08 to 0.68) *	0.23 (95% CI = 0.08 to 0.68) *	0%	0%
	RR Random effects	Treatment arm	0.20 (95% CI = 0.06 to 0.70)*	0.20 (0.06 to 0.70) *	0%	0%
	Peto OR	No CC	0.26 (95% CI = 0.14 to 0.49)*	0.26 (95% CI = 0.14 to 0.49*)	0%	0%
<b>Fatal PE</b> <sup>3-5,6</sup>	RR Random effects	0.1	0.01 (95% CI = 0 to 425.491)	0.005 (95% CI = 0 to 425.5)	0 %	0%
	RR Random effects	0.5	0.22 (95% CI = 0.04 to 1.16)	0.22 (95% CI = 0.04 to 1.16)	0%	0%
	RR Random effects	Treatment arm	0.09 (95% CI = 0.01 to .76) *	0.09 (0.01 to 0.81) *	0%	0%
	Peto OR	No CC	0.22 (95% CI = 0.08 to 0.58) *	0.22 (95% CI = 0.08 to 0.58) *	0%	0%
<b>Mortality</b> <sup>3-5</sup>	RR Random effects	0.1	0.70 (95% CI = 0.44 to 1.11)	0.7 (95% CI = 0.44 to 1.11)	0 %	0%
	RR Random effects	0.5	0.70 (95% CI = 0.41 to 1.19)	0.71 (95% CI = 0.41 to 1.20)	4.6%	4.7%
	RR Random effects	Treatment arm	0.70 (95% CI = 0.40 to 1.22)	0.70 (0.40 to 1.23)	6.6%	6.7%
	Peto OR	No CC	0.66 (95% CI = 0.39 to 1.09)	0.66 (95% CI = 0.39 to 1.09)	20.3%	20.3%
<b>DVT</b> <sup>1,4,5</sup>	RR Random effects	0.1	1.69 (95% CI = 0.41 to 6.99)	1.69 (95% CI = 0.41 to 6.99)	57.2%	57.2%
	RR Random effects	0.5	1.74 (95% CI = 0.49 to 6.077)	1.74 (95% CI = 0.5 to 6.07)	56.5	56.4%
	RR Random effects	Treatment arm	1.76 (95% CI = 0.50 to 6.19)	1.76 (0.5 to 6.19)	56.8%	56.7%
	Peto OR	No CC	1.67 (95% CI = 0.81 to 3.47)	1.67 (95% CI = 0.81 to 3.47)	60.6%	60.6%

\* Statistically significant

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**Table 2. Sensitivity analysis for KQ 6**

Outcome	Meta-analysis	Continuity correction	Effect estimate and 95% CI	Effect estimate and 95% CI (Stata)	Statistical heterogeneity	Statistical heterogeneity (Stata)
<b>PE</b> <sup>1-5</sup>	RR Random effects	0.1	1.30 (95% CI = 0.57 to 3.01)	1.30 (95% CI = 0.57 to 3.01)	11.2%	11.2%
	RR Random effects	0.5	1.16 (95% CI = 0.51 to 2.66)	1.17 (95% CI = 0.51 to 2.67)	16.0%	16.0%
	RR Random effects	Treatment arm	1.21 (95% CI = 0.57 to 2.56)	1.21 (95% CI = 0.57 to 2.56)	6.9%	6.9%
	Peto OR	No CC	0.99 (95% CI = 0.49 to 2.00)	0.99 (95% CI = 0.49 to 1.96)	36.2%	36.2%
<b>Mortality</b> <sup>1-4</sup>	RR Random effects	0.1	5.95 (95% CI = 1.99 to 17.81)	5.95 (95% CI = 1.99 to 17.81) *	0%	0%
	RR Random effects	0.5	4.45 (95% CI = 1.55 to 12.72)	4.45 (95% CI = 1.55 to 12.72) *	4.1%	4.1%
	RR Random effects	Treatment arm	4.30 (95% CI = 1.60 to 11.54)	4.30 (95% CI = 1.60 to 11.54) *	0%	0%
	Peto OR	No CC	3.87 (95% CI = 1.32 to 11.35) *	3.87 (95% CI = 1.32 to 11.35) *	70.5%	70.5%
<b>DVT</b> <sup>1,3-5</sup>	RR Random effects	0.1	2.94 (95% CI = 1.35 to 6.38)	2.93 (95% CI = 1.35 to 6.38) *	40.3%	42.2%
	RR Random effects	0.5	2.94 (95% CI = 1.35 to 6.38)	3.13 (95% CI = 1.39 to 7.06) *	40.3%	40.3%
	RR Random effects	Treatment arm	2.94 (95% CI = 1.35 to 6.38)	2.93 (95% CI = 1.35 to 6.38) *	40.3%	40.3%
	Peto OR	No CC	2.93 (95% CI = 1.49 to 5.78) *	2.93 (95% CI = 1.49 to 5.78) *	78%	78%

\* Statistically significant

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## Appendix I. Clinical Trials

**Table 1. Clinical Trials**

<b>Clinical Trial Name and Identifier</b>	<b>Relevant To KQ</b>	<b>Comments</b>
Delayed Versus Early Enoxaparin Prophylaxis After Traumatic Brain Injury (TBI) (DEEP) NCT01014403	KQ2	Included in our review
Fondaparinux 1.5 mg for the Prevention of Venous Thromboembolism (VTE) in Medical Patients With Renal Insufficiency NCT00927602	KQ8	Study was terminated due to slow recruitment; there are no published results; these study results would be relevant to KQ8
A Comparison of Certoparin and Unfractionated Heparin in the Prevention of Thromboembolic Events in Acutely Ill Medical Patients NCT00451412	KQ4,5,7,8	Included in our review
Efficacy of the Association Mechanical Prophylaxis + Anticoagulant Prophylaxis on Venous Thromboembolism Incidence in Intensive Care Unit (ICU) (CIREA2) NCT00740987	KQ4,5,7,8	Recruiting patients, results not available yet; unlikely to inform any of the key questions when available
Safety of Fondaparinux as Routine VTE Prophylaxis in Medical ICU Patients NCT00493896	KQ4,5,7,8	Study was terminated for slow enrollment; no published results
Fondaparinux in Critically Ill Patients With Renal Failure NCT01467583	KQ8	Recruiting patients, results not available yet; results on the subgroup of patients with acute renal failure but not on dialysis will inform KQ8
Thromboprophylaxis and Bariatric Surgery NCT00444652	KQ6	Recruiting patients, results not available yet but will inform KQ6; will not obviate the need for future research regarding pharmacoprophylaxis; this is an industry sponsored study of intermediate outcomes
Prospective, Multi-center, Single-arm Study to Assess the Safety of Retrieval of the Recovery G2 Filter (EVEREST) NCT00556426	KQ1,KQ6	Study completed; no published results; results will be informative to our key questions if results are reported by patient subgroups; will not obviate the need for future research for these questions
IVC Filter Registry NCT01158482	KQ1,KQ6	Recruiting patients; will allow for observational studies
National Inferior Vena Cava (IVC) Filter Registry NCT01367184	KQ1,KQ6	Recruiting patients; will allow for observational studies
Crux Biomedical Vena Cava Filter Study - United States (RETRIEVE 2) NCT01120509	KQ1,KQ6	Study completed; no published results; observational study relevant to KQ1 and KQ6 if subgroups are reported
Crux Biomedical IVC Filter - Evaluation of the Crux Inferior Vena Cava Filter System (Retrieve) NCT00605332	KQ1,KQ6	Study completed; no published results; observational study relevant to KQ1 and KQ6 if subgroups are reported; does not obviate need for additional research