Evidence-based Practice Center Rapid Response Protocol

Project Title: *Making Healthcare Safer IV: Protocols for High-Risk Drugs: Reducing Adverse Drug Events Related to Anticoagulants*

Review Questions

1. What are the frequency and severity of harms associated with anticoagulant use in the inpatient and outpatient settings and anticoagulation after discharge among adults?

2. What patient safety measures or indicators have been used to examine the harm associated anticoagulant use in the inpatient and outpatient settings and anticoagulation after discharge?

3. What patient safety practices (PSPs) have been used to ensure safe transitions and continuation of patients' anticoagulants after discharge, and in what settings have these practices been applied?

4. What is the rationale for these PSPs that been used to prevent or mitigate the harm associated with anticoagulant use in the inpatient and outpatient settings and anticoagulation after discharge?

5. What studies have assessed the effectiveness and unintended effects of PSPs (i.e., PSP 1 anticoagulant management in ambulatory settings, and PSP 2 interventions to support safe transition for patients with anticoagulation post-discharge) and what new evidence has been published since the search was done for the Making Healthcare Safer (MHS) III report in 2019?

6. What are the common barriers and facilitators to implementing these PSPs?

7. What resources (e.g., cost, staff, time) are required for the implementation of these PSPs?

8. What toolkits are available to support the implementation of the PSPs?

Context and Domain Being Studied

The Agency for Healthcare Research and Quality (AHRQ) Making Healthcare Safer (MHS) reports consolidate information for healthcare providers, health system administrators, researchers, and government agencies about practices that can improve patient safety across the healthcare system—from hospitals to primary care practices, long-term care facilities, and other healthcare settings. In Spring of 2023, AHRQ launched its fourth iteration of the MHS Report (MHS IV). The "Protocols for High-Risk Drugs: Reducing Adverse Drug Events Related to Anticoagulants" as a patient safety practice (PSP) was identified as a high priority for inclusion in the MHS IV reports using a modified Delphi technique by a Technical Expert Panel (TEP) that met in December 2022. The TEP included 15 experts in patient safety with representatives of governmental agencies, healthcare stakeholders, clinical specialists, experts in patient safety issues, and a patient/consumer perspective. See the Making Healthcare Safer IV Prioritization Report for additional details.[1]

Professional organizations widely endorse anticoagulants for preventing and treating blood clots in conditions that have a higher risk of leading to venous thromboembolism and stroke (e.g., chronic atrial fibrillation, artificial heart valves, antiphospholipid syndrome, genetic or acquired thrombophilia, cancer).[2,3] While anticoagulants may reduce morbidity and mortality in some patients,[4–6] they may also lead to serious adverse effects (e.g., bleeding).[7,8] The 2019 National Action Plan for Adverse Drug Event Prevention (ADE Action Plan) identified anticoagulants as a leading cause of adverse drug events.[9] For example, between 2013 and 2014, anticoagulants were implicated in 38.8% (95% CI: 33.7% to 43.8%) of all U.S. emergency department visits for adverse drug events among adults aged ≥80 years.[8] A few PSPs have been designed to address the potential harms of anticoagulants. Dosing protocols, nomograms, automatic infusion devices, and pharmacist-led administration are a few examples of PSPs intended to ensure proper anticoagulation and intended to reduce the risk of adverse events.[10]

Overview of the PSP

The quality of individual studies in the MHS III report[11] concerning anticoagulation management services (pharmacist or nurse-led) was deemed moderate to high (6 systematic reviews supplemented with 5 studies). The report stated that the evidence for this PSP indicates a moderately positive effect on time to therapeutic range, but the evidence was low or mixed quality for bleeding and thromboembolic events. The same report stated that the evidence for the effects of interventions for the safe transition of patients receiving anticoagulants after hospital or ED discharge is poor quality (5 studies, n=620). The effects of this PSP remain understudied.

The MHS I report centered its analysis on the interventions for heparin, focusing on the implementation of dosing protocols and the role of inpatient anticoagulation services. MHS II[10] expanded this scope to include interventions aimed at reducing adverse events linked to intravenous heparin in inpatient settings, and excluded interventions for subcutaneous or oral anticoagulant administration. MHS III reviewed the evidence for PSPs relevant to various settings: inpatient, ambulatory, and long-term care.[11] The three PSPs included in MHS III were anticoagulant management in ambulatory settings, the use of dosing protocols, and interventions to support safe transition for patients with anticoagulation post-discharge. We determined PSPs related to dosing protocols as a lower priority for the MHS IV report and will therefore will not be included. For MHS IV, we will focus on the anticoagulation management services and interventions to support safe transitions and the continuation of anticoagulants post-discharge, highlighting both inpatient and outpatient settings.

Purpose of the Review

The overall purpose of this rapid response is to summarize the literature on PSPs designed or hypothesized to prevent adverse events related to anticoagulants. We also will summarize effects associated with PSPs for anticoagulation management services in ambulatory settings (PSP 1) and interventions to support safe transitions and continuation of anticoagulants post-discharge (PSP 2).

Methodologic Approach

For this rapid response, strategic adjustments will be made to streamline traditional systematic review processes and deliver an evidence product in the allotted time. We will follow adjustments and streamlining processes proposed by the AHRQ Evidence-based Practice Center (EPC) Program. Adjustments include being as specific as possible about the questions, limiting the number of databases searched, modifying search strategies to focus on finding the most valuable studies (i.e., being flexible on sensitivity to increase the specificity of the search), restricting the search to studies published recently (i.e., since 2019, as MHS III searches were run through 2018) in English and performed in countries rated as “very high” Human Development Index (according to the United Nations, 2019), and having each study assessed by a single reviewer. We will use the artificial intelligence (AI) feature of DistillerSR (AI Classifier Manager), such that we will re-review the top 10 percent of excluded citations that the AI Classifier Manager notes as potentially includable.

We will search for high quality systematic reviews and will rely on the content of any such systematic review that is found. We will not independently assess original studies included in any such systematic review.

For this topic that focuses on a PSP that may address a variety of different harms, we will answer Review Questions 1 and 2 by focusing on the harms and patient safety measures or indicators that are addressed in the studies we find for Review Question 5. For Review Question 2, we will focus on identifying relevant measures that are included in the Centers for Medicare & Medicaid Services (CMS) patient safety measures, AHRQ’s Patient Safety Indicators, or the National Committee for Quality Assurance (NCQA) patient safety-related measures.

We will ask our content experts to answer Review Questions 3 and 4 by citing selected references, including PSPs used and explanations of the rationale presented in the studies we find for Review Question 5.

For Review Questions 6 and 7, we will focus on the barriers, facilitators, and required resources reported in the studies we find for Review Question 5 and supplementary literature identified by the search.

For Review Question 8, we will identify publicly available patient safety toolkits developed by AHRQ or other organizations that could help to support implementation of the PSPs. To accomplish that task, we will review AHRQ's Patient Safety Network (PSNet) (https:/psnet.ahrq.gov) and listing of patient safety related toolkits (see https://www.ahrq.gov/tools/index.html?search_api_views_fulltext=&field_toolkit_topics=14170&sort_by=title&sort_order=ASC) and we will include any toolkits mentioned in the studies we find for Review Question 5. We will identify toolkits without assessing or endorsing them.

Eligibility Criteria for Studies of Effectiveness

We will search for original studies and systematic reviews on the review questions according to the inclusion and exclusion criteria presented in Table 1.

Table 1. Inclusion and Exclusion Criteria

Study Parameter	Inclusion criteria	Exclusion criteria
Population	**All Review Questions (RQs)**: Adults (aged 18 years and older) who receive anticoagulants.	Studies exclusively conducted with children and adolescents (aged <18 years), pregnant and lactating individuals, prison inmates, and individuals with active cancer.
Intervention	**RQs 1-4**: Not applicable (description of harms associated with anticoagulant use in the inpatient and outpatient settings and anticoagulation after discharge among adults) **KQ 5-7**: PSPs designed or hypothesized to prevent adverse events related to (PSP 1) anticoagulation management services and (PSP 2) interventions to support safe transitions and continuation of patients' anticoagulants post-discharge.	None
Comparator	**RQ 5**: Any comparator (e.g., standard care without specific PSPs), including pre-intervention measurements. **All other RQs**: Comparator is not required	**RQ 5:** • No comparator • Comparator group is not appropriate (would not have equivalent need for the intervention)
Outcome	RQ 5 **Safety** • All-cause and cause-specific mortality, bleeding, hemorrhage, stroke, quality of life, adverse events associated with drug-drug interaction, thrombotic events, time to therapeutic range **Harms associated with the use of PSPs (i.e., unintended negative consequences)** **Utilization of healthcare services** • ED utilization • Hospital admission/readmission	Other unspecified outcomes

Study Parameter	Inclusion criteria	Exclusion criteria
	Implementation • Barriers and facilitators to implementation • Resources (i.e., cost, staff, time) required for implementation. **Contextual information**: • Rationale for PSPs • Patient safety measures or indicators • Toolkits and availability	
Timing	Any	
Setting	**All RQs:** Inpatient and outpatient	Studies conducted in emergency medical services settings; specific long-term living facilities (e.g., prisons, inpatient mental health).
Type of studies	**All RQs:** Systematic reviews. If systematic reviews are not available: randomized controlled trials, observational studies with a comparison group, including before-after studies, published since 2019, the date of the search done for the MHS III report on this topic. **Questions 6, 8**: All study design included for other questions, qualitative studies, supplementary sources.	• Unspecified study designs or comparison group not described. • Not peer-reviewed publications.

ED = emergency department; IOM = Institute of Medicine; MHS = Making Healthcare Safer; PSPs = Patient Safety Practices; RQ = review question; TEP = technical expert panel

Literature Searches for Studies of Effectiveness

We will search PubMed published since 2019 (as MHS III searches were run through 2018), the year of the search completed for the MHS III report on this topic, that address the rapid response questions. If no recent high-quality systematic reviews are identified, we will conduct searches of PubMed for primary studies from 2019.

Description of Included Studies

To efficiently describe eligible studies, the full text of each potentially eligible article will be reviewed by a single team member to confirm eligibility and prepare a summary of the study, including author, year, study design, number of study participants, and main findings for each of the review questions. We will use the DistillerSR AI Classifier Manager to identify potentially highly relevant studies excluded during the initial screening. To accomplish this, after a single team member reviews each citation, they will re-review the top 30 percent of abstracts noted by the AI Classifier Manager as potentially relevant.

The full text of each remaining potentially eligible article will be reviewed by a single team member to confirm eligibility and extract data. The team will decide whether it has enough time and resources to ask a second team member to check a randomly selected 10 percent sample of the articles to verify that important studies were not excluded and confirm the accuracy of extracted data.

To describe eligible systematic reviews, a single team member will prepare a summary including the author, year, number of studies by study design, and main findings relevant to each of the rapid response questions.

For Review Question 8, we will create a table to record the source of each relevant toolkit along with a 1–2 sentence description. We will not endorse any specific toolkit.

Risk of Bias (Quality) Assessment

For studies that address Review Question 5 about the effectiveness of PSPs, the primary reviewer will use the Cochrane Collaboration's tool for assessing the risk of bias of randomized controlled trials (RCTs)[12] or the ROBINS-I tool for assessing the Risk Of Bias In Non-randomized Studies – of Interventions.[13] When assessing RCTs, we will use the 7 items in the Cochrane Collaboration's tool that cover the domains of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. When assessing non-randomized studies, we will use specific items in the ROBINS-I tool that assess bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported results. The risk of bias assessments will focus on the main outcome of interest in each study.

If we identify a recent eligible systematic review, the reviewer will use the criteria developed by the United States Preventive Services Task Force Methods Workgroup for assessing the quality of systematic reviews.[14]

- **Good** - Recent relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.

- **Fair** - Recent relevant review that is not clearly biased but lacks comprehensive sources and search strategies.
- **Poor** - Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

The Task Leader will review the risk of bias assessments and any disagreements will be resolved through discussion with the team.

EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators from participation in the review.

Role of the Funder

This project is funded under Contract No. 75Q80120D00003/75Q80122F32009 from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services. The AHRQ Task Order Officer will review contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by AHRQ or the U.S. Department of Health and Human Services.

Format and Content of Report

The report will follow the most recent template approved by AHRQ at the time of approval of the protocol.

References:

1. Rosen M, Dy SM, Stewart CM, Shekelle P, Tsou A, Treadwell J, Sharma R, Zhang A, Vass M, Motala A, Bass EB. Final report on prioritization of patient safety practices for a new rapid review or rapid response. Making Healthcare Safer IV. (Prepared by the Johns Hopkins, ECRI, and Southern California Evidence-based Practice Centers under Contract No. 75Q80120D00003). AHRQ Publication No. 23-EHC019-1. Rockville (MD): Agency for Healthcare Research

and Quality; 2023 Jul [accessed 2023 Aug 04]. https://effectivehealthcare.ahrq.gov/products/prioritization-patient-safety-practices.
2. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart . *Circulation*. 2019;140(2):e125-e151. doi:10.1161/CIR.0000000000000665
3. Farge D, Bounameaux H, Brenner B, et al. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2016;17(10):e452-e466. doi:10.1016/S1470-2045(16)30369-2
4. Kakkar AK, Cimminiello C, Goldhaber SZ, Parakh R, Wang C, Bergmann J-F. Low-Molecular-Weight Heparin and Mortality in Acutely Ill Medical Patients. *N Engl J Med*. 2011;365(26):2463-2472. doi:10.1056/NEJMoa1111288
5. Wang C, Chi C, Guo L, et al. Heparin therapy reduces 28-day mortality in adult severe sepsis patients: a systematic review and meta-analysis. *Crit Care*. 2014;18(5):563. doi:10.1186/s13054-014-0563-4
6. Giossi R, Menichelli D, Pani A, et al. A Systematic Review and a Meta-Analysis Comparing Prophylactic and Therapeutic Low Molecular Weight Heparins for Mortality Reduction in 32,688 COVID-19 Patients. *Front Pharmacol*. 2021;12:698008. doi:10.3389/fphar.2021.698008
7. Crowther MA, Warkentin TE. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. *Blood*. 2008;111(10):4871-4879. doi:10.1182/blood-2007-10-120543
8. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. *JAMA*. 2016;316(20):2115-2125. doi:10.1001/jama.2016.16201
9. Harris Y, Hu DJ, Lee C, Mistry M, York A, Johnson TK. Advancing Medication Safety: Establishing a National Action Plan for Adverse Drug Event Prevention. *Jt Comm J Qual patient Saf*. 2015;41(8):351-360. doi:10.1016/s1553-7250(15)41046-3
10. Pfoh E, Thompson D, Dy S. High-Alert Drugs: Patient Safety Practices for Intravenous Anticoagulants. In: *Making Healthcare Safer II: An Updated Critical Analysis of the Evidence for Patient Safety Practices*. II. Rockville (MD), USA; 2012:23-30.
11. Shoemaker-Hunt SJ, Wyant B. Harms Due to Anticoagulants. In: *Making Healthcare Safer III: A Critical Analysis of Existing and Emerging Patient Safety Practices*. III. Rockville, Maryland; 2020:1-43.
12. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi:10.1136/bmj.d5928
13. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. doi:10.1136/bmj.i4919
14. U.S. Preventive Services Task Force. Appendix VI. Criteria for assessing internal validity of individual studies. U.S. Preventive Services Task Force Procedure

Manual. https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual/procedure-manual-appendix-vi-criteria-assessing-internal-validity-individual-studies. Published 2017. Accessed July 27, 2023.