Appendix A. Exact Search Strings

PubMed® Search Strategy (June 23, 2017)

KQ1 & KQ2: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic and patient outcome efficacy) of available clinical and imaging tools and associated risk factors for predicting thromboembolic risk? In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?

| #1 | "Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR "Atrial Flutter"[Mesh] OR "atrial flutter"[tiab] |
| #4 | #1 AND #2 AND #3 |
| #5 | #4 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) |
| #6 | #5 NOT ("Animals"[MeSH Terms] NOT "Humans"[MeSH Terms]) |
| #7 | #6 NOT ("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]) NOT "Adult"[Mesh]) |
KQ3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:

a) In patients with nonvalvular atrial fibrillation?

b) In specific subpopulations of patients with nonvalvular atrial fibrillation?

#1 "Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR "Atrial Flutter"[Mesh] OR "atrial flutter"[tiab]


#4 #1 AND #2 AND #3

KQ1: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of available clinical and imaging tools for predicting thromboembolic risk?
KQ2: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?

KQ3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:
(a) In patients with nonvalvular atrial fibrillation?
(b) In specific subpopulations of patients with nonvalvular atrial fibrillation?
**KQ4:** What are the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular atrial fibrillation who are undergoing invasive procedures?

| #1 | "Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab] |
| #4 | #1 AND #2 AND #3 |

#7 AND #6

#8 AND #6

#8 NOT (animals[mh] NOT humans[mh]), Limits: English, Publication Date from 2000 to present
# KQ5: What are the comparative safety and effectiveness of available strategies for switching between warfarin and other novel oral anticoagulants, in patients with nonvalvular atrial fibrillation?

**#1**  "Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]

**#2**  "warfarin"[MeSH Terms] OR warfarin[tw] OR coumadin[tw]


**#6**  #1 AND #2 AND (#3 OR #4) AND #5

**#7**  #6 NOT (animals[mh] NOT humans[mh]), Limits: English, Publication Date from 2000 to present

# KQ6: What are the comparative safety and effectiveness of available strategies for resuming anticoagulation therapy or performing a procedural intervention as a stroke prevention strategy following a hemorrhagic event (stroke, major bleed, or minor bleed) in patients with nonvalvular atrial fibrillation?

**#1**  "Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR (atrial[tiab] AND fibrillation[tiab]) OR afib[tiab] OR "atrial flutter"[MeSH Terms] OR "atrial flutter"[tiab]


**#6**  #1 AND #2 AND (#3 OR #4) AND #5

**#7**  #6 NOT (animals[mh] NOT humans[mh]), Limits: English, Publication Date from 2000 to present
Embase® Search Strategy (June 23, 2017)

Platform: Embase.com

KQ1 & KQ2: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic and patient outcome efficacy) of available clinical and imaging tools and associated risk factors for predicting thromboembolic risk? & In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?

#1 'atrial fibrillation'/exp OR 'heart atrium flutter'/exp OR 'atrial fibrillation':ab,ti OR 'atrial flutter':ab,ti

#2 'cerebrovascular disease'/de OR 'cerebrovascular accident'/exp OR 'thromboembolism'/exp OR 'bleeding'/de OR 'brain hemorrhage'/exp OR 'brain ischemia'/exp OR 'prothrombin time'/exp OR stroke:ab,ti OR strokes:ab,ti OR thromboembolism:ab,ti OR thromboembolisms:ab,ti OR thromboembolic:ab,ti OR thromboses:ab,ti OR hemorrhage:ab,ti OR hemorrhages:ab,ti OR hemorrhaging:ab,ti OR hemorrhagic:ab,ti OR haemorrhage:ab,ti OR haemorrhages:ab,ti OR haemorrhaging:ab,ti OR haemorrhagic:ab,ti OR ((bleeding OR bleed OR bleeds) NEAR/2 (major OR risk OR event)):ab,ti OR ((systemic OR paradoxic OR crossed) NEXT/2 (embolism OR embolisms)):ab,ti OR ((brain OR cerebral OR brainstem OR 'brain stem') NEXT/2 (ischemia OR ischaemia OR ischaemias OR ischaemia OR infarction OR infarctions)):ab,ti OR (transient NEXT/2 (ischemic OR ischaemic OR ischaemia OR ischemia) NEXT/2 (attack OR attacks)):ab,ti OR tia:ab,ti OR tias:ab,ti OR cerebrovascular accident:ab,ti OR cerebrovascular accidents:ab,ti OR cva:ab,ti OR cvas:ab,ti OR 'brain vascular accident':ab,ti OR 'brain vascular accidents':ab,ti

#3 'risk'/exp OR risk:ab,ti OR risks:ab,ti OR 'prediction and forecasting'/exp OR predict:ab,ti OR predicts:ab,ti OR predicting:ab,ti OR predictor:ab,ti OR predictors:ab,ti OR predictive:ab,ti

#4 #1 AND #2 AND #3

#5 #4 NOT ('case report'/exp OR 'case study'/exp OR 'a case report':ti OR ': case report':ti OR
KQ3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:

a) In patients with nonvalvular atrial fibrillation?

b) In specific subpopulations of patients with nonvalvular atrial fibrillation?

| #1 | 'atrial fibrillation'/exp OR 'heart atrium flutter'/exp OR 'atrial fibrillation':ab,ti OR 'atrial flutter':ab,ti |
| #2 | 'cerebrovascular disease'/de OR 'cerebrovascular accident'/exp OR 'thomboembolism'/exp OR 'bleeding'/de OR 'brain hemorrhage'/exp OR 'brain ischemia'/exp OR 'prothrombin time'/exp OR stroke:ab,ti OR strokes:ab,ti OR thromboembolism:ab,ti OR thromboembolisms:ab,ti OR thromboembolic:ab,ti OR thromboses:ab,ti OR hemorrhaging:ab,ti OR hemorrhages:ab,ti OR hemorrhaging:ab,ti OR hemorrhagic:ab,ti OR haemorrhaging:ab,ti OR haemorrhages:ab,ti OR haemorrhaging:ab,ti OR haemorrhagic:ab,ti OR ((bleeding OR bleed OR bleeds) NEAR/2 (major OR risk OR event)):ab,ti OR ((systemic OR paradoxical OR crossed) NEXT/2 (embolism OR embolisms)):ab,ti OR ((brain OR cerebral OR brainstem OR 'brain stem') NEXT/2 (ischemia OR ischaemia OR ischemias OR ischaemias OR infarction OR infarctions)):ab,ti OR (transient NEXT/2 (ischemic OR ischaemic OR ischemia OR ischemia) NEXT/2 (attack OR attacks)):ab,ti OR tia:ab,ti OR tias:ab,ti OR 'cerebrovascular accident':ab,ti OR 'cerebrovascular accidents':ab,ti OR cva:ab,ti OR cvs:ab,ti OR 'brain vascular accident':ab,ti OR 'brain vascular accidents':ab,ti |
| #3 | 'risk'/exp OR risk:ab,ti OR risks:ab,ti OR 'safety'/exp OR safety:ab,ti OR 'incidence'/exp OR efficacy:ab,ti OR efficacious:ab,ti OR 'prevention':lnk OR prevent:ab,ti OR prevents:ab,ti OR preventing:ab,ti OR prevention:ab,ti OR prevention:ab,ti OR 'treatment outcome'/exp OR 'adverse drug reaction':lnk OR (side NEXT/1 effect*:ab,ti OR (adverse NEXT/3 (interaction* OR response* OR effect* OR event* OR reaction* OR outcome*))):ab,ti OR (unintended NEXT/3 (interaction* OR response* OR effect* OR event* OR reaction* OR outcome*)):ab,ti OR (unexpected NEXT/3 (interaction* OR response* OR effect* OR event* OR reaction* OR outcome*)):ab,ti OR (undesirable NEXT/3 (interaction* OR response* OR effect* OR event* OR reaction* OR outcome*)):ab,ti OR 'drug safety':ab,ti OR 'drug toxicity':ab,ti OR tolerability:ab,ti OR harm:ab,ti OR harms:ab,ti OR harmful:ab,ti OR 'treatment emergent':ab,ti OR complication*:ab,ti OR toxicity:ab,ti |
Embase® Search Strategy (August 14, 2012)
Platform: Embase.com

KQ1: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of available clinical and imaging tools for predicting thromboembolic risk?
KQ2: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?

| #1 | "heart atrium fibrillation"/exp OR "heart atrium flutter"/exp OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti |
| #2 | "age"/exp OR "dementia"/exp OR "falling"/exp OR "international normalized ratio"/exp OR "age factors":ab,ti OR "age factor":ab,ti OR age:ab,ti OR dementia:ab,ti OR INR:ab,ti OR fall:ab,ti OR fails:ab,ti OR "international normalized ratio":ab,ti OR paroxysmal:ab,ti OR persistent:ab,ti OR permanent:ab,ti OR stratification:ab,ti OR classification:ab,ti OR schema:ab,ti OR has-bled:ab,ti OR (cognitive:ab,ti AND impairment:ab,ti) OR cognition:ab,ti OR ((prior:ab,ti OR previous:ab,ti OR first:ab,ti) AND stroke:ab,ti) |
| #3 | "brain hemorrhage"/exp OR "bleeding"/exp OR hemorrhage:ab,ti OR hemorrhaging:ab,ti OR bleeding:ab,ti OR bleed:ab,ti OR hemorrhagic:ab,ti OR haemorrhage:ab,ti OR haemorrhagic:ab,ti |
| #4 | #1 AND #2 AND #3 |
| #5 | "diagnosis"/exp OR "treatment outcome"/exp OR "sensitivity and specificity"/exp OR "clinical decision making"/exp OR "decision making"/exp OR diagnosis:ab,ti OR outcome:ab,ti OR outcomes:ab,ti OR reliability:ab,ti OR accuracy:ab,ti OR accurate:ab,ti OR Sensitivity:ab,ti OR specificity:ab,ti OR valid:ab,ti OR validity:ab,ti OR validation:ab,ti OR decision:ab,ti OR decisions:ab,ti OR assessment:ab,ti |
| #6 | #5 AND #4 |
| #7 | #6 Limits: Humans, English, 2000 - present |
| #8 | #7 AND [embase]/lim NOT [medline]/lim |

KQ3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:

(a) In patients with nonvalvular atrial fibrillation?
(b) In specific subpopulations of patients with nonvalvular atrial fibrillation?

| #1 | "heart atrium fibrillation"/exp OR "heart atrium flutter"/exp OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti |
| #2 | "anticoagulant agent"/exp OR "warfarin"/exp OR "vitamin K group"/exp OR "heparin"/exp OR "enoxaparin"/exp OR "rivaroxaban"/exp OR "dabigatran etexilate"/exp OR "apixaban"/exp OR "edoxaban"/exp |
| #3 | warfarin:ab,ti OR coumadin:ab,ti OR vitamin k:ab,ti OR enoxaparin:ab,ti OR lovenox:ab,ti OR rivaroxaban:ab,ti OR xarelto:ab,ti OR dabigatran:ab,ti OR pradaxa:ab,ti OR |
KQ4: What are the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular atrial fibrillation who are undergoing invasive procedures?

| #1 | 'heart atrium fibrillation'/exp OR 'heart atrium flutter'/exp OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti |
| #2 | 'anticoagulant agent'/exp OR 'warfarin'/exp OR 'vitamin K group'/exp OR 'heparin'/exp OR 'enoxaparin'/exp OR 'rivaroxaban'/exp OR 'dabigatran etexilate'/exp OR 'apixaban'/exp OR 'edoxaban'/exp |
| #3 | warfarin:ab,ti OR coumadin:ab,ti OR vitamin k:ab,ti OR enoxaparin:ab,ti OR lovenox:ab,ti OR rivaroxaban:ab,ti OR xarelto:ab,ti OR dabigatran:ab,ti OR pradaxa:ab,ti OR heparin:ab,ti OR apixaban:ab,ti OR eliquis:ab,ti OR edoxaban:ab,ti OR lixiana:ab,ti |
| #4 | #2 OR #3 |
| #5 | 'surgery'/exp OR 'dental care'/exp OR ((surgical:ab,ti OR invasive:ab,ti) AND (procedure:ab,ti OR procedures:ab,ti)) OR (dental:ab,ti AND (procedure:ab,ti OR procedures:ab,ti)) OR surgery:ab,ti OR procedures:ab,ti OR procedure:ab,ti |
| #6 | #1 AND #4 AND #5 |
| #7 | ('randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR clinical study'/exp OR 'clinical trial':ti,ab OR "clinical trials":ab,ti OR controlled study'/exp OR 'evaluation'/exp OR "evaluation study":ab,ti OR intervention study':ab,ti OR intervention studies':ab,ti OR "case control":ab,ti OR cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR (comparative effectiveness'/exp OR comparative study'/exp OR "comparative study":ab,ti OR "comparative studies":ab,ti OR "systematic review":ab,ti OR meta-analysis'/exp OR meta-analyses':ab,ti) NOT ('editorial'/exp OR 'letter'/exp OR "case report":exp)
KQ5: What are the comparative safety and effectiveness of available strategies for switching between warfarin and other novel oral anticoagulants, in patients with nonvalvular atrial fibrillation?

| #1 | "heart atrium fibrillation"/exp OR "heart atrium flutter"/exp OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti |
| #2 | 'warfarin'/exp OR warfarin:ab,ti OR coumadin:ab,ti |
| #3 | antithrombins:ab,ti OR (direct:ab,ti AND thrombin:ab,ti AND inhibitors:ab,ti) OR (direct:ab,ti AND thrombin:ab,ti AND inhibitor:ab,ti) OR "Antithrombin III":ab,ti OR "Antithrombin Proteins":ab,ti OR argatruban:ab,ti OR bivalirudin:ab,ti OR "Heparin Cofactor II":ab,ti OR Hirudins:ab,ti OR inogatan:ab,ti OR lepirudin:ab,ti OR melagatanab,ti OR "SDZ MTH 958":ab,ti OR ximelagatan:ab,ti |
| #4 | anticoagulant agent'/exp OR anticoagulant:ab,ti OR anticoagulants:ab,ti |
| #5 | ('randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'random*':ab,ti OR 'factorial*':ab,ti OR crossover*':ab,ti OR 'cross NEAR/1 over*':ab,ti OR placebo*':ab,ti OR 'doubl* NEAR/1 blind*':ab,ti OR 'singl* NEAR/1 blind*':ab,ti OR assign*':ab,ti OR allocat*':ab,ti OR volunteer*':ab,ti OR 'clinical study'/exp OR 'clinical trial':ti,ab,ti OR 'clinical trials':ti,ab,ti OR 'controlled study'/exp OR 'evaluation'/exp OR 'evaluation study':ab,ti OR 'evaluation studies':ab,ti OR 'intervention study':ab,ti OR 'intervention studies':ab,ti OR 'case control':ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR 'follow up'/exp OR 'follow up*:ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR 'comparative studies':ab,ti OR 'evidence based medicine'/exp OR "systematic review":ab,ti OR "meta-analysis":ab,ti OR "meta-analyses":ab,ti NOT ('editorial'/exp OR 'letter'/exp OR 'case report'/exp) |

KQ6: What are the comparative safety and effectiveness of available strategies for resuming anticoagulation therapy or performing a procedural intervention as a stroke prevention strategy following a hemorrhagic event (stroke, major bleed, or minor bleed) in patients with nonvalvular atrial fibrillation?

| #1 | "heart atrium fibrillation"/exp OR "heart atrium flutter"/exp OR "atrial fibrillation":ab,ti OR (atrial:ab,ti AND fibrillation:ab,ti) OR afib:ab,ti OR "atrial flutter":ab,ti |
| #2 | 'anticoagulant agent'/exp OR 'warfarin'/exp OR 'vitamin K group'/exp OR 'heparin'/exp OR 'enoxaparin'/exp OR 'rivaroxaban'/exp OR 'dabigatran etexilate'/exp OR 'apixaban'/exp OR 'edoxaban'/exp |
| #3 | warfarin:ab,ti OR coumadin:ab,ti OR vitamin k:ab,ti OR enoxaparin:ab,ti OR lovenox:ab,ti |
Cochrane Search Strategy (June 23, 2017)
Platform: Wiley
Database searched: Cochrane Database of Systematic Reviews

KQ1 & KQ2: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic and patient outcome efficacy) of available clinical and imaging tools and associated risk factors for predicting thromboembolic risk? & In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?

| #1 | [mh "Atrial Fibrillation"] OR "atrial fibrillation":ab,ti OR [mh "Atrial Flutter"] OR "atrial flutter":ab,ti |
| #2 | [mh "Cerebrovascular Disorders"[mj]] OR [mh Stroke] or [mh Thromboembolism] or [mh "Hemorrhage"] or [mh "Intracranial Hemorrhages"] or [mh "Brain Ischemia"] or [mh "Prothrombin Time"] or stroke:ab,ti or strokes:ab,ti or thromboembolism:ab,ti or thromboembolisms:ab,ti or thromboembolic:ab,ti or thromboses:ab,ti or hemorrhage:ab,ti or hemorrhages:ab,ti or hemorrhaging:ab,ti or hemorrhagic:ab,ti or haemorrhage:ab,ti or haemorrhages:ab,ti or haemorrhaging:ab,ti or haemorrhagic:ab,ti or ((bleeding or bleed or bleeds) near/2 (major or risk or event)):ab,ti or ((brain or cerebral or brainstem or 'brain stem') next/2 (ischemia or ischaemia or ischaeasias or ischaemia or infarction or infarctions)):ab,ti or (transient next/2 (ischemic or ischaemic or ischaemia or ischemia) next/2 (attack or attacks)):ab,ti or TIA:ab,ti or TIAs:ab,ti or "cerebrovascular accident":ab,ti or "cerebrovascular accidents":ab,ti or CVA:ab,ti or CVAs:ab,ti or
KQ3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:
   a) In patients with nonvalvular atrial fibrillation?
   b) In specific subpopulations of patients with nonvalvular atrial fibrillation?

| #1 | [mh "Atrial Fibrillation"] OR "atrial fibrillation":ab,ti OR [mh "Atrial Flutter"] OR "atrial flutter":ab,ti |
| #2 | [mh "Cerebrovascular Disorders"[mj]] or [mh Stroke] or [mh Thromboembolism] or [mh Hemorrhage] or [mh "Intracranial Hemorrhages"] or [mh "Brain Ischemia"] or [mh "Prothrombin Time"] or stroke:ab,ti or strokes:ab,ti or thromboembolism:ab,ti or thromboembolisms:ab,ti or thrombosis:ab,ti or hemorraging:ab,ti or hemorrhaging:ab,ti or hemorrhagic:ab,ti or hemorrhages:ab,ti or hemorrhage:ab,ti or hemorrhaging:ab,ti or haemorrhage:ab,ti or haemorrhaging:ab,ti or haemorrhagic:ab,ti or ((bleeding or bleed or bleeds) near/2 (major or risk or event)):ab,ti or ((systemic or paradoxical or crossed) next/2 (embolism or embolisms)):ab,ti or ((brain or cerebral or brainstem or 'brain stem') next/2 (ischemia or ischaemia or ischemias or ischaemias or infarction or infarctions)):ab,ti or (transient next/2 (ischemic or ischaemic or ischaemia or ischemia) next/2 (attack or attacks)):ab,ti or TIA:ab,ti or TIAs:ab,ti or "cerebrovascular accident":ab,ti or "cerebrovascular accidents":ab,ti or CVA:ab,ti or CVAs:ab,ti or "brain vascular accident":ab,ti or "brain vascular accidents":ab,ti |
| #3 | [mh Risk] or risk:ab,ti or risks:ab,ti or [mh "Predictive Value of Tests"] or predict:ab,ti or predicts:ab,ti or predicting:ab,ti or predictor:ab,ti or predictors:ab,ti or predictive:ab,ti |
| #4 | (and #1-#3) |
| #5 | Publication Year from 2011 |

| #6 | [mh "Platelet Aggregation Inhibitors"] or [mh Aspirin] or [mh Dipyridamole] or clopidogrel:ab,ti or plavix:ab,ti or aspirin:ab,ti or dipyridamole:ab,ti or aggrenox:ab,ti or persantine:ab,ti or curantil:ab,ti or antiplatelet:ab,ti or anti-platelet:ab,ti or antiplatelets:ab,ti or anti-platelets:ab,ti or "platelet aggregation inhibitors":ab,ti or "platelet aggregation inhibitor":ab,ti or "platelet inhibitors":ab,ti or "platelet inhibitor":ab,ti or "platelet antagonists":ab,ti or "platelet antagonist":ab,ti |
| #7 | [mh "atrial appendage"[SU]] or [mh "Septal Occluder Device"] or "atrial appendage":ab,ti or "atrial appendages":ab,ti or "atrium appendage":ab,ti or "auricular appendage":ab,ti or "auricular appendages":ab,ti or LAA:ab,ti or occluder:ab,ti or occluders:ab,ti or occlusion:ab,ti or AMPLATZER:ab,ti or AtriClip:ab,ti or PLAATO:ab,ti or Watchman:ab,ti or (atrial:ab,ti and
Cochrane Search Strategy (August 14, 2012)

Platform: Wiley
Database searched: Cochrane Database of Systematic Reviews

KQ1: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of available clinical and imaging tools for predicting thromboembolic risk?

| #1       | (atrial fibrillation OR atrial flutter):ti,ab,kw |
| #2       | Magnetic Resonance Imaging explode all trees OR MeSH descriptor Cardiac Imaging Techniques explode all trees OR MeSH descriptor Tomography, X-Ray Computed explode all trees OR MeSH descriptor Echocardiography explode all trees OR (chads2 OR chads2-vasc OR TEE OR TTE OR ct-scan OR transthoracic echo OR transesophageal echo):ti,ab,kw |
| #3       | MeSH descriptor Stroke explode all trees OR MeSH descriptor Thromboembolism explode all trees OR MeSH descriptor Brain Ischemia explode all trees OR (thromboembolism OR thromboembolic OR brain ischemia OR brain ischaemia OR tia):ti,ab,kw OR (transient ischemic attack):ti,ab,kw OR (transient ischaemic attack):ti,ab,kw OR (transient ischemia attack):ti,ab,kw OR (transient ischaemic attack):ti,ab,kw |
| #4       | #1 AND #2 AND #3 |
| #5       | #4, Limits: Cochrane Reviews, 2000 to 2012 |

KQ2: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decisionmaking (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?

| #1       | (atrial fibrillation OR atrial flutter):ti,ab,kw |
| #2       | MeSH descriptor Age Factors explode all trees OR MeSH descriptor Dementia explode all trees OR MeSH descriptor Accidental Falls explode all trees OR MeSH descriptor International Normalized Ratio explode all trees OR age:ti,ab,kw OR dementia:ti,ab,kw OR INR:ti,ab,kw OR fall:ti,ab,kw OR falls:ti,ab,kw OR "international normalized ratio":ti,ab,kw OR paroxysmal:ti,ab,kw OR persistent:ti,ab,kw OR permanent:ti,ab,kw OR stratification:ti,ab,kw OR classification:ti,ab,kw OR schema:ti,ab,kw OR has-bleed:ti,ab,kw OR cognitive impairment:ti,ab,kw OR cognition:ti,ab,kw OR ((prior:ti,ab,kw OR previous:ti,ab,kw OR first:ti,ab,kw) AND stroke:ti,ab,kw) |
| #3       | MeSH descriptor Intracranial Hemorrhages explode all trees OR MeSH descriptor Hemorrhage explode all trees OR hemorrhage:ti,ab,kw OR hemorrhaging:ti,ab,kw OR bleeding:ti,ab,kw OR bleed:ti,ab,kw OR hemorrhagic:ti,ab,kw OR haemorrhage:ti,ab,kw OR haemorrhaging:ti,ab,kw OR haemorrhagic:ti,ab,kw |
| #4       | #1 AND #2 AND #3 |
| #5       | MeSH descriptor Diagnosis explode all trees OR MeSH descriptor Treatment Outcome explode all trees OR MeSH descriptor Sensitivity and Specificity explode all trees OR MeSH descriptor Decision Making explode all trees OR diagnosis:ti,ab,kw OR outcome:ti,ab,kw OR outcomes:ti,ab,kw OR reliability:ti,ab,kw OR accuracy:ti,ab,kw OR accurate:ti,ab,kw OR Sensitivity:ti,ab,kw OR specificity:ti,ab,kw OR valid:ti,ab,kw OR validity:ti,ab,kw OR validation:ti,ab,kw OR decision:ti,ab,kw OR decisions:ti,ab,kw OR assessment:ti,ab,kw |
| #6       | #4 AND #5 |
| #7       | #6, Limits: Cochrane Reviews, 2000 to 2012 |
KQ3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:
(a) In patients with nonvalvular atrial fibrillation?
(b) In specific subpopulations of patients with nonvalvular atrial fibrillation?

| #1 | MeSH descriptor Anticoagulants explode all trees OR warfarin:ti,ab,kw OR coumadin:ti,ab,kw OR vitamin k:ti,ab,kw OR enoxaparin:ti,ab,kw OR lovenox:ti,ab,kw OR rivaroxaban:ti,ab,kw OR xarelto:ti,ab,kw OR dabigatran:ti,ab,kw OR pradaxa:ti,ab,kw OR heparin:ti,ab,kw OR axipta:ti,ab,kw OR eliquis:ti,ab,kw OR edoxaban:ti,ab,kw OR lixiana:ti,ab,kw OR anticoagulants:ti,ab,kw OR anticoagulant:ti,ab,kw |
| #2 | MeSH descriptor Platelet Aggregation Inhibitors explode all trees OR clopidogrel:ti,ab,kw OR plavix:ti,ab,kw OR aspirin:ti,ab,kw OR dipyridamole:ti,ab,kw OR aggregan:ti,ab,kw OR persantine:ti,ab,kw OR antiplatelet:ti,ab,kw OR anti-platelet:ti,ab,kw OR antiplatelets:ti,ab,kw |
| #3 | MeSH descriptor Atrial Appendage explode all trees OR atrial appendage:ti,ab,kw OR LAA:ti,ab,kw OR occluder:ti,ab,kw OR ATRIClip:ti,ab,kw OR PLAATO:ti,ab,kw OR Watchman:ti,ab,kw OR (atrial:ti,ab,kw AND modification:ti,ab,kw) OR "atriacure isolator":ti,ab,kw |
| #4 | MeSH descriptor Stroke explode all trees OR MeSH descriptor Thromboembolism explode all trees OR MeSH descriptor Brain Ischemia explode all trees OR (thromboembolism OR thromboembolic OR brain ischemia OR brain ischaemia OR tia):ti,ab,kw OR (transient ischemic attack):ti,ab,kw OR (transient ischaemic attack):ti,ab,kw |
| #5 | #1 AND (#2 OR #3 OR #4) AND #5 |
| #6 | #6, Limits: Cochrane Reviews, 2000 to 2012 |

KQ4: What are the comparative safety and effectiveness of available strategies for anticoagulation in patients with nonvalvular atrial fibrillation who are undergoing invasive procedures?

| #1 | (atrial fibrillation OR atrial flutter):ti,ab,kw |
| #2 | MeSH descriptor Anticoagulants explode all trees OR warfarin:ti,ab,kw OR coumadin:ti,ab,kw OR vitamin k:ti,ab,kw OR enoxaparin:ti,ab,kw OR lovenox:ti,ab,kw OR rivaroxaban:ti,ab,kw OR xarelto:ti,ab,kw OR dabigatran:ti,ab,kw OR pradaxa:ti,ab,kw OR heparin:ti,ab,kw OR axipta:ti,ab,kw OR eliquis:ti,ab,kw OR edoxaban:ti,ab,kw OR lixiana:ti,ab,kw OR anticoagulants:ti,ab,kw OR anticoagulant:ti,ab,kw |
| #3 | MeSH descriptor Surgical Procedures, Operative explode all trees OR MeSH descriptor Dental Care explode all trees OR Surgical Procedures, Operative explode all trees OR Surgical:ti,ab,kw OR invasive:ti,ab,kw OR procedures:ti,ab,kw OR surgery:ti,ab,kw OR procedure:ti,ab,kw |
| #4 | #1 AND #2 AND #3 |
| #5 | #4, Limits: Cochrane Reviews, 2000 to 2012 |

KQ5: What are the comparative safety and effectiveness of available strategies for switching between warfarin and other novel oral anticoagulants, in patients with nonvalvular atrial fibrillation?

| #1 | (atrial fibrillation OR atrial flutter):ti,ab,kw |
| #2 | warfarin:ti,ab,kw OR coumadin:ti,ab,kw |
| #3 | MeSH descriptor Antithrombins explode all trees OR antithrombins:ti,ab,kw OR (direct:ti,ab,kw AND thrombin:ti,ab,kw AND inhibitors:ti,ab,kw) OR "direct thrombin
KQ6: What are the comparative safety and effectiveness of available strategies for resuming anticoagulation therapy or performing a procedural intervention as a stroke prevention strategy following a hemorrhagic event (stroke, major bleed, or minor bleed) in patients with nonvalvular atrial fibrillation?

PubMed® Search Strategy (June 15, 2017)

Contextual Question: What are currently available shared decision-making tools for patient and provider use for stroke prophylaxis in atrial fibrillation, and what are their relative strengths and weaknesses?
# Grey Literature Searches

## ClinicalTrials.gov (November 13, 2017)

<table>
<thead>
<tr>
<th>KQ1, KQ2, KQ3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Condition</strong></td>
<td>atrial fibrillation OR afib OR atrial flutter</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>stroke OR thromboembolism OR thromboembolic OR &quot;brain ischemia&quot; OR &quot;brain ischaemia&quot; OR (transient AND ischemic AND attack) OR TIA OR hemorrhage OR hemorrhaging OR bleeding OR bleed OR hemorrhagic OR haemorrhage OR haemorrhaging OR haemorrhagic</td>
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</tbody>
</table>

Total number of results: 301

## ClinicalTrials.gov (August 22, 2012)

<table>
<thead>
<tr>
<th>KQ1, KQ2, KQ3, KQ6</th>
<th></th>
</tr>
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<tbody>
<tr>
<td><strong>Condition</strong></td>
<td>atrial fibrillation OR afib OR atrial flutter</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>stroke OR thromboembolism OR thromboembolic OR &quot;brain ischemia&quot; OR &quot;brain ischaemia&quot; OR (transient AND ischemic AND attack) OR TIA OR hemorrhage OR hemorrhaging OR bleeding OR bleed OR hemorrhagic OR haemorrhage OR haemorrhaging OR haemorrhagic</td>
</tr>
</tbody>
</table>

## KQ4

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Condition</strong></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td><strong>Search Terms</strong></td>
</tr>
</tbody>
</table>

Total number of results: 186

## WHO: International Clinical Trials Registry Platform Search Portal (August 17, 2012)

<table>
<thead>
<tr>
<th>KQs 1-6</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Condition</strong></td>
<td>atrial fibrillation OR afib OR atrial flutter</td>
</tr>
<tr>
<td><strong>Recruiting status</strong></td>
<td>ALL</td>
</tr>
</tbody>
</table>

Total number of results: 858
ProQuest COS Conference Papers Index (August 14, 2012)

<table>
<thead>
<tr>
<th>KQ1, KQ2, KQ3, KQ6</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 All (atrial fibrillation OR afib OR atrial flutter)</td>
</tr>
<tr>
<td>#3 All (stroke OR thromboembolism OR thromboembolic OR “brain ischemia” OR “brain ischaemia” OR (transient AND (ischemic OR ischaemic) AND attack) OR TIA OR hemorrhage OR hemorrhaging OR bleeding OR bleed OR hemorrhagic OR haemorrhage OR haemorrhaging OR haemorrhagic)</td>
</tr>
<tr>
<td>#4 #1 AND #2 AND #3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KQ4</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 All (atrial fibrillation OR afib OR atrial flutter)</td>
</tr>
<tr>
<td>#2 All (Anticoagulants OR anticoagulation OR warfarin OR coumadin OR vitamin k OR Heparin OR enoxaparin OR lovenox OR rivaroxaban OR xarelto OR dabigatran OR pradaxa OR apixaban OR eliquis OR edoxaban OR lixiana)</td>
</tr>
<tr>
<td>#3 All (Surgery OR procedures OR procedure)</td>
</tr>
<tr>
<td>#4 #1 AND #2 AND #3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KQ5</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 All (atrial fibrillation OR afib OR atrial flutter)</td>
</tr>
<tr>
<td>#2 All (warfarin OR Coumadin)</td>
</tr>
<tr>
<td>#3 All (Antithrombins OR antithrombin OR (direct AND thrombin AND (inhibitors OR inhibitor)) OR anticoagulant OR anticoagulants)</td>
</tr>
<tr>
<td>#6 #1 AND #2 AND #3</td>
</tr>
</tbody>
</table>

Total number of results: 352
Appendix B. Data Abstraction Elements

Study Characteristics

- Study Identifiers
  - Study Name or Acronym
  - Last name of first author
  - Publication Year
- Additional Articles Used in This Abstraction
- Study Objective(s)
- Study Dates
  - Enrollment start (Mon and YYYY)
  - Enrollment end (Mon and YYYY)
  - Follow-up end (Mon and YYYY)
- Study Sites
  - Single center, Multicenter, Unclear/Not reported
  - Number of sites
- Geographic Location (Select all that apply)
  - US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ,
    Unclear/Not reported, Other (specify)
- Study Design
  - Prospective RCT
  - Prospective Cohort
  - Retrospective Cohort
  - Case-control
  - Cross-sectional
  - Other (specify)
- Funding Source (Select all that apply)
  - Government, Industry, Non-government/non-industry, Unclear/Not reported,
    Other (specify)
- Setting (Select all that apply)
  - In-patient, Out-patient, Emergency Room, Unclear/Not reported, Other (specify)
- Enrollment Approach (Select all that apply)
  - Consecutive patients, Convenience sample, Unclear/Not reported, Other (specify)
- Study Inclusion and Exclusion Criteria
  - Copy/paste inclusion and exclusion criteria as reported
  - Is the study entirely composed of patients with any of the following characteristics/conditions?
    - Paroxysmal Atrial Fibrillation (AF)
    - Persistent AF
    - Permanent AF
    - Patients with atrial fibrillation who experience acute coronary syndrome
    - Age
    - Women
    - Pregnant women
    - Race/ethnicity
- Presence of heart disease
- Type of AF
- Patients in the therapeutic range
- Patients with prior bleed
- Patients with prior stroke
- Patients with comorbid conditions such as dementia, renal failure, or hepatic failure
- Patients with multiple coexisting conditions (e.g. combinations of hypertension, diabetes, CHF, CAD, and high cholesterol)
- Patients non-compliant with treatment
- None of the above

- Study Enrollment/Study Completion
  - N assessed for eligibility
  - N eligible
  - N enrolled/included
  - N completed follow-up (most distal timepoint of the primary outcome)
  - N analyzed

- Key Question Applicability (Select all that apply)
  - KQ1, KQ2, KQ3, KQ4, KQ5, KQ6

- Comments

**Baseline Characteristics** – Record the following elements for Total Population, Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable)

- Number of Patients, Age, Ethnicity, and Race
  - Number of Patients
    - Total
    - Female
    - Male
  - Percentage
    - Female
    - Male
  - Age
    - Mean
    - Standard Deviation
    - Standard Error
    - Median
    - IQR
    - Min
    - Max
    - NR
  - Ethnicity
    - Hispanic or Latino
    - Not Hispanic or Latino
    - NR
  - Race
    - Black/African American
- American Indian or Alaska Native
- Asian
- Native Hawaiian or other Pacific Islander
- White
- Multiracial
- Other (specify)
- NR

- Baseline Characteristics
  - Diabetes
    - N
    - %
  - Heart failure (NYHA Class), N and % for the following:
    - Class I
    - Class II
    - Class III
    - Class IV
    - All classes
  - Sleep apnea
    - N
    - %
  - Hyperlipidemia
    - N
    - %
  - Hypertension
    - N
    - %
  - Kidney disease
    - N
    - %
  - Congestive Heart Failure (CHF)
    - N
    - %
  - Coronary Artery Disease (CAD)
    - N
    - %
  - Prior Myocardial Infarction (MI)
    - N
    - %
  - Prior Percutaneous Coronary Intervention (PCI)
    - N
    - %
  - Prior CABG
    - N
    - %
  - Left Ventricular Ejection Fraction (LVEF), Mean or median
    - Mean or median
- SD, SE, or IQR
- LVEF, Number of patients (<35% or other [define])
  - N
  - %
- Evidence of Left Atrial Appendage (LAA) thrombus
  - N
  - %
- Any Left Ventricular (LV) dysfunction
  - N
  - %
- Prior stroke or Transient Ischemic Attack (TIA), N and % for the following types:
  - Ischemic
  - Hemorrhagic
  - TIA
  - All types
- Tobacco use
  - N
  - %
- Obesity (define)
  - N
  - %
- Patients non-compliant with treatment
  - N
  - %
- Prior vascular disease
  - N
  - %
- Prior bleed
  - N
  - %
- CHADS2 score
  - Mean or median
  - SD, SE, or IQR
- CHADS2, N and % of patients with the following scores:
  - 0
  - 1
  - 2+
- CHA2DS2-VASc score
  - Mean or median
  - SD, SE, or IQR
- CHA2DS2-VASc, N and % of patients with the following scores:
  - 0
  - 1
  - 2+
- HAS-BLED score
  - Mean or median
- SD, SE, or IQR
  - HAS-BLED, N and % of patients with the following scores:
    - <3
    - ≥3
  - Duration of AF
    - Mean or median
    - SD, SE, or IQR
- Paroxysmal AF
  - N
  - %
- Persistent AF
  - N
  - %
- Permanent AF
  - N
  - %

- Comments

**Intervention Characteristics** – Record the following elements for Total Population, Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable)

- Interventions (Check all that apply)
  - Placebo or control; Clinical & imaging tools for thromboembolic risk; Clinical tools & individual factors for bleeding risk; Anticoagulation therapy (all oral anticoagulants); Procedural interventions; Antiplatelet therapy; Anticoagulation bridging therapies
    - If ‘Placebo or control’ selected:
      - Placebo/control
        - Placebo, Usual care/Optimal medical therapy (OMT), Other (specify)
    - If ‘Clinical & imaging tools for thromboembolic risk’ selected:
      - Thromboembolic risk tools
        - CHADS₂ score, CHA₂DS₂-VASc score, Transthoracic echo (TTE), Transesophageal echo (TEE), CT scan, Cardiac MRI, Framingham Score
    - If ‘Clinical tools & individual factors for bleeding risk’ selected:
      - Intracerebral bleeding risk tools/factors
        - Patient age, Prior stroke, Type of AF (paroxysmal, persistent, permanent), International normalized ratio (INR), Dementia/cognitive impairment, Falls risk, CHADS₂ score, CHA₂DS₂-VASc score, HEMORR3HAGES, HAS-BLED, ATRIA, Bleeding Risk Index, Framingham
    - If ‘Anticoagulation therapy (all oral anticoagulants)’ selected:
      - Anticoagulation therapy
        - Vitamin K antagonists
          - If ‘Vitamin K antagonists’ selected:
• Warfarin (Coumadin), Other
  o Newer anticoagulants (direct oral anticoagulants [DOACS])
  o Direct thrombin Inh-DTI:
    ▪ Dabigatran (Pradaxa)
  o Factor Xa inhibitors:
    ▪ Rivaroxaban (Xarelto), Apixaban (Eliquis), Edoxaban (DU-176b)

  ▪ If ‘Procedural interventions’ selected:
    • Procedural interventions
      o Surgical LAA resection, Surgical LAA ligation, Surgical LAA occlusion, Surgical – other (specify), Minimally invasive – Atriclip, Minimally invasive – LARIAT, Minimally invasive – other (specify), Transcatheter – WATCHMAN, Transcatheter – AMPLATZER, Transcatheter – PLAATO, Transcatheter – Other (specify)

  ▪ If ‘Antiplatelet therapy’ selected:
    • Antiplatelet therapy
      o Clopidogrel (Plavix), Aspirin (ASA), ASA + dipyridamole (Aggrenox), Dipyridamole (Persantine), Other (specify)

  ▪ If ‘Anticoagulation bridging therapies’ selected:
    • Anticoagulation bridging
      o Unfractionated Heparin, Low Molecular Weight Heparin (LMWH), Factor IIa Inhibitors, Factor Xa Inhibitors, Other (specify)
        ▪ If ‘Unfractionated Heparin’ selected:
          • IV Heparin, Other
        ▪ If ‘LMWH’ selected:
          • Bemiparin, Certoparin, Dalteparin, Enoxaparin, Nadroparin, Parnaparin, Reviparin, Tinzaparin, Other
        ▪ If ‘Factor IIa Inhibitors’ selected:
          • Dabigatran, Other
        ▪ If ‘Factor Xa Inhibitors’ selected:
          • Apixaban, Edoxaban, Rivaroxaban, Other

• Intervention Descriptors
  o Describe the intervention received by each patient group. If the intervention includes medication(s), include pertinent details such as dose, frequency, and potential for adjustment.

• Duration of Follow-up: Record the following elements for Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable)
  o Mean or median (include units)
  o SD, SE, or IQR
  o NR

Clinical/ Patient-Centered Outcomes
• Select the outcome reported on this form:
  o Cerebrovascular infarction
  o Transient ischemic attack (TIA)
  o Systemic embolism (excludes pulmonary embolism and deep vein thrombosis)
  o CV infarction/stroke
  o Ischemic stroke
  o Hemorrhagic stroke
  o Intercerebral hemorrhage
  o Extracranial hemorrhage
  o Subdural hematoma
  o Major bleed
  o Minor bleed
  o Myocardial infarction
  o All-cause mortality
  o CV mortality
  o Infection
  o Heart block
  o Esophageal fistula
  o Cardiac tamponade
  o Health-related QOL/Functional capacity
  o Healthcare utilization – Hospital admissions
  o Healthcare utilization – Other measures
  o Long-term adherence to therapy
  o Cognitive function
  o Time in therapeutic range
  o Composite outcome
  o No clinical or patient-centered outcomes of interest reported

• Define/specify the following for the outcome, if applicable
  o Major bleed type and location
  o Minor bleed type and location
  o Health-related QOL/Functional capacity measure/scale
  o Other Healthcare utilization measure/scale
  o Components of composite outcomes:
    • Cerebrovascular infarction; Transient ischemic attack (TIA); Systemic embolism (excludes pulmonary embolism and deep vein thrombosis); CV infarction/stroke; Intercerebral hemorrhage; Subdural hematoma; Major bleed; Minor bleed; Myocardial infarction; All-cause mortality; CV mortality; Infection; Heart block; Esophageal fistula; Tamponade; Dyspepsia; Health-related QOL/Functional capacity; Healthcare utilization – Hospital admissions; Healthcare utilization – Other measures; Long-term adherence to therapy; Time in therapeutic range; Ischemic stroke

• Record additional details to describe outcome measure, as needed
• Timepoints to be abstracted (Check all that apply)
  o Close to 1 month
  o Close to 3 months
• Close to 6 months
• Close to 1 yr
• Most distal timepoint after one year
• Untimed measure (e.g., time to event)

• For each timepoint, record the following elements as applicable:
  • Specify actual timing of outcome (in months)
  • Group: Arm 1, Arm 2, Arm 3, Arm 4
  • N Analyzed (enter UNK if unknown)
  • Unadjusted Result
    ▪ Mean
    ▪ Median
    ▪ Mean within group change
    ▪ Mean between group change
    ▪ Number of patients with outcome
    ▪ % of patients with outcome
    ▪ Events/denominator
    ▪ Odds ratio
    ▪ Hazard ratio
    ▪ Relative risk
    ▪ Other (specify)
  • Unadjusted Result Variability
    ▪ Standard Error (SE)
    ▪ Standard Deviation (SD)
    ▪ IQR
    ▪ 95% CI
    ▪ Other % CI (specify)
    ▪ Other (specify)
  • Unadjusted Result, p-value between groups
  • Unadjusted Result, Reference group (for comparison between groups)
  • Adjusted Result
    ▪ Mean
    ▪ Median
    ▪ Mean within group change
    ▪ Mean between group change
    ▪ Number of patients with outcome
    ▪ % of patients with outcome
    ▪ Events/denominator
    ▪ Odds ratio
    ▪ Hazard ratio
    ▪ Relative risk
    ▪ Other (specify)
  • Adjusted Result Variability
    ▪ Standard Error (SE)
    ▪ Standard Deviation (SD)
    ▪ IQR
    ▪ 95% CI
• Other % CI (specify)
  ▪ Other (specify)
    ▪ Adjusted Result, p-value between groups
    ▪ Adjusted Result, Reference group (for comparison between groups)
    ▪ If adjusted data is recorded, indicate the adjustments applied
• Does the study report any subgroup analyses for this outcome? (Yes/No)
  ▪ If Yes, describe the subgroup analyses and summarize results
• Comments

**Adverse Events**
• Are adverse events reported? (Yes/No)
• Record the Number of patients, % of patients, and exact p-value for the Total Population, Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable) for the following:
  ▪ Infection
  ▪ Heart block
  ▪ Esophageal fistula
  ▪ Tamponade
  ▪ Dyspepsia
• Does the study report any AE subgroup analyses? (Yes/No)
  ▪ If Yes, describe the subgroup analyses and summarize results
• Comments

**KQ1/2 Diagnostic Efficacy**
• Type of risk being evaluated
  ▪ Thromboembolic risk
  ▪ Intracerebral hemorrhage bleeding risk
• Tool or individual risk factor being tested
  ▪ CHADS2 score
  ▪ CHA2DS2-VASc score
  ▪ ABC stroke risk score
  ▪ Transthoracic echo (TTE)
  ▪ Transesophageal echo (TEE)
  ▪ CT scan
  ▪ Cardiac MRI
  ▪ HEMORR2HAGES
  ▪ HAS-BLED
  ▪ ATRIA
  ▪ Framingham score
  ▪ Bleeding Risk Index
  ▪ Patient age
  ▪ Prior stroke
  ▪ Type of AF (paroxysmal, persistent, permanent)
  ▪ International normalized ratio (INR)
  ▪ Dementia/cognitive impairment
  ▪ Falls risk
  ▪ INR level
- Duration and frequency of AF
- Presence of heart disease
- Presence and severity of CKD
- DM
- Sex
- Race/ethnicity
- Cancer
- HIV

- Additional details describing risk being evaluated
- Outcomes reported on this form for this tool or risk factor (Select all that apply):
  Diagnostic Accuracy; Diagnostic Thinking/Therapeutic Efficacy; Patient Outcome Efficacy
  - If Diagnostic Accuracy:
    - Timing of the outcome data reported
    - Total Population, Group 1, Group 2, Group 3, Group 4, Group 5, Group 6
      - N and %
      - C statistic
      - C statistic CI (Lower – Upper bound)
        - 95% CI
        - Other % (specify)
      - Hazard Ratio
      - Hazard Ratio (Lower – Upper bound)
        - 95% CI
        - Other % (specify)
      - Event rate (define)
      - Event rate (Lower – Upper bound)
        - 95% CI
        - Other % (specify)
      - True positive (# patients)
      - True negative (# patients)
      - False positive (# patients)
      - False negative (# patients)
      - Indeterminate/inadequate results (# patients)
      - Sensitivity (%)
      - Sensitivity (SD)
      - Sensitivity CI (Lower – Upper bound)
        - 95% CI
        - Other % (specify)
      - Specificity (%)
      - Specificity (SD)
      - Specificity CI (Lower – Upper bound)
        - 95% CI
        - Other % (specify)
      - Positive predictive value (%)
      - Positive predictive value (Std dev)
• Positive predictive value (Lower – Upper bound)
  o 95% CI
  o Other % (specify)
• Negative predictive value (%)
• Negative predictive value (SD)
• Negative predictive value (Lower – Upper bound)
  o 95% CI
  o Other % (specify)
• Positive likelihood ratio
• Negative likelihood ratio
• Other (specify)
  o If Diagnostic Thinking/Therapeutic Efficacy: Describe
  o If Patient Outcome Efficacy: Describe
• Does the study report any subgroup analyses for this tool/ outcome? (Yes/No)
  o If Yes, describe the subgroup analyses and summarize results
• QUADAS 2 Tool for Quality Assessment of Study of Diagnostic Accuracy. (2017 and 2013 Studies) Indicate Yes, No, or Unclear for the following:
  o Signaling questions
    ▪ Patient Selection
      • Was a consecutive or random sample of patients enrolled?
      • Was a case-control design avoided?
      • Did the study avoid inappropriate exclusions?
    ▪ Index Test
      • Were the index test results interpreted without knowledge of the results of the reference standard?
      • If a threshold was used, was it pre-specified?
    ▪ Reference Standard
      • Is the reference standard likely to correctly classify the target condition?
      • Were the reference standard results interpreted without knowledge of the results of the index test?
    ▪ Flow & Timing
      • Was there an appropriate interval between index test(s) and reference standard?
      • Did all patients receive a reference standard?
      • Did all patients receive the same reference standard?
      • Were all patients included in the analysis?
  o Risk of bias
    ▪ Patient Selection
      • Could the selection of patients have introduced bias?
    ▪ Index Test
      • Could the conduct or interpretation of the index test have introduced bias?
    ▪ Reference Standard
• Could the reference standard, its conduct or its interpretation have introduced bias?
  ▪ Flow & Timing
  • Could the patient flow have introduced bias?
  o Concerns regarding applicability
    ▪ Patient Selection
      • Are there concerns that the included patients do not match the review question?
    ▪ Index Test
      • Are there concerns that the index test, its conduct, or interpretation differ from the review question?
  ▪ Reference Standard
    • Are there concerns that the target condition as defined by the reference standard does not match the review question?

• Overall study rating
  o High risk of bias/ Low risk of bias/ Unclear

• Comments

• ROBINS-I (The Risk of Bias in Non-Randomized Studies—of Interventions). (2017 Studies Only) Indicate Yes, No, or Unclear for the following:
  o Bias due to confounding
    ▪ Was there any bias arising in the randomization process or due to confounding?
  o Bias in selection of participants into the study
    ▪ Was there any bias in selecting participants into the study?
  o Bias in classification of interventions
    ▪ Was there any bias in classifying interventions?
  o Bias due to deviations from intended intervention
    ▪ Was there any bias due to departures from intended interventions?
  o Bias due to missing data
    ▪ Was there any bias due to missing data?
  o Bias in measurement of outcomes
    ▪ Was there any bias in the measurement of outcomes?
  o Bias in selection of the reported result
    ▪ Was there any bias in reporting results selectively?

• Overall Bias
  o Risk of Bias Judgment:
    ▪ Low/Moderate/High

• Overall ROB outcome-specific quality rating
  o Do you think that any of the outcomes abstracted for this study should be assigned a quality rating DIFFERENT from the overall study rating?
    ▪ No/Yes
  o Comments

• Cochrane Quality Tool (2017 Studies Only). Select Low/High/Unclear risk of bias for each of the following questions:
o Random sequence generation
  ▪ Low risk/High risk/Unclear risk
  ▪ Describe the method used to generate the allocation sequence in sufficient
detail to allow an assessment of whether it should produce comparable
groups

o Allocation concealment
  ▪ Low risk/High risk/Unclear risk
  ▪ Describe the method used to conceal the allocation sequence in sufficient
detail to determine whether intervention allocations could have been
foreseen before or during enrolment

o Blinding of participants and personnel
  ▪ Low risk/High risk/Unclear risk
  ▪ Describe all measures used, if any, to blind trial participants and
researchers from knowledge of which intervention a participant received.
Provide any information relating to whether the intended blinding was
effective

o Blinding of outcome assessment
  ▪ Low risk/High risk/Unclear risk
  ▪ Describe all measures used, if any, to blind outcome assessment from
knowledge of which intervention a participant received. Provide any
information relating to whether the intended blinding was effective

o Incomplete Outcome Data
  ▪ Low risk/High risk/Unclear risk
  ▪ Describe the completeness of the outcome data for each main outcome,
including attrition and exclusions from the analysis. State whether attrition
and exclusions were reported, the numbers in each intervention group
(compared with total randomized participants), reasons for attrition or
exclusions where reported, and any reinclosures in analyses for the review

o Selective Reporting
  ▪ Low risk/High risk/Unclear risk
  ▪ State how selective outcome reporting was examined and what was found

o Other Bias
  ▪ Low risk/High risk/Unclear risk
  ▪ State any important concerns about bias not covered in the other domains
in the tool

• Overall Study Quality Rating
  o Good/Fair/Poor

• Overall ROB Quality Rating
  o Do you think that any of the outcomes abstracted for this study should be assigned
a quality rating DIFFERENT from the overall study rating?
    ▪ No/Yes

  o Comments

Quality (2013 Studies Only)
• Study Type (select one): RCT, Cohort, Case-control, Cross-sectional
• If RCT, select Yes/No/Unclear for each of the following questions:
  o Selection Bias
    ▪ Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?
    ▪ Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization or use of sequentially numbered sealed envelopes)?
    ▪ Were participants analyzed within the groups they were originally assigned to?
    ▪ Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?
  o Performance Bias
    ▪ Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
    ▪ Did the study maintain fidelity to the intervention protocol?
  o Attrition Bias
    ▪ If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?
  o Detection Bias
    ▪ In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome different for cases and controls?
    ▪ Were the outcome assessors blinded to the intervention or exposure status of participants?
    ▪ Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?
    ▪ Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?
  o Reporting Bias
    ▪ Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?
• If Cohort, select Yes/No/Unclear for each of the following questions:
  o Selection Bias
    ▪ Were participants analyzed within the groups they were originally assigned to?
    ▪ Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?
    ▪ Did the strategy for recruiting participants into the study differ across study groups?
    ▪ Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?
  o Performance Bias
- Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
- Did the study maintain fidelity to the intervention protocol?

  o **Attrition Bias**
    - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?

  o **Detection Bias**
    - In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome different for cases and controls?
    - Were the outcome assessors blinded to the intervention or exposure status of participants?
    - Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?
    - Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?
    - Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?

  o **Reporting Bias**
    - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?

- If Case-Control, select Yes/No/Unclear for each of the following questions:

  o **Selection Bias**
    - Were cases and controls selected appropriately (e.g., appropriate diagnostic criteria or definitions, equal application of exclusion criteria to case and controls, sampling not influenced by exposure status) (Yes/No/Unclear)
    - Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?

  o **Performance Bias**
    - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
    - Did the study maintain fidelity to the intervention protocol?

  o **Attrition Bias**
    - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?

  o **Detection Bias**
    - In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome different for cases and controls?
    - Were the outcome assessors blinded to the intervention or exposure status of participants?
Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?

Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?

Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?

- Reporting Bias
  - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?

- If Cross-sectional, select Yes/No/Unclear for each of the following questions:
  - Selection Bias
    - Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?
    - Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?
  - Performance Bias
    - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
  - Attrition Bias
    - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?
  - Detection Bias
    - Were the outcome assessors blinded to the intervention or exposure status of participants?
    - Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?
    - Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?
    - Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?
  - Reporting Bias
    - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?

- Other Bias
  - If applicable, describe any other concerns that may impact risk of bias

- Overall Study Rating (Good/Fair/Poor)
  - Good (low risk of bias). These studies have the least bias, and the results are considered valid. These studies adhere to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
  - Fair. These studies are susceptible to some bias, but not enough to invalidate the results. They do not meet all the criteria required for a rating of good quality
because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

- **Poor** (high risk of bias). These studies have significant flaws that may have invalidated the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

- If the study is rated as “Fair” or “Poor,” provide rationale.

**Applicability** – Use the PICOS format to identify specific issues, if any, that may limit the applicability of the study to this review.

- **Population (P)**
  - Narrow eligibility criteria and exclusion of those with comorbidities
  - Large differences between demographics of study population and community patients
  - Narrow or unrepresentative severity, stage of illness, or comorbidities
  - Run-in period with high-exclusion rate for nonadherence or side effects
  - Event rates much higher or lower than observed in population-based studies

- **Intervention (I)**
  - Doses or schedules not reflected in current practice
  - Monitoring practices or visit frequency not used in typical practice
  - Older versions of an intervention no longer in common use
  - Cointerventions that are likely to modify effectiveness of therapy
  - Highly selected intervention team or level of training/proficiency not widely available

- **Comparator (C)**
  - Inadequate comparison therapy
  - Use of substandard alternative therapy

- **Outcomes (O)**
  - Composite outcomes that mix outcomes of different significance
  - Short-term or surrogate outcomes

- **Setting (S)**
  - Standards of care differ markedly from setting of interest
  - Specialty population or level of care differs from that seen in community

- **Comments**
Appendix C. List of Included Studies

*Denotes 2017 update


*Coleman CI, Peacock WF and Antz M. Comparative Effectiveness and Safety of Apixaban and Vitamin K Antagonist Therapy in Patients with Nonvalvular Atrial Fibrillation Treated in Routine German Practice. Heart Lung Circ 2017. PMID: 28528780.


*Fraenkel L, Street RL, Jr., Towe V, et al. A pilot randomized controlled trial of a decision support tool


*Hijazi Z, Hohnloser SH, Oldgren J, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with


Kiviniemi T, Karjalainen P, Pietilä M, et al. Comparison of additional versus no additional heparin during therapeutic oral anticoagulation in


C-11


Appendix D. List of Excluded Studies

All studies listed below were reviewed in their full-text version and excluded for the reasons cited. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles. Not all of the same exclusion reasons were used for the 2017 update as were used for the 2012 report. The 2017 excluded studies are all listed before the 2012 excluded studies.

Not a full publication, publication retracted/withdrawn, full text not obtainable, or full text not obtainable in English--2017


Dürschmied D, Moser M and Bode C. Newest data and practical experience with new oral anticoagulants (NOAK) - Which patients benefit from these drugs?. Klinikerzt 2013;42(SUPPL. 1):9-14.

Erlikh AD, Kharchenko MS, Barbarash OL, et al. [Adherence to guidelines on management of acute coronary syndrome in Russian hospitals and outcomes of hospitalization (data from the


Lopes RD, Alings M, Connolly SJ, et al. Rationale and design of the Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA)


Mavri A and Štalc M. Dabigatran and rivaroxaban in the patients with atrial fibrillation and venous thrombembolism: Our first clinical experience. Zdravniški Vestnik 2014;83(12):849-856


Shevelev VI and Kanorskii SG. [Comparison of three methods of antithrombotic therapy in elderly patients with nonvalvular atrial fibrillation]. Kardiologiya 2012;52(7):56-60. PMID: 22839715.


Wang J, Yang YM, Zhu J, et al. [The impact of hypertension history and baseline blood pressure levels on the cardiovascular outcomes in Chinese emergency atrial fibrillation patients]. Zhonghua Xin


Does not meet study design or sample size requirements--2017


Dahal K, Kunwar S, Rijal J, et al. Stroke, Major Bleeding, and Mortality Outcomes in Warfarin Users...


Lüscher TF. Atrial fibrillation and thromboembolism: Anticoagulants or devices?. European Heart Journal 2017;38(12):839-842.

Masbah N and Macleod MJ. The cost savings of Newer oral anticoagulants in atrial fibrillation-related...


Stevens RE. How the clot factors. 2013;79.

Does not meet study population requirements--2017


Al-Turaiki AM, Al-Ammari MA, Al-Harbi SA, et al. Assessment and comparison of CHADS2, CHA2DS2-VASc, and HAS-BLED scores in patients...


Arbring K, Uppugunduri S and Lindahl TL. Comparison of prothrombin time (INR) results and main characteristics of patients on warfarin treatment in primary health care centers and anticoagulation clinics. BMC Health Serv Res 2013;13:85. PMID: 23497203.


Caballero L, Ruiz-Nodar JM, Marin F, et al. Oral anticoagulation improves the prognosis of octogenarian patients with atrial fibrillation undergoing percutaneous coronary intervention and...


Chao TF, Lin YJ, Tsao HM, et al. CHADS(2) and CHA(2)DS(2)-VASc scores in the prediction of clinical outcomes in patients with atrial fibrillation after catheter ablation. J Am Coll Cardiol 2011;58(23):2380-5. PMID: 22115643.


Diaconu CC and Balaceanu A. Atrial fibrillation and comorbidities in very elderly patients. Archives of the Balkan Medical Union 2015;50(2):190-193.


Erkuner O, Claessen R, Pisters R, et al. Poor anticoagulation relates to extended access times for cardioversion and is associated with long-term major cardiac and cerebrovascular events. Int J Cardiol 2016;225:337-341. PMID: 27756038.


Kim TH, Yang PS, Uhm JS, et al. CHA2DS2-VASc Score (Congestive Heart Failure, Hypertension, Age
D-23


Kornej H, Hindricks G, Kosiuk J, et al. Renal dysfunction, stroke risk scores (CHADS2,
CHA2DS2-VASc, and R2CHADS2), and the risk of thromboembolic events after catheter ablation of atrial fibrillation: the Leipzig Heart Center AF Ablation Registry. Circ Arrhythm Electrophysiol 2013;6(5):868-74. PMID: 24047706.


McAlister FA, Jacka M, Graham M, et al. The prediction of postoperative stroke or death in patients with preoperative atrial fibrillation undergoing non-


Ntaios G, Lip GY, Makaris K, et al. CHADS<sup>2</sup>, CHA2DS2-VASc, and long-term stroke


D-30


Špinar J, Vítovc J, Soucek M, et al. He First Registry. Comparison of anticoagulant treatment in


Wasmer K, Kobe J, Dechering D, et al. CHADS(2) and CHA(2)DS (2)-VASc score of patients with atrial fibrillation or flutter and newly detected left atrial thrombus. Clin Res Cardiol 2013;102(2):139-44. PMID: 2293022.


Xing Y, Ma Q, Ma X, et al. CHADS2 score has a better predictive value than CHA2DS2-VASc score in elderly patients with atrial fibrillation. Clin Interv Aging 2016;11:941-6. PMID: 27478371.


Yin L, Ling X, Zhang Y, et al. CHADS2 and CHA2DS2-VASc scoring systems for predicting


Does not meet tool/intervention or comparator requirements--2017


Faustino A, Providencia R, Barra S, et al. Which method of left atrium size quantification is the most accurate to recognize thromboembolic risk in patients


Marzona I, O'Donnell M, Teo K, et al. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and


Numa S, Hirai T, Nakagawa K, et al. Hyperuricemia and transesophageal echocardiographic


Proietti M, Lane DA and Lip GY. Relation of the SAMe-TT2R2 score to quality of anticoagulation control and thromboembolic events in atrial fibrillation patients: Observations from the SPORTIF trials. Int J Cardiol 2016;216:168-72. PMID: 27156060.


Vanerio G. International Normalized Ratio Variability: A Measure of Anticoagulation Quality or


No outcomes of interest--2017


Macario E, Schneider YT, Campbell SM, et al. Quality of Life Experiences among Women with


Roldan V, Marín F, Manzano-Fernandez S, et al. The HAS-BLED score has better prediction accuracy for
major bleeding than CHADS2 or CHA2DS2-VASc scores in anticoagulated patients with atrial fibrillation. J Am Coll Cardiol 2013;62(23):2199-204. PMID: 24057544.


Not Available in English--2012


Not a Clinical Study--2012


D-58


Sawaya FJ, Musallam KM, Arnaout S, et al. Switching patients from warfarin to dabigatran


**Not Original Peer-Reviewed Data/Abstract Only--2012**


No Intervention/Comparator of Interest--2012


Poli D, Antonucci E, Grifoni E, et al. Low bleeding risk of very old atrial fibrillation women on VKA treatment: Results from a prospective collaborative study. on behalf of the ad hoc Study Group of FCSA. Eur Heart J. 2011;32(Suppl.1):8.


Tinmouth AH, Morrow BH, Cruickshank MK, et al. Dalteparin as periprocedure anticoagulation for patients on warfarin and at high risk of thrombosis.
No Outcomes of Interest--2012


1035. PMID: 19738136.


Giralt-Steinhauer E, Cuadrado-Godia E, Ois A, et al. Comparison between CHADS (2) and CHA (2) DS (2)-VASc score in a stroke cohort with atrial fibrillation. Eur J Neurol. 2012. PMID: 22834861.


McBane RD, Hodge DO, Wysokinski WE. Clinical and echocardiographic measures governing
thromboembolism destination in atrial fibrillation.


Viles-Gonzalez JF, Kar S, Douglas P, et al. The clinical impact of incomplete left atrial appendage closure with the Watchman Device in patients with atrial fibrillation: a PROTECT AF (Percutaneous


## Appendix E. Key to Included Primary and Companion Articles

*Companion articles marked with an asterisk did not individually meet criteria for inclusion but were considered for supplemental information (e.g., methods data pertinent to an included study).

<table>
<thead>
<tr>
<th>Study Designation</th>
<th>Primary Abstracted Article</th>
<th>Companion Articles*</th>
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<tr>
<td>ACE (Anticoagulation in Cardioversion Using Enoxaparin)</td>
<td>Stellbrink, 2004(^1)</td>
<td>Stellbrink, 2002(^2)*</td>
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<tr>
<td>ACTIVE-A (The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events - A)</td>
<td>Connolly, 2009(^3)</td>
<td>Connolly, 2006(^4)*</td>
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</table>
| ACTIVE-W (The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events - W) | Connolly, 2006\(^5\)       | Flaker, 2010\(^6\)  
|                                                             |                             | Healey, 2008\(^7\)  
|                                                             |                             | Hohnloser, 2007\(^8\) |
| AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) | Bousser, 2008\(^9\)        | Apostolakis, 2012\(^10\)  
|                                                             |                             | Apostolakis, 2013\(^11\) |
|                                                             |                             | Apostolakis, 2013\(^12\) |
|                                                             |                             | Lane, 2011\(^13\)        
|                                                             |                             | Senoo, 2016\(^14\)       |
| ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) | Granger, 2011\(^15\)       | Easton, 2012\(^16\)  
|                                                             |                             | Hohnloser, 2012\(^17\)  
|                                                             |                             | Lopes, 2012\(^18\)      
|                                                             |                             | Lopes, 2010\(^19\)*     
|                                                             |                             | Lopes, 2017\(^20\)      
|                                                             |                             | Cowper, 2017\(^21\)     
|                                                             |                             | Westenbrink, 2017\(^22\) |
|                                                             |                             | Hu, 2017\(^23\)         
|                                                             |                             | Guimaraes, 2017\(^24\)  
|                                                             |                             | Bahit, 2017\(^25\)      
|                                                             |                             | Alexander, 2016\(^26\)  
|                                                             |                             | Hijazi, 2016\(^27\)     
|                                                             |                             | De Caterina, 2016\(^28\) |
|                                                             |                             | Durheim, 2016\(^29\)    
|                                                             |                             | Vinereau, 2015\(^30\)  
|                                                             |                             | Avezum, 2015\(^31\)    
|                                                             |                             | Ezekowitz, 2015\(^32\)  
|                                                             |                             | Held, 2015\(^33\)      
|                                                             |                             | Hylek, 2014\(^34\)     
|                                                             |                             | Halvorsen, 2014\(^35\) |
|                                                             |                             | Alexander, 2014\(^36\)  
|                                                             |                             | Wallentin, 2013\(^37\) |
|                                                             |                             | Al-Khatib, 2013\(^38\)  
<p>|                                                             |                             | McMurray, 2013(^39)  |
| ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) | Fang, 2011(^40)         | None                |
|                                                             | Fang, 2008(^41)         | None                |
|                                                             | Hylek, 2003(^42)        | Go, 1999(^43)*     |</p>
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<td>Eikelboom, 2012[^46]</td>
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<td><strong>ENGAGE-AF-TIMI 48 (The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48)</strong></td>
<td>Giugliano, 2013[^70]</td>
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<td>Breithardt, 2016[131]</td>
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<td>DeVore, 2016[132]</td>
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<td>Fordyce, 2016[133]</td>
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<td>Fox, 2011[134]</td>
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<td>Goodman, 2014[135]</td>
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<td>Halperin, 2014[136]</td>
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<td>Hankey, 2012[137]</td>
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<td>Orgel, 2017[141]</td>
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<td>Patel, 2013[142]</td>
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<td>Piccini, 2014[143]</td>
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<td>Shah, 2016[145]</td>
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<td>Sherwood, 2015[146]</td>
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<td>van Diepen, 2013[148]</td>
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<td>Vemulapalli, 2016[149]</td>
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<td>Lip, 2010[152]</td>
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<td>Lip, 2011[153]</td>
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<td>Olsson, 2003[154]</td>
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<td>Proietti, 2016[155]</td>
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<td>Study Designation</td>
<td>Primary Abstracted Article</td>
<td>Companion Articles*</td>
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<tr>
<td>Swedish Atrial Fibrillation cohort study</td>
<td>Friberg, 2012&lt;sup&gt;157&lt;/sup&gt;</td>
<td>Friberg, 2015&lt;sup&gt;158&lt;/sup&gt;</td>
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<td>None</td>
<td>Hansen, 2010&lt;sup&gt;159&lt;/sup&gt;</td>
<td>Hansen, 2008&lt;sup&gt;160*&lt;/sup&gt;</td>
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<tr>
<td>None</td>
<td>Inoue, 2006&lt;sup&gt;161&lt;/sup&gt;</td>
<td>Nozawa, 2004&lt;sup&gt;162*&lt;/sup&gt;</td>
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<td>None</td>
<td>Poli, 2009&lt;sup&gt;163&lt;/sup&gt;</td>
<td>Poli, 2009&lt;sup&gt;164&lt;/sup&gt;</td>
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<td>None</td>
<td>Rietbrock, 2008&lt;sup&gt;165&lt;/sup&gt;</td>
<td>Rietbrock, 2009&lt;sup&gt;166&lt;/sup&gt;</td>
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<tr>
<td>None</td>
<td>Sadanaga, 2010&lt;sup&gt;167&lt;/sup&gt;</td>
<td>Sadanaga, 2010&lt;sup&gt;168*&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**References to Appendix E**


10. Apostolakis S, Lane DA, Guo Y, et al. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED Bleeding Risk-Prediction Scores in Patients With Atrial Fibrillation Undergoing Anticoagulation: The AMADEUS (Evaluating the Use of SR34006


52. Lip GY, Connolly S, Yusuf S, et al. Modification of outcomes with aspirin or apixaban in relation to CHADS(2) and CHA(2)DS(2)-VASc scores.


92. Wang TJ, Massaro JM, Levy D, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the


### Appendix F. Study Characteristics Tables

#### Appendix Table F-1. Study characteristics—KQ 1

<table>
<thead>
<tr>
<th>Study Author Year Acronym</th>
<th>Study Design Setting Location Funding Source Quality</th>
<th>Tools Assessed</th>
<th>Total N</th>
<th>Follow-up period</th>
<th>Age</th>
<th>Special Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abraham, 2013¹</td>
<td>Prospective cohort; Uncl/NR; US; Uncl/NR; Low risk of bias</td>
<td>Clinical: CHADS2 score, CHADS2-VASc score</td>
<td>Patients on Warfarin: 5,981</td>
<td>Total: 11.8 years (IQR 8.0-13.6)</td>
<td>Total: 65.85 (SD: 7.18)</td>
<td>Age; Sex</td>
</tr>
<tr>
<td>Abumuail, 2015²</td>
<td>Retrospective cohort; Emergency Room; Europe; Uncl/NR; Low risk of bias</td>
<td>Clinical: CHADS2-VASc score</td>
<td>Non-anticoagulated: 154 Anticoagulated: 911</td>
<td>Non-anticoagulated: 11 months (SD: 2.7) Anticoagulated: 10 months (SD: 3)</td>
<td>Non-anticoagulated: 74 (SD: 12) Anticoagulated: 73 (SD: 11)</td>
<td>None</td>
</tr>
<tr>
<td>Ad, 2010³</td>
<td>Prospective cohort; Outpatient; US; Uncl/NR; Low risk of bias</td>
<td>Clinical: CHADS2 score</td>
<td>Total: 347</td>
<td>Total: 32.77 months (SD: 16.33)</td>
<td>Total: 64.5 (SD: 11.6)</td>
<td>None</td>
</tr>
<tr>
<td>Allan, 2017⁴</td>
<td>Prospective cohort; Inpatient, Outpatient; UK Government, Non-govt, Non-industry; Medium risk of bias</td>
<td>Clinical: CHADS2-VASc score</td>
<td>Total: 70,206</td>
<td>Total: 2.20 years (IQR 0.02-12.2)</td>
<td>Total: 77.9 (IQR 18.0-108.7)</td>
<td>None</td>
</tr>
<tr>
<td>An, 2017⁵</td>
<td>Retrospective cohort; Inpatient, Outpatient; US; Industry; Low risk of bias</td>
<td>Clinical: N/A Individual risk factors include: INR level</td>
<td>Total: 32,207</td>
<td>Total median: 3.8 years</td>
<td>Total: 72.2 (SD: 10.7)</td>
<td>None</td>
</tr>
<tr>
<td>Study Author Year</td>
<td>Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Tools Assessed</td>
<td>Total N</td>
<td>Follow-up period</td>
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<tr>
<td>Ashburner, 2016*</td>
<td>ATRIA</td>
<td>Retrospective cohort; Unclear/NR; US; Government, Non-govt, Non-industry; Low risk of bias</td>
<td><strong>Individual risk factors</strong> include: Diabetes and glycemic control</td>
<td>Total: 2,101</td>
<td>Non Diabetics: 3.09 years (SD: 2.48)</td>
<td>Non Diabetics: 71.8 (SD: 12.7)</td>
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<td>Diabetes: 2.48 years (SD: 2.23)</td>
<td>Diabetes broken down by duration: 0 to 3 years: 69.0 (SD: 11) 3 years: 71.7 (SD: 8.9)</td>
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<td></td>
<td>HbA1c values: &lt;7.0: 71.5 (SD: 9.6) 7.0 – 8.9: 70.5 (SD: 9.7) &gt;9.0 67.9(SD: 9.8)</td>
<td></td>
</tr>
<tr>
<td>Baruch, 2007†</td>
<td>SPORTIF</td>
<td>RCT; Outpatient; Unclear/NR; Industry; Low risk of bias</td>
<td><strong>Clinical</strong>: HAS-BLED CHADS2 score CHA2DS2-VASc score</td>
<td>Total: 7,329</td>
<td>Total: 1.5 years</td>
<td>Arm 1: 73.9 (SD: 8.6) Arm 2: 70.9 (SD: 8.9)</td>
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<td></td>
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<td></td>
<td><strong>Individual risk factors</strong>: TTR for warfarin-treated patients</td>
<td></td>
<td>Proietti, 2016*: Median follow-up 566 days (IQR 495-653)</td>
<td>Proietti, 2016*: Median 61 (IQR 56-64)</td>
</tr>
<tr>
<td>Beinart, 2011†</td>
<td></td>
<td>Retrospective cohort; Inpatient, Outpatient; US; Non-govt, Non-industry; High risk of bias</td>
<td><strong>Individual risk factors</strong>: Cardiac MRI</td>
<td>Total: 144</td>
<td>Unclear/NR</td>
<td>Total: 54.5 (SD: 9.9)</td>
</tr>
<tr>
<td>Study Author</td>
<td>Year</td>
<td>Acronym</td>
<td>Study Design</td>
<td>Setting</td>
<td>Location</td>
<td>Funding Source</td>
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<td>Bonde, 2014</td>
<td>10</td>
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<td>Retrospective cohort; Inpatient, Outpatient; Europe; Industry, Non-govt, Non-industry; Low risk of bias</td>
<td>Clinical: CHADS2-VASc score HAS-BLED</td>
<td>Total: 12,856</td>
<td>Non-CKD patients: 1,179 days (IQR 397-2,412)</td>
</tr>
<tr>
<td>Bonde, 2016</td>
<td>11</td>
<td>Danish Patient Registry</td>
<td>Retrospective cohort; Inpatient; Europe; Government; Medium risk of bias</td>
<td>Clinical: CHADS2-VASc score HAS-BLED</td>
<td>Total: 17,349</td>
<td>Total: 4.1 years</td>
</tr>
<tr>
<td>Bouillon, 2015</td>
<td>12</td>
<td>SNIIRAM</td>
<td>Retrospective cohort; Unclear/NR; Europe; Unclear/NR; Low risk of bias</td>
<td>Clinical: HAS-BLED score</td>
<td>Total: 17,410</td>
<td>Total: 10 months (IQR 9.8-10)</td>
</tr>
<tr>
<td>Bousser, 2008</td>
<td>13</td>
<td>Paper for KQ 1: Apostolakis, 2013</td>
<td>RCT; Unclear/NR; US, Canada, UK, Europe, Australia/NZ; Industry; Low risk of bias</td>
<td>Clinical: CHADS2 score CHADS2-VASc score HEMORR2HAGES HAS-BLED ATRIA</td>
<td>Total: 2,293</td>
<td>Total: 429 days (SD: 118)</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Tools Assessed</td>
<td>Total N</td>
<td>Follow-up period</td>
<td>Age</td>
<td>Special Population</td>
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<tr>
<td>Connolly, 2009&lt;sup&gt;13&lt;/sup&gt;</td>
<td>RCT; Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Industry; Low risk of bias</td>
<td>Clinical: CHADS&lt;sub&gt;2&lt;/sub&gt; score</td>
<td>Total: 18,113</td>
<td>Total median: 2.0 years</td>
<td>Total Median: 71</td>
<td>None</td>
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<tr>
<td>Marijon, 2013&lt;sup&gt;17&lt;/sup&gt;</td>
<td>RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy)</td>
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<td>Oldgren, 2016&lt;sup&gt;16&lt;/sup&gt;</td>
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<tr>
<td>Connolly, 2011&lt;sup&gt;18&lt;/sup&gt;</td>
<td>RCT; Outpatient; Unclear/NR; Industry; Low risk of bias</td>
<td>Clinical: CHADS&lt;sub&gt;2&lt;/sub&gt; score CHADS2-VASc score by ASA and Apixaban use</td>
<td>Total: 5,599 ASA: 2,791 Apixaban: 2,808</td>
<td>Total: 1.1 years</td>
<td>Total: 69.9 (SD: 9.6) years ASA: 70.0 (SD: 9.7) years Apixaban: 69.7 (SD: 9.4) years</td>
<td>None</td>
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<td>Lip, 2013&lt;sup&gt;19&lt;/sup&gt;</td>
<td>AVERROES</td>
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<td>Fauchier, 2016&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient; Europe; Unclear/NR; Moderate risk of bias</td>
<td>Clinical: CHADS2-VASc score</td>
<td>Total: 2,208</td>
<td>Total: 1,028 days (SD: 1,189)</td>
<td>Total: 55 (SD: 14)</td>
<td>None</td>
</tr>
<tr>
<td>Crandall, 2009&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Retrospective cohort; Unclear/NR; US; Non-govt, Non-industry; High risk of bias</td>
<td>Clinical: CHADS&lt;sub&gt;2&lt;/sub&gt; score</td>
<td>Total: 343</td>
<td>AF patients: 9.1 years (SD: 1.8)</td>
<td>AF patients: 69 (SD: 10)</td>
<td>None</td>
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<tr>
<td>Fang, 2008&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Retrospective cohort; Outpatient; US; Government, Non-govt, Non-industry; Low risk of bias</td>
<td>Clinical: CHADS2 score Framingham score</td>
<td>Total: 10,932</td>
<td>Total median: 6.0 years (IQR 3.1 – 6.7)</td>
<td>Total mean: 72</td>
<td>None</td>
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<tr>
<td>ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)</td>
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**Note:** Papers designated as KQ 1 for 2017: Marijon, 2013<sup>17</sup>
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<th>Study Author Year Acronym</th>
<th>Study Design Setting Location Funding Source Quality</th>
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<th>Follow-up period</th>
<th>Age</th>
<th>Special Population</th>
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<tr>
<td>Flaker, 2010&lt;sup&gt;21&lt;/sup&gt;</td>
<td>RCT; Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Industry, Non-govt, Non-industry; Unclear</td>
<td>Individual risk factors: INR level (TTR) Cognitive impairment</td>
<td>Total: 3,371</td>
<td>Total: 1.3 years</td>
<td>Total: 70.9 (SD: 9.5)</td>
<td>None</td>
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<tr>
<td>Forslund, 2014&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient, Outpatient; Europe; Government, Non-govt, Non-industry; Low risk of bias</td>
<td>Clinical: CHADS2 score CHADS2-VASc score Individual risk factors: Age Sex Hypertension</td>
<td>Total: 41,810</td>
<td>Total: 1 year</td>
<td>Total mean: 73.2</td>
<td>None</td>
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<td>Friberg, 2012&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient, Outpatient; Europe; Government, Non-govt, Non-industry</td>
<td>Clinical: CHADS2 score CHADS2-VASc score Individual risk factors: Sex</td>
<td>Total: 100,802</td>
<td>Total: 1.2 years (IQR 0-3.5)</td>
<td>Women: 80.9 (SD: 10.6) Men: 74.7 (SD: 13.5)</td>
<td>None</td>
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<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Tools Assessed</td>
<td>Total N</td>
<td>Follow-up period</td>
<td>Age</td>
<td>Special Population</td>
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<tr>
<td>Friberg, 2012(^{27})</td>
<td>Prospective cohort; Inpatient, Outpatient; Europe; Government, Non-govt, Non-industry; Low risk of bias</td>
<td>Clinical: CHADS(_2) score CHA(_2)DS(_2)-VASc score Framingham score HAS-BLED HEMORR(_2)-HAGES Individual risk factors: Presence and severity of CKD</td>
<td>Total: 283,969 Friberg, 2015(^{28}): Renal failure: 13,435 No Renal failure: 270,534</td>
<td>Total median: 1.4 years (IQR 1.8) Friberg, 2015(^{28}): Median: 2.1 years</td>
<td>Total: 76.2 Friberg, 2015(^{28}): Renal failure: 78.4 (SD: 10.3) No renal failure: 74.8 (SD: 12.5)</td>
<td>None</td>
</tr>
<tr>
<td>Gage, 2001(^{29})</td>
<td>Retrospective cohort; Outpatient; US; Government; Low risk of bias</td>
<td>Clinical: CHADS(_2) score</td>
<td>Total: 1,733</td>
<td>Total: 1.2 years</td>
<td>Total: 81</td>
<td>None</td>
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<tr>
<td>Giugliano, 2013(^{30})</td>
<td>RCT; Unclear/NR; US; Industry; Low risk of bias</td>
<td>Clinical: CHADS(_2) score CHADS(_2)-VASc score Individual risk factors: Gupta, 2016(^{32}): TTE elements Link, 2017(^{33}): Individual risk factors: paroxysmal (&lt;7 days duration), persistent (≥7 days but &lt;1 year), or permanent (≥1 year or failed cardioversion) AF patterns</td>
<td>Total: 21,105 Fanola, 2017(^{31}): 2,898 VKA naïve patients Gupta, 2016(^{32}): 971 Ruff, 2016(^{34}): 4,880 with biomarker available</td>
<td>Total median: 2.8 years Fanola, 2017(^{31}): 7,272.7 PY follow-up Gupta, 2016(^{32}): 2.5 years Link, 2017(^{33}): Median 2.8 years</td>
<td>Total: 72 (IQR 64-78) Fanola, 2017(^{31}): Median 71 (IQR 63-77) Link, 2017(^{33}): Paroxysmal: 70.5 (SD: 9.5); Persistent: 70.2 (SD: 9.7); Permanent: 70.8 (SD: 9.2) Ruff, 2016(^{34}): Median 71 years (IQR 64-77)</td>
<td>None</td>
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ENGAGE-AF
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<th>Study Author Year Acronym</th>
<th>Study Design Setting Location Funding Source Quality</th>
<th>Tools Assessed</th>
<th>Total N</th>
<th>Follow-up period</th>
<th>Age</th>
<th>Special Population</th>
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</thead>
</table>
| Granger, 2011 ARISTOTLE    | RCT; Unclear/NR; US, Canada, Europe, Asia, Australia/NZ; Industry; Low risk of bias | **Individual risk factors:** LVD <=40% HF symptoms | Total: 18,201  
Murray, 2013;  
Out of the 18,201 HF and LVD status: 14671  
No HF and EF >40%: 8,728  
LVD status: 2,736  
HF-PEF: 3,207 | Granger, 2011:  
Arm 1: Median: 70  
(IQR 63 to 76)  
Arm 2: Median: 70  
(IQR 63 to 76)  
McMurray, 2013:  
No LVD/no HF  
LVD Median: 71 (IQR 64-76)  
LVD Median: 68 (IQR 60-74)  
HF-PEF Median: 69 (IQR 61-75) | None |
| Haas, 2016 GARFIELD-AF Companions: Camm, 2017 Bassand, 2016 | Retrospective cohort; Inpatient, Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Industry; Low risk of bias | **Individual risk factors:** INR level (TTR) Sex Treatment with and without OAC | Total: 28,624 | Outcomes only reported out to 1 year | Haas, 2016:  
70.7 (SD: 10.6) years for TTR <65%  
71.9 (SD: 9.7) years for TTR =>65%  
Camm, 2017:  
Women: 72.4 (SD: 10.4)  
Men: 67.6 (SD: 11.7)  
Bassand, 2016:  
69.8 (SD: 11.4) | Camm, 2017: Newly diagnoses (<= 6 weeks duration) |
<table>
<thead>
<tr>
<th>Study Author Year Acronym</th>
<th>Study Design Setting Location Funding Source Quality</th>
<th>Tools Assessed</th>
<th>Total N</th>
<th>Follow-up period</th>
<th>Age</th>
<th>Special Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hijazi, 2016¹⁰</td>
<td>Created from ARISTOTLE (derivation) and STABILITY (for external validity)</td>
<td>RCT; Unclear/NR; US, Canada, UK, Europe, Australia/NZ; Government, Industry; Low risk of bias</td>
<td>Clinical: CHADS2 score ABC stroke risk score</td>
<td>Derivation cohort: 14,701 External validation cohort: 1,400</td>
<td>Derivation cohort Total median: 70.0 (IQR 19-97) External validation cohort Total median: 69.0 (IQR 37-88)</td>
<td>None</td>
</tr>
<tr>
<td>Hylek, 2003¹¹</td>
<td>ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)</td>
<td>Retrospective cohort; Outpatient; US; Government; Low risk of bias</td>
<td>Individual risk factors: INR level</td>
<td>Total: 596</td>
<td>Unclear/NR</td>
<td>Arm 1: 79 Arm 2: 80 Arm 3: 76</td>
</tr>
<tr>
<td>Jun, 2017¹²</td>
<td>Retrospective cohort; Inpatient, Outpatient, Emergency Room; Canada; Government; Low risk of bias</td>
<td>Clinical: HAS-BLED score Individual risk factors include: Presence and severity of CKD</td>
<td>Total: 14,892 Total: 1-year</td>
<td>Total: 78.1 (SD: 6.8)</td>
<td>Age Comorbid conditions (such as advanced CKD (eGFR&lt;60), dementia)</td>
<td></td>
</tr>
<tr>
<td>Larsen, 2012¹³</td>
<td>Prospective cohort; Unclear/NR; Europe; Government; Low risk of bias</td>
<td>Clinical: CHADS2 score CHADS2-VASc score</td>
<td>Total: 1,603 Mean follow up period Total: 5.4 (SD: 3.7)</td>
<td>Unclear/NR</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Lind, 2012¹⁴</td>
<td>Retrospective cohort; Outpatient; Europe; Unclear/NR; High risk of bias</td>
<td>Individual risk factors: INR</td>
<td>Total: 19,180</td>
<td>Unclear/NR</td>
<td>Unclear/NR</td>
<td>None</td>
</tr>
<tr>
<td>Study Author Year</td>
<td>Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Tools Assessed</td>
<td>Total N</td>
<td>Follow-up period</td>
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<tr>
<td>Lip, 2010[^45]</td>
<td>Euro Heart Survey for AF</td>
<td>Retrospective cohort; Outpatient; UK, Europe; Industry, Non-govt, Non-industry; Low risk of bias</td>
<td><strong>Clinical:</strong> CHADS₂ score Framingham score CHA₂DS²-VASc score</td>
<td>Total: 1,084</td>
<td>Total: 1 years</td>
<td>Total: 66 (SD: 14)</td>
</tr>
<tr>
<td>Lip, 2012[^46]</td>
<td>Loire Valley AF Project Companions: Olesen, 2012[^47]; Banerjee, 2014[^48]; Banerjee, 2013[^49]</td>
<td>Retrospective cohort; Inpatient; Europe; Unclear/NR; Moderate risk of bias</td>
<td><strong>Clinical:</strong> CHADS₂ score CHA₂DS²-VASc score</td>
<td>Total: 7,156</td>
<td>Arm 1: 1.65 years (SD: 2.44) Arm 2: 2.45 years (SD: 3.56)</td>
<td>Arm 1: 77.7 (SD: 8.2) Arm 2: 73.8 (SD: 11.6) Arm 3: 49.0 (SD: 13.1) Banerjee, 2014[^48]: Stroke/Bleeds No CKD- 69.7 (SD: 12.6) CKD – 72.7 (SD: 11.7) Stroke/TE No CKD- 69.8 (SD: 12.5) CKD – 73.6 (SD: 12.0)</td>
</tr>
<tr>
<td>McAlister, 2017[^50]</td>
<td></td>
<td>Retrospective cohort; Inpatient, Outpatient, Emergency Room; Canada; Government; Low risk of bias</td>
<td><strong>Clinical:</strong> CHADS₂ score CHA₂DS²-VASc score</td>
<td>Total: 58,451</td>
<td>Total median: 31 months (IQR 13-59)</td>
<td>Total: 66 years</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
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<tr>
<td>Mikkelsen, 2012</td>
<td>Retrospective cohort; Inpatient, Outpatient; Europe; Unclear/NR; Low risk of bias</td>
<td>Individual risk factors include: Sex</td>
<td>Total: 87,202</td>
<td>Women: 795 days (IQR 231–1785) Men: 897 days (IQR 274–1990)</td>
<td>Women: 78.2 (SD: 12.1) Men: 71.0 (SD: 14.3)</td>
<td>Sex</td>
</tr>
<tr>
<td>Morgan, 2009</td>
<td>Retrospective cohort; Inpatient; UK; Industry; High risk of bias</td>
<td>Clinical: CHADS&lt;sub&gt;2&lt;/sub&gt; score</td>
<td>Total: 5,513</td>
<td>Total: 1,025.1 days (SD: 714.8) Arm 1: 986.4 days (SD: 722) Arm 1: 72.5 (SD: 10.4) Arm 2: 77.8 (SD: 12.1)</td>
<td>None</td>
<td></td>
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<tr>
<td>Nair, 2009</td>
<td>Prospective cohort; Unclear/NR; US; Unclear/NR; Low risk of bias</td>
<td>Individual risk factors: TEE</td>
<td>Total: 226</td>
<td>Arm 1: 13 months (SD: 17) Arm 2: 93 months (SD: 173) Arm 1: 72 (SD: 11) Arm 2: 70 (SD: 12)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Nielsen, 2016</td>
<td>Retrospective; Inpatient, Outpatient; Europe; Non-govt, Non-industry; Medium risk of bias</td>
<td>Clinical: CHADS&lt;sub&gt;2&lt;/sub&gt;-VASc score</td>
<td>Total: 198,697</td>
<td>Total: 2.9 years</td>
<td>Total: 75</td>
<td>None</td>
</tr>
<tr>
<td>Olesen, 2011</td>
<td>Retrospective cohort; Inpatient; Europe; Unclear/NR; High risk of bias</td>
<td>Clinical: CHADS&lt;sub&gt;2&lt;/sub&gt; score CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc score</td>
<td>Total: 132,372</td>
<td>Total: Max 12 years Arm 1: 72.8 (SD: 14.4) Arm 2: 70.6 (SD: 11.1) Arm 3: 78.1 (SD: 11.2) Arm 4: 73.1 (SD: 9.6)</td>
<td>None</td>
<td></td>
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<tr>
<td>Olesen, 2011</td>
<td>Retrospective cohort; Outpatient; Europe; Unclear/NR; Low risk of bias</td>
<td>Clinical: CHADS&lt;sub&gt;2&lt;/sub&gt; score CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc score</td>
<td>Total: 73,538</td>
<td>Unclear/NR</td>
<td>Unclear/NR</td>
<td>None</td>
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<tr>
<td>Study Author Year Acronym</td>
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<tr>
<td>Olese, 201217</td>
<td>Retrospective cohort; Outpatient; Europe; Unclear/NR; Low risk of bias</td>
<td><strong>Clinical</strong>: CHADS² score CHA²DS₂-VASc score</td>
<td>Total: 47,576</td>
<td>Total: 12 years Arm 1: 12 years Arm 2: 12 years</td>
<td>Total: 69.4 (SD: 14.7)</td>
<td>None</td>
</tr>
<tr>
<td>Olese, 201218</td>
<td>Danish National Patient Registry</td>
<td><strong>Clinical</strong>: CHADS² score</td>
<td>Total: 87,202</td>
<td>Unclear/NR</td>
<td>Arm 1: 74.2 (SD: 14.2) Arm 2: 76.9 (SD: 10.3)</td>
<td>None</td>
</tr>
<tr>
<td>Orkaby, 201719</td>
<td>Retrospective cohort; Inpatient, Outpatient; US; Government; Moderate risk of bias</td>
<td><strong>Individual risk factors include</strong>: Cognitive impairment</td>
<td>Total: 2,572</td>
<td>Total: 2.2 PY following diagnosis of dementia</td>
<td>Total: 79.5 (SD: 6.0)</td>
<td>Patients with newly diagnosed dementia; Older Adults</td>
</tr>
<tr>
<td>Philippart, 201640</td>
<td>Retrospective cohort; Inpatient; Europe; Unclear/NR; Moderate risk of bias</td>
<td><strong>Clinical</strong>: CHADS2 score CHA2DS2-VASc score</td>
<td>Total: 8,602</td>
<td>Total Mean: 876 days (SD: 1048)</td>
<td>Non-valvular AF: 71 (SD: 15) Valvular AF: 75 (SD: 8) Valvular AF, with aortic bioprosthesis: 76 (SD: 8) Other AF: 73 (SD: 8)</td>
<td>None</td>
</tr>
<tr>
<td>Poli, 200941</td>
<td>Prospective cohort; Inpatient, Outpatient; Europe; Unclear/NR; Low risk of bias</td>
<td><strong>Clinical</strong>: CHADS2 score</td>
<td>Total: 662</td>
<td>Total median: 3.1 years</td>
<td>Total: 75</td>
<td>None</td>
</tr>
<tr>
<td>Poli, 201142</td>
<td>Prospective cohort; Unclear/NR; Europe; None; Low risk of bias</td>
<td><strong>Clinical</strong>: CHADS2 score</td>
<td>Total: 3,302</td>
<td>Total median: 2.3 years (IQR 0.8 - 4.4)</td>
<td>Total median: 74 (IQR 68 - 80)</td>
<td>None</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
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<tr>
<td>Poli, 2011(^{63})</td>
<td>Prospective cohort; Outpatient; Europe; Unclear/NR; Low risk of bias</td>
<td><strong>Clinical</strong>: CHADS(_2) score CHA(_2)DS(_2)-VASc score</td>
<td>Total: 662</td>
<td>Total: 3.6 years (SD: 2.7)</td>
<td>Total: 74 (SD: 7.7)</td>
<td>None</td>
</tr>
<tr>
<td>Potpara, 2012(^{64})</td>
<td>Prospective cohort; Unclear/NR; Europe; Government; Low risk of bias</td>
<td><strong>Clinical</strong>: CHADS(_2) score CHA(_2)DS(_2)-VASc score</td>
<td>Total: 345</td>
<td>Total: 12.1 years (SD: 7.3)</td>
<td>Total: 43.2 (SD: 9.9)</td>
<td>None</td>
</tr>
<tr>
<td>Renoux, 2017(^{65})</td>
<td>Retrospective cohort; Inpatient, Outpatient; Canada; Industry; Non-govt, Non-industry; Low risk of bias</td>
<td><strong>Clinical</strong>: HAS-BLED Individual risk factors include: Age Sex Prior stroke *Duration and frequency of AF Presence and severity of CKD</td>
<td>Total: 147,622</td>
<td>Total: 2.9 years</td>
<td>Total: 75.5 (SD: 11.4)</td>
<td>None</td>
</tr>
<tr>
<td>Rietbrock, 2008(^{66})</td>
<td>Retrospective cohort; Outpatient; UK; Industry; Low risk of bias</td>
<td><strong>Clinical</strong>: CHADS(_2) score</td>
<td>Total: 51,807</td>
<td>Total median: 2.5 years</td>
<td>Total: 76.01 (SD: 10.13)</td>
<td>None</td>
</tr>
<tr>
<td>Ruiz Ortiz, 2008(^{67})</td>
<td>Prospective cohort; Outpatient; Europe; Non-govt, Non-industry; Low risk of bias</td>
<td><strong>Clinical</strong>: CHADS(_2) score</td>
<td>Total: 296</td>
<td>Total: 21 months (SD: 17)</td>
<td>Total: 75 (SD: 9)</td>
<td>Permanent AF</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
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<tr>
<td>Ruiz Ortiz, 2010*8</td>
<td>Prospective cohort; Outpatient; Europe; Non-govt, Non-industry; Low risk of bias</td>
<td>Clinical: CHADS(_2) score</td>
<td>Total: 796</td>
<td>Total: 2.4 years (SD: 1.9)</td>
<td>Total: 73 (SD: 8)</td>
<td>Permanent AF</td>
</tr>
<tr>
<td>Ruiz-Nodar, 2011*9</td>
<td>Retrospective cohort; Outpatient; Europe; Unclear/NR; Low risk of bias</td>
<td>Clinical: CHADS(_2) score</td>
<td>Total: 604</td>
<td>Total: 642 days (SD: 503) Arm 1: 642 days (SD: 503) Arm 2: 642 days (SD: 503)</td>
<td>Total: 71.8 (SD: 8.4)</td>
<td>None</td>
</tr>
<tr>
<td>Ruiz-Nodar, 2012*10</td>
<td>Retrospective cohort; Unclear/NR; Europe; Unclear/NR; High risk of bias</td>
<td>Clinical: HAS-BLED CHA(_2)DS(_2)-VASc score</td>
<td>Total: 590</td>
<td>Total: ~12 months</td>
<td>Total: 72.2 (SD: 8.1)</td>
<td>None</td>
</tr>
<tr>
<td>Singer, 2013*1</td>
<td>Retrospective cohort; Outpatient, US; Government; Low risk of bias</td>
<td>Clinical: CHADS2 score CHADS2-VASc score</td>
<td>Total: 10,927</td>
<td>Total: 32,609</td>
<td>Unclear/NR</td>
<td>None</td>
</tr>
<tr>
<td>Stoddard, 2003*2</td>
<td>Prospective cohort; Outpatient; US; Unclear/NR; Low risk of bias</td>
<td>Individual risk factors: TEE</td>
<td>Total: 272</td>
<td>Total: 30.3 months (SD: 20.6) Arm 1: 28.3 months (SD: 23.3) Arm 2: 30.9 months (SD: 20)</td>
<td>Total: 66 (SD: 11)</td>
<td>None</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
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<tr>
<td>Stollberger, 2004 ELAT (Embolism in Left Atrial Thrombi)</td>
<td>Prospective cohort; Outpatient; Europe; Unclear/NR; Low risk of bias</td>
<td>Individual risk factors: TTE TEE</td>
<td>Total: 409</td>
<td>Total: 101 months (SD: 2)</td>
<td>Total: 62 (IQR 61 - 64)</td>
<td>None</td>
</tr>
<tr>
<td>Thambidorai, 2005 ACUTE</td>
<td>RCT; Outpatient; US; Non-govt, Non-industry</td>
<td>Imaging: Transesophageal echo (TEE)</td>
<td>Total: 571</td>
<td>Unclear/NR</td>
<td>Thromboembolism: 62.2 (SD: 14.1) No-Thromboembolism: 65.0 (SD: 13)</td>
<td>None</td>
</tr>
<tr>
<td>van den Ham, 2015</td>
<td>Retrospective cohort; Outpatient; UK; Unclear/NR; Low risk of bias</td>
<td>Clinical: CHADS2 score CHA2DS2-VASc score ATRIA</td>
<td>Total: 60,594</td>
<td>Total: 2.81 years</td>
<td>Total Mean Age: 74.4</td>
<td>None</td>
</tr>
<tr>
<td>Van Staa, 2011</td>
<td>Retrospective cohort; Outpatient; UK; Unclear/NR; High risk of bias</td>
<td>Clinical: CHADS2 score CHA2DS2-VASc score Framingham score</td>
<td>Total: 79,844</td>
<td>Total: 4.0 years</td>
<td>Total: 73.3 (SD: 12.5)</td>
<td>None</td>
</tr>
<tr>
<td>Wang, 2003 Framingham Heart Study</td>
<td>Prospective cohort; Outpatient; US; Government, Non-govt, Non-industry; Low risk of bias</td>
<td>Clinical: Framingham score</td>
<td>Total: 705</td>
<td>Total: 4.0 years</td>
<td>Total: 75 (SD: 9)</td>
<td>None</td>
</tr>
<tr>
<td>Yarmohammadi, 2013</td>
<td>Retrospective cohort, Outpatient; US; Unclear/NR; Low risk of bias</td>
<td>Imaging: Transesophageal echo (TEE)</td>
<td>Total: 2,369</td>
<td>Total: 37 months (SD: 35)</td>
<td>Total Mean Age: 66 (SD: 13)</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: AF=atrial fibrillation; IQR=interquartile range; N=number of patients; NR=not reported; PY=patient years; RCT=randomized controlled trial; SD=standard deviation
## Appendix Table F-2. Study characteristics—KQ 2

<table>
<thead>
<tr>
<th>Study Author Year Acronym</th>
<th>Study Design Setting Location Funding Source Quality</th>
<th>Tools Assessed</th>
<th>Total N</th>
<th>Follow-up period</th>
<th>Age</th>
<th>Special Population</th>
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</thead>
<tbody>
<tr>
<td>An, 2017&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient, Outpatient; US; Industry; Low risk of bias</td>
<td>Individual risk factors include: INR level</td>
<td>Total: 32,074</td>
<td>Total: 5 years</td>
<td>Total: 72.2 (10.7)</td>
<td>None</td>
</tr>
<tr>
<td>Aspinall, 2005&lt;sup&gt;79&lt;/sup&gt;</td>
<td>Retrospective cohort; Outpatient; US; Unclear/NR; Low risk of bias</td>
<td>Clinical: Bleeding Risk Index</td>
<td>Total: 1,269</td>
<td>Unclear/NR</td>
<td>Total: 67.9 (SD: 11.4)</td>
<td>None</td>
</tr>
<tr>
<td>Barnes, 2014&lt;sup&gt;10&lt;/sup&gt; MAQI</td>
<td>Prospective cohort; Outpatient; US; Industry; Low risk of bias</td>
<td>Clinical: HAS-BLED score HEMORR2HAGES score ATRIA score</td>
<td>Total: 2,600</td>
<td>Total: 1.0 years (SD: 0.8)</td>
<td>Total: 70.1 (SD: 12.8)</td>
<td>None</td>
</tr>
<tr>
<td>Baruch, 2007&lt;sup&gt;17&lt;/sup&gt; SPORTIF Companions: Proietti, 2016&lt;sup&gt;81&lt;/sup&gt;</td>
<td>RCT; Outpatient; Unclear/NR; Industry; Low risk of bias</td>
<td>Clinical: HAS-BLED CHADS2 score CHA2DS2-VASc score Proietti, 2016&lt;sup&gt;81&lt;/sup&gt; Clinical: HAS-BLED score HEMORR2HAGES score ATRIA score</td>
<td>Total: 7,329</td>
<td>Total: 1.5 years Proietti, 2016&lt;sup&gt;81&lt;/sup&gt; Median: 1.6 years (IQR=1.3-1.8)</td>
<td>Arm 1: 73.9 (SD: 8.6) Arm 2: 70.9 (SD: 8.9) Proietti, 2016&lt;sup&gt;81&lt;/sup&gt; Median: 72 (IQR 66-77)</td>
<td>None</td>
</tr>
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<tr>
<td>Bonde, 2016 ¹¹</td>
<td>Danish Patient Registry</td>
<td>Retrospective cohort; Inpatient, Outpatient; Europe; Government; Medium risk of bias</td>
<td>Clinical HAS-BLED score</td>
<td>17,349</td>
<td>Median follow-up was 4.0 (IQR, 1.4–7.8), 4.9 (IQR, 2.0–8.1), 3.5 (IQR 1.3–6.7), 1.3 (IQR, 0.3–3.5), and 0.5 (IQR, 0.1–1.4) years in patients with eGFR ≥ 90, 60 to 89, 30 to 59, 15 to 29, and &lt;15 mL/min per 1.73 m² at baseline, respectively.</td>
<td>Total: 73 (IQR 64–81)</td>
</tr>
<tr>
<td>Bouillon, 2015 ¹²</td>
<td>SNIIRAM</td>
<td>Retrospective cohort; Unclear/NR; Europe; Unclear/NR; Low risk of bias</td>
<td>Clinical: HAS-BLED score</td>
<td>17,410</td>
<td>Total median: 10 months (IQR 9.8–10)</td>
<td>Non-Switchers median: 75 (IQR 67–82)</td>
</tr>
<tr>
<td>Bousser, 2008 ¹³</td>
<td>Papers for KQ 2: Apostolakis, 2013 ¹⁴; Senoo, 2016 ²²</td>
<td>RCT; Unclear/NR; US, Canada, UK, Europe, Australia/NZ; Industry; Low risk of bias</td>
<td>Clinical: HEMORR2HAGES HAS-BLED ATRIA</td>
<td>2,293</td>
<td>Total: 429 days (SD: 118)</td>
<td>Total: 70.2 (SD: 9.1)</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
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<tr>
<td>Connolly, 2009&lt;sup&gt;15&lt;/sup&gt; Paper for KQ 2: Marijon, 2013&lt;sup&gt;17&lt;/sup&gt; RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy)</td>
<td>RCT; Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Industry; Low risk of bias</td>
<td>Clinical: CHADS2 score</td>
<td>Total: 18,113</td>
<td>Total median: 2.0 years</td>
<td>Total: 71</td>
<td>None</td>
</tr>
<tr>
<td>Esteve-Pastor, 2016&lt;sup&gt;41&lt;/sup&gt; FANTASIIA Registry</td>
<td>Prospective cohort; Inpatient; Europe; Industry, Government; Low risk of bias</td>
<td>Clinical: HAS-BLED score ORBIT</td>
<td>ECV cohort: 406 FANTASIIA: 1,276</td>
<td>ECV = median follow-up of 1,005 days (IQR 619–1,489) FANTASIIA = follow-up of 1 years</td>
<td>ECV = 66.9 (SD: 10.9) FANTASIIA = 73.9 (9.4)</td>
<td>Persistent nonvalvular AF who underwent one or more programmed ECV procedures</td>
</tr>
<tr>
<td>Fang, 2011&lt;sup&gt;34&lt;/sup&gt; ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)</td>
<td>Retrospective cohort; Outpatient; US; Government, Industry, Non-govt, Non-industry; Low risk of bias</td>
<td>Clinical: ATRIA HEMORR&lt;sub&gt;H&lt;/sub&gt;HAGES Bleeding Risk Index</td>
<td>Total: 9,186</td>
<td>Total median: 3.5 years (IQR 1.2-6.0)</td>
<td>Unclear/NR</td>
<td>None</td>
</tr>
<tr>
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<tr>
<td>Friberg, 2012&lt;sup&gt;27&lt;/sup&gt; Swedish Atrial Fibrillation cohort study</td>
<td>Prospective cohort; Inpatient, Outpatient; Europe; Government, Non-govt, Non-industry; Low risk of bias</td>
<td>Clinical: CHADS2 score, CHA2DS2-VASc score, Framingham score, HAS-BLED, HEMORR2HAGES</td>
<td>Total: 170,291</td>
<td>Total median: 1.4 years</td>
<td>Friberg, 2015&lt;sup&gt;28&lt;/sup&gt;; Total: Renal Failure group: 78.4 (SD: 10.3) No renal failure group: 74.8 (SD: 12.5)</td>
<td>None</td>
</tr>
<tr>
<td>Friberg, 2015&lt;sup&gt;28&lt;/sup&gt;; Friberg, 2012&lt;sup&gt;27&lt;/sup&gt;</td>
<td></td>
<td>Friberg, 2015&lt;sup&gt;28&lt;/sup&gt;: Clinical: HAS-BLED, HEMORR2HAGES</td>
<td>Friberg, 2012&lt;sup&gt;27&lt;/sup&gt;: Individual risk factors: Presence and severity of CKD</td>
<td>Friberg, 2015&lt;sup&gt;28&lt;/sup&gt;; Total median: 2.1 years</td>
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<tr>
<td>Friberg, 2015&lt;sup&gt;28&lt;/sup&gt;</td>
<td></td>
<td>Friberg, 2012&lt;sup&gt;27&lt;/sup&gt;: Clinical: HAS-BLED, HEMORR2HAGES</td>
<td>Friberg, 2015&lt;sup&gt;28&lt;/sup&gt;: Individual risk factors: Age, Prior stroke, Presence of heart disease, Presence and severity of CKD, DM, Sex, Cancer</td>
<td>Friberg, 2015&lt;sup&gt;28&lt;/sup&gt;; Total median: 2.1 years</td>
<td></td>
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</tr>
<tr>
<td>Friberg, 2012&lt;sup&gt;27&lt;/sup&gt;</td>
<td></td>
<td>Total: 182,678</td>
<td>Total median: 1.4 years</td>
<td></td>
<td></td>
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<tr>
<td>Friberg, 2015&lt;sup&gt;28&lt;/sup&gt;</td>
<td></td>
<td>Total: 283,969</td>
<td>Total median: 2.1 years</td>
<td></td>
<td></td>
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<tr>
<td>Friberg, 2015&lt;sup&gt;28&lt;/sup&gt;</td>
<td></td>
<td>Total: 76.2</td>
<td>Total median: 2.1 years</td>
<td></td>
<td></td>
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<tr>
<td>Friberg, 2012&lt;sup&gt;27&lt;/sup&gt;</td>
<td></td>
<td>Total: 78.4 (SD: 10.3) No renal failure group: 74.8 (SD: 12.5)</td>
<td></td>
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<tr>
<td>Friberg, 2012&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Retrospective cohort; Outpatient; US; Government, Non-govt, Non-industry; Low risk of bias</td>
<td>Clinical: HEMORR2HAGES Bleeding Risk Index</td>
<td>Total: 3,791</td>
<td>Total: 0.82 years (3138 PY / 3791 PY)</td>
<td>Total: 80.2</td>
<td>None</td>
</tr>
<tr>
<td>Gage, 2006&lt;sup&gt;85&lt;/sup&gt; NRAF (National Registry of Atrial Fibrillation)</td>
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<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Tools Assessed</td>
<td>Total N</td>
<td>Follow-up period</td>
<td>Age</td>
<td>Special Population</td>
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<tr>
<td>Gallego, 2012**</td>
<td>Retrospective cohort; Outpatient; Europe; Government; Moderate risk of bias</td>
<td>Clinical: HAS-BLED</td>
<td>Total: 965</td>
<td>Total median: 861 days</td>
<td>Total median: 76 (IQR 70-81)</td>
<td>Patients in the therapeutic range</td>
</tr>
<tr>
<td>Granger, 2011**</td>
<td>RCT; Unclear/NR; US, Canada, Europe, Asia, Australia/NZ; Industry; Low risk of bias</td>
<td>Individual risk factors: Presence of heart disease (ISTH/ GUSTO/ TIMI)</td>
<td>Total: 18,201</td>
<td>Total: ~2 years</td>
<td>Arm 1 median: 70 (IQR 63-76)</td>
<td>None</td>
</tr>
<tr>
<td>McMurray, 2013**</td>
<td>ARISTOTLE</td>
<td></td>
<td>McMurray, 2013*: Total median: 18 months</td>
<td></td>
<td>McMurray, 2013*: LVSD: group median: 68 (IQR 60-74)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>HF-PEF group median: 69 (IQR 61-75)</td>
<td></td>
<td>No LVSD/No HF median: 71 (IQR 64-76)</td>
<td></td>
</tr>
<tr>
<td>Giugliano, 2013**</td>
<td>RCT; Outpatient; US; Industry; Low risk of bias</td>
<td>Clinical: Developed a clinical tool</td>
<td>Total: 2,898</td>
<td>Total: 3 years</td>
<td>Total: 71 (IQR 63-77)</td>
<td>VKA naïve patients only</td>
</tr>
<tr>
<td>Paper for KQ 2: Fanola, 2017**</td>
<td>ENGAGE-AF</td>
<td>Individual risk factors include:</td>
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<td>Study Author Year Acronym</td>
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<td>Haas, 2016 &lt;sup&gt;37&lt;/sup&gt; GARFIELD-AF Companions: Bassand, 2016 &lt;sup&gt;39&lt;/sup&gt;, Camm, 2017 &lt;sup&gt;38&lt;/sup&gt;</td>
<td>Prospective cohort; Unclear/NR; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Industry; Low risk of bias</td>
<td>Clinical: None</td>
<td>Total: 9,934</td>
<td>Total: 1 years</td>
<td>Total: 71.2 (SD: 10.2)</td>
<td>None</td>
</tr>
<tr>
<td>Hijazi, 2016 &lt;sup&gt;67&lt;/sup&gt;</td>
<td>RCT; Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia; Industry; Low risk of bias</td>
<td>Clinical: HAS-BLED score ABC Bleeding Risk score Individual risk factors include: INR level</td>
<td>ARISTOTLE: 14,537 RE-LY: 8,461</td>
<td>ARISTOTLE Median follow up 1.2 years RE-LY Median follow-up 1.9 years</td>
<td>ARISTOTLE Median 70 (IQR 19-97) RE-LY Median 72 (IQR 22-95)</td>
<td>None</td>
</tr>
<tr>
<td>Hylek, 2003 &lt;sup&gt;41&lt;/sup&gt; ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)</td>
<td>Retrospective cohort; Outpatient; US; Government; Low risk of bias</td>
<td>INR</td>
<td>Total: 596</td>
<td>Unclear/NR</td>
<td>Arm 1: 79 Arm 2: 80 Arm 3: 76</td>
<td>Patients with prior stroke</td>
</tr>
<tr>
<td>Jaspers, 2016 &lt;sup&gt;88&lt;/sup&gt;</td>
<td>Prospective cohort; Outpatient; Europe; Unclear/NR; Low risk of bias</td>
<td>Clinical: HAS-BLED score HEMORR2HAGES score ATRIA score Individual risk factors include: None</td>
<td>Total: 1,157</td>
<td>Total: 30 months (SD: 10)</td>
<td>Total median: 84 (IQR 82-87)</td>
<td>Age (Very Elderly)</td>
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<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Tools Assessed</td>
<td>Total N</td>
<td>Follow-up period</td>
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<tr>
<td>Jun, 2017&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient, Outpatient, Emergency Room; Canada; Government; Low risk of bias</td>
<td>Clinical: HAS-BLED score Individual risk factors include: Presence and severity of CKD</td>
<td>Total: 14,892</td>
<td>Total: 1 year</td>
<td>Total: 78.1 (SD: 6.8)</td>
<td>Age; Comorbid conditions (such as advanced CKD (eGFR&lt;60), dementia)</td>
</tr>
<tr>
<td>Lind, 2011&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Retrospective cohort; Outpatient; Europe; Unclear/NR; High risk of bias</td>
<td>Individual risk factors include: INR</td>
<td>Total: 19,180</td>
<td>Unclear/NR</td>
<td>Unclear/NR</td>
<td>None</td>
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<tr>
<td>Lip, 2012&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient; Europe; Unclear/NR; Medium risk of bias</td>
<td>Clinical: HAS-BLED HEMORR2HAGES ATRIA Bleeding Risk Index Individual risk factors include: Presence and severity of CKD</td>
<td>Total: 7,156</td>
<td>Banerjee, 2013&lt;sup&gt;49&lt;/sup&gt;: 5,912</td>
<td>Banerjee, 2014&lt;sup&gt;48&lt;/sup&gt;: 36077,156</td>
<td>Arm 1: 77.7 (SD: 8.2) Arm 2: 73.8 (SD: 11.6) Arm 3: 49.0 (SD: 13.1)</td>
</tr>
<tr>
<td>Loire Valley AF Project Companions: Olesen, 2012&lt;sup&gt;47&lt;/sup&gt;; Banerjee, 2013&lt;sup&gt;49&lt;/sup&gt;; Banerjee, 2014&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient; Outpatient; Canada; Government, Industry, Non-govt, Non-industry; Low risk of bias</td>
<td>Clinical: HAS-BLED HEMORR2HAGES ATRIA Bleeding Risk Index</td>
<td>Total: 58,451</td>
<td>Total median: 31 months (IQR 13-59)</td>
<td>Total: 66</td>
<td>Comorbid conditions (such as advanced CDK (eGFR&lt;60))</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Tools Assessed</td>
<td>Total N</td>
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<tr>
<td>O'Brien, 2015 ORBIT-AF</td>
<td>Prospective cohort; Outpatient; US; Government, Industry; Low risk of bias</td>
<td>Clinical: HAS-BLED score ATRIA score (ORBIT –AF) Individual risk factors: Age Presence and severity of CKD</td>
<td>Total: 7411</td>
<td>Total median: 2 years (IQR 1.6-2.5)</td>
<td>Total median: 75 (IQR 68–82)</td>
<td>None</td>
</tr>
<tr>
<td>Olesen, 2011</td>
<td>Retrospective cohort; Inpatient; Europe; Unclear/NR; High risk of bias</td>
<td>Clinical: CHADS2 score CHA2DS2-VASc score</td>
<td>Total: 132,372</td>
<td>Total: Max 12</td>
<td>Arm 1: 72.8 (SD: 14.4) Arm 2: 70.6 (SD: 11.1) Arm 3: 78.1 (SD: 11.2) Arm 4: 73.1 (SD: 9.6)</td>
<td>None</td>
</tr>
<tr>
<td>Olesen, 2011</td>
<td>Retrospective cohort; Inpatient; Europe; Unclear/NR; Low risk of bias</td>
<td>Clinical: HAS-BLED HEMORR2HAGES</td>
<td>Total: 118,584</td>
<td>Total: 10</td>
<td>Arm 1: 78.6 (SD: 10.6) Arm 2: 74.7 (SD: 13.6) Arm 3: 74.6 (SD: 9.2) Arm 4: 71.2 (SD: 10.7)</td>
<td>None</td>
</tr>
<tr>
<td>Orkaby, 2017 VARIA</td>
<td>Retrospective cohort; Inpatient, Outpatient; US; Government; Medium risk of bias</td>
<td>Clinical: N/A Individual risk factors include: Cognitive impairment</td>
<td>Total: 2,572</td>
<td>Total: 2.2 PY following diagnosis of dementia</td>
<td>Total: 79.5 (SD: 6.0)</td>
<td>Patients with newly diagnosed dementia; Older Adults</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Tools Assessed</td>
<td>Total N</td>
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<tr>
<td>Patel, 2011&lt;sup&gt;91&lt;/sup&gt;</td>
<td>RCT; Outpatient; US, Canada, UK, Europe, S. America, Asia, Africa, Australia/NZ; Industry; Low risk of bias; Hankey, 2014&lt;sup&gt;93&lt;/sup&gt;; Moderate risk of bias</td>
<td>Sherwood, 2015&lt;sup&gt;92&lt;/sup&gt;; Clinical: HAS-BLED score Individual risk factors: Age INR level Presence and severity of CKD Sex Hankey, 2014&lt;sup&gt;93&lt;/sup&gt;; Individual risk factors: Age Prior stroke Presence of heart disease Race/ethnicity Goodman, 2014&lt;sup&gt;94&lt;/sup&gt;; Clinical: HAS-BLED score ATRIA</td>
<td>Total: 14,264 Arm 1. 7,131 Arm 2. 7,133</td>
<td>Total median: 707 days Hankey, 2014&lt;sup&gt;93&lt;/sup&gt;; Total median: 1.94 years (IQR 1.42-2.41)</td>
<td>Total median: 73 Arm 1 median: 73 (IQR 65-78) Arm 2 median: 73 (IQR 65-78)</td>
<td>None</td>
</tr>
<tr>
<td>Sherwood, 2015&lt;sup&gt;92&lt;/sup&gt;; Hankey, 2014&lt;sup&gt;93&lt;/sup&gt;; Goodman, 2014&lt;sup&gt;94&lt;/sup&gt;</td>
<td>ROCKET-AF</td>
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<tr>
<td>Peacock, 2017&lt;sup&gt;95&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient, Outpatient, Emergency Room; US; Industry, Non-govt, Non-industry; Low risk of bias</td>
<td>Individual risk factors include: Age Prior stroke *Type of AF Presence of heart disease DM Sex</td>
<td>Total: 44,793</td>
<td>Total: 2.5 years</td>
<td>Total: 78.7 (SD: 7.9)</td>
<td>Military Personnel or Veterans</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Tools Assessed</td>
<td>Total N</td>
<td>Follow-up period</td>
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<tr>
<td>Pisters, 2010&lt;sup&gt;86&lt;/sup&gt; Euro Heart Survey for AF</td>
<td>Prospective cohort; Inpatient, Outpatient; Europe; Industry; Low risk of bias</td>
<td><strong>Clinical:</strong> HAS-BLED HEMORR2HAGES  <strong>Individual risk factors:</strong> Age Prior stroke Presence of heart disease Presence and severity of CKD</td>
<td>Total: 3,456</td>
<td>Total: ~1 years</td>
<td>Total: 66.8 (SD: 12.8)</td>
<td>None</td>
</tr>
<tr>
<td>Poli, 2011&lt;sup&gt;82&lt;/sup&gt;</td>
<td>Prospective cohort; Unclear/NR; Europe; None; Low risk of bias</td>
<td><strong>Clinical:</strong> CHADS&lt;sub&gt;2&lt;/sub&gt; score Bleeding Risk Index</td>
<td>Total: 3,302</td>
<td>Total median: 2.3 (IQR 0.8- 4.4)</td>
<td>Total median: 74 (IQR 68-80)</td>
<td>None</td>
</tr>
<tr>
<td>Renoux, 2017&lt;sup&gt;85&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient, Outpatient; Canada; Industry, Non-govt, Non-industry; Low risk of bias</td>
<td><strong>Clinical:</strong> HAS-BLED  <strong>Individual risk factors include:</strong> Age Sex Prior stroke *Duration and frequency of AF Presence and severity of CKD</td>
<td>Total: 147,622</td>
<td>Total median: 2.9 years</td>
<td>Total median: 75.5 (SD: 11.4)</td>
<td>None</td>
</tr>
<tr>
<td>Roldan, 2012&lt;sup&gt;77&lt;/sup&gt;</td>
<td>Retrospective cohort; Outpatient; Europe; Unclear/NR; Medium risk of bias</td>
<td><strong>Clinical:</strong> ATRIA HAS-BLED</td>
<td>Total: 937</td>
<td>Total median: 952 days (IQR 785-1074)</td>
<td>Total median: 76 (IQR 70-81)</td>
<td>Patients in the therapeutic range</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Tools Assessed</td>
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<td>Ruiz-Nodar, 2012&lt;sup&gt;70&lt;/sup&gt;</td>
<td>Retrospective cohort; Unclear/NR; Europe; Unclear/NR; High risk of bias</td>
<td><strong>Clinical:</strong> HAS-BLED CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc score</td>
<td>Total: 590</td>
<td>Total: ~12 months</td>
<td>Total: 72.2 (SD: 8.1)</td>
<td>None</td>
</tr>
<tr>
<td>Shireman, 2006&lt;sup&gt;71&lt;/sup&gt;</td>
<td>Retrospective cohort; Outpatient; US; Government; Low risk of bias</td>
<td><strong>Clinical:</strong> Bleeding Risk Index</td>
<td>Total: 26,345</td>
<td>Unclear/NR</td>
<td>Unclear/NR</td>
<td>None</td>
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</table>

Abbreviations: AF = atrial fibrillation; IQR = interquartile range; N = number of patients; NR = not reported; PY = patient years; RCT = randomized controlled trial; SD = standard deviation
<table>
<thead>
<tr>
<th>Study Author Year Acronym</th>
<th>Study Design Setting Location Funding Source Quality</th>
<th>Intervention or Tool and Comparators</th>
<th>Total N Interventions (N)</th>
<th>Follow-up period</th>
<th>Age</th>
<th>Special Population</th>
<th>Outcomes Assessed</th>
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</thead>
<tbody>
<tr>
<td>Abraham, 2015&lt;sup&gt;(st)&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient, Outpatient, Emergency Room; US; Non-govt, Non-industry; Low risk of bias</td>
<td>Arm 1: Warfarin Arm 2: Dabigatran Arm 3: Rivaroxaban</td>
<td>Arm 1: 22,787 (full) Arm 2: 7846 (matched 7749 per arm W &amp; D) Arm 3: 5434 (matched 5166 per arm W &amp; R)</td>
<td>Unclear/NR</td>
<td>Arm 1: 72.2 (SD: 9.9) Arm 2: 67.0 (SD: 11.3) Arm 3: 68.4 (SD: 11.1)</td>
<td>None</td>
<td>Bleeding events; GI event</td>
</tr>
<tr>
<td>Abraham, 2017&lt;sup&gt;(st)&lt;/sup&gt; OptumLabs Data Warehouse</td>
<td>Retrospective cohort; Inpatient; Outpatient; US; Non-govt, Non-industry; Low risk of bias</td>
<td>Sub-Study 1: Arm 1: Apixaban Arm 2: Dabigatran Sub-Study 2: Arm 1: Apixaban Arm 2: Rivaroxaban Sub-Study 3: Arm 1: Rivaroxaban Arm 2: Dabigatran</td>
<td>Total: 43,303; Sub-Study 1: 13,084 (6542 per arm) Sub-Study 2: 13,130 (6565 per arm) Sub-Study 3: 31,574 (15,787 per arm)</td>
<td>Sub-Study 1: Arm 1. 89 days (IQR 30-194) Arm 2. 120 (IQR 30-338) Sub-Study 2: Arm 1. 89 (IQR 30-194) Arm 2. 106 (IQR 30-260) Sub-Study 3: Arm 1. 113 (IQR 30-271) Arm 2. 120 (IQR 30-340)</td>
<td>Sub-Study 1: Arm 1. 72.2 (SD: 11.1) Arm 2. 72.1 (SD: 10.5) Sub-Study 2: Arm 1. 72.3 (SD: 11.1) Arm 2. 72.1 (SD: 11.2) Sub-Study 3: Arm 1. 69.2 (SD: 11.6) Arm 2. 69.7 (SD: 11.2)</td>
<td>None</td>
<td>GI bleeding</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Intervention or Tool and Comparators</td>
<td>Total N Interventions (N)</td>
<td>Follow-up period</td>
<td>Age</td>
<td>Special Population</td>
<td>Outcomes Assessed</td>
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<tr>
<td>Azoulay, 2012</td>
<td>Case-control; Outpatient; UK; Industry; Fair</td>
<td>Arm 1: No therapy Arm 2: VKA (warfarin) Arm 3: Aspirin</td>
<td>Total: 70,766 Total: 3.9 years (SD: 3.3) Total: 74.1 (SD: 11.8)</td>
<td>None</td>
<td>Ischemic stroke Intracerebral hemorrhage Composite outcome (CV infarction/stroke, Intracerebral hemorrhage)</td>
<td></td>
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<tr>
<td>Study Author Year Acronym</td>
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<td>Intervention or Tool and Comparators</td>
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<td>Bengtson, 2017&lt;sup&gt;103&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient, Outpatient; US Government, Non-Industry, Non-govt; Low risk of bias</td>
<td>Sub-Study 1: Arm 1. Dabigatran Arm 2. Warfarin Sub-Study 2: Arm 1. Rivaroxaban Arm 2. Warfarin</td>
<td>Sub-Study 1: Arm 1. 18,981 Arm 2. 37,707 Sub-Study 2: Arm 1. 3301 (new and switchers) Arm 2 (8280)</td>
<td>Dabigatran (new users) Median 15 months Rivaroxaban user (new and switchers) Median 8 months</td>
<td>Dabigatran (new users) 68.5 (SD: 12.3) Matched warfarin user 70.8 (SD: 12.1) Rivaroxaban user (new and switchers) 70.4 (SD: 12.0) Matched warfarin user 72.5 (SD: 12.2)</td>
<td>None</td>
<td>Intracranial bleed Ischemic stroke Myocardial infarction Gastrointestinal bleed</td>
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<tr>
<td>Berge, 2000&lt;sup&gt;114&lt;/sup&gt;</td>
<td>RCT; Inpatient; Europe; Non-govt, Non-industry; Good</td>
<td>Arm 1: LMWH (Dalteparin) Arm 2: Aspirin</td>
<td>Total: 449; Arm 1. 224 Arm 2. 225</td>
<td>Total: 14 days</td>
<td>Arm 1: Median 80 (IQR 55-96) Arm 2: Median 80 (IQR 44-98)</td>
<td>Patients with prior stroke</td>
<td>Ischemic stroke Intracerebral hemorrhage All-cause mortality</td>
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<tr>
<td>Study Author Year Acronym</td>
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<td>Beyer-Westendorf, 2016*65</td>
<td>Retrospective cohort; Primary Care; Germany; Industry High risk of bias</td>
<td>Arm 1. VKA Arm 2. Dabigatran Arm 3. Rivaroxaban</td>
<td>Total: 8,607 Arm 1. VKA at 180 days 5,127; VKA at 360 days 2,978 Arm 2. Dabigatran at 180 days 821; Dabigatran at 360 days 374 Arm 3. Rivaroxaban at 180 days 1,317; Rivaroxaban at 360 days 433</td>
<td>Follow-up period of 180 days and 360 days</td>
<td>Arm 1. 74.7 (SD: 9.8); 74.6 (SD: 9.7) Arm 2. 73.9 (10.1); 74.0 (9.8) Arm 3. 74.8 (10.4); 74.3 (10.0)</td>
<td>None</td>
<td>Long-term adherence/persistence to therapy</td>
</tr>
<tr>
<td>Bjorck, 2016*66 Swedish National Patient Register (NPR) and Swedish Prescribed Drug Register</td>
<td>Retrospective cohort; Inpatient, Outpatient; Sweden; Government; High risk of bias</td>
<td>Arm 1. Warfarin with additional anti-platelet therapy Arm 2. Warfarin and aspirin</td>
<td>Total: 40,449 Arm 1. 34,851 Arm 2. 4,311</td>
<td>Unclear/NR</td>
<td>Total: 72.5 (SD: 10.1)</td>
<td>None</td>
<td>Thromboembolism • Arterial • Myocardial infarction • Venous Major bleeding • Gastrointestinal • Intracranial • Other All-cause mortality</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
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<td>Bouillon, 2015 SNIIRAM</td>
<td>Retrospective cohort; Inpatient; Europe (France); Unclear/NR; Low risk of bias</td>
<td>Arm 1: VKA switched to NOAC (rivaroxaban, dabigatran) Arm 2: stayed on VKA therapy (fluindione, warfarin or acenocoumarol)</td>
<td>Total: 17,410; Arm 1 (6,705) Arm 2 (10,705)</td>
<td>Total: 10.0 months (IQR 9.8-10.0)</td>
<td>Total: 75 (IQR 67-82)</td>
<td>None</td>
<td>Intracranial bleeding GIB Ischemic CVA Systemic embolism Death First/recurrent MI Composite: bleeding (any bleeding); ischemic CVA + systemic embolism; Any event of the above</td>
</tr>
<tr>
<td>Bousser, 2008 AMADEUS</td>
<td>RCT; Unclear/NR; US, Canada, UK, Europe, Australia/NZ; Industry; Good</td>
<td>Arm 1: Factor Xa Inhibitors (idraparinux) Arm 2: VKA (Warfarin or acenocoumarol)</td>
<td>Total: 4,576; Arm 1 (2,283) Arm 2 (2,293)</td>
<td>Arm 1: 311 (SD: 161) Arm 2: 339 (SD: 165)</td>
<td>Total: 70.1 (SD: 9.1) Arm 1: 70.1 (SD: 9.0) Arm 2: 70.2 (SD: 9.1)</td>
<td>None</td>
<td>Time in therapeutic range Ischemic stroke Intracerebral hemorrhage Myocardial infarction Systemic embolism Major bleed All-cause mortality Composite outcome: Cerebral infarction, Systemic embolism Composite outcome: Intracerebral hemorrhage, Subdural hematoma, Major bleed, Minor bleed Diagnostic Accuracy</td>
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<td>Study Author Year Acronym</td>
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<tr>
<td>Brown, 2016</td>
<td>Prospective cohort; Inpatient, Outpatient; US; Government, Non-govt, Non-industry; High risk of bias</td>
<td>Arm 1. Rivaroxaban Arm 2. Dabigatran Arm 3. Apixaban</td>
<td>Total: 5,223 Arm 1. 3,455 Arm 2. 1,264 Arm 3. 504</td>
<td>Follow-up period at 3, 6, 9 months</td>
<td>Arm 1. 68.1 (SD: 12.4) Arm 2. 66.5 (SD: 12.3) Arm 3. 70.3 (SD: 12.2)</td>
<td>None</td>
<td>Long-term adherence to therapy</td>
</tr>
<tr>
<td>Burton, 2006</td>
<td>Retrospective cohort; Unclear/NR; UK; Government, Non-govt, Non-industry; Poor</td>
<td>Arm 1: Usual care/OMT Arm 2: Aspirin Arm 3: VKA (Warfarin)</td>
<td>Total: 601</td>
<td>Total: up to 5 years</td>
<td>Total: 77 years Arm 1: 458 PY (SD: 21.48) Arm 2: 721 PY (SD: 33.82) Arm 3: 953 PY (SD: 44.7)</td>
<td>Persistent AF</td>
<td>CV infarction/stroke All-cause mortality Composite outcome: Major bleed, Minor bleed</td>
</tr>
<tr>
<td>Cafolla, 2012</td>
<td>Prospective cohort; Outpatient; Europe; Unclear/NR; Fair</td>
<td>Arm 1: VKA (Warfarin INR 1.5-2.5) Arm 2: VKA (Warfarin INR 2.0-3.0)</td>
<td>Total: 112; Arm 1. 55 Arm 2. 57</td>
<td>Total: 18 months</td>
<td>Arm 1: 86 Arm 2: 85</td>
<td>None</td>
<td>Long-term adherence to therapy</td>
</tr>
<tr>
<td>Chun, 2013</td>
<td>Prospective cohort; Inpatient; Europe; Unclear/NR; High risk of bias</td>
<td>Arm 1: Watchman Arm 2: ACP device</td>
<td>Total: 80</td>
<td>Total: 6-week follow-up</td>
<td>Total: 76 (SD: 9)</td>
<td>None</td>
<td>Thromboembolic events (Thrombus) Cardiac tamponade Safety Duration of follow-up Long-term adherence to therapy</td>
</tr>
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<tr>
<td>Coleman, 2016[1]</td>
<td>Retrospective; Inpatient, Outpatient; US; Industry, Non-govt, Non-industry; Low risk of bias</td>
<td>Arm 1: Rivaroxaban Arm 2: Dabigatran Arm 3: Warfarin</td>
<td>Total: 32,634</td>
<td>Arm 1: 329 days Arm 2: 482 days Arm 3: 454 days</td>
<td>Arm 1: 71.3 (SD: 11.1) Arm 2: 70.9 (SD: 10.8) Arm 3: 71.5 (SD: 11.3)</td>
<td>None</td>
<td>Medication persistence (defined as absent refill gap &gt; 60 days)</td>
</tr>
<tr>
<td>Coleman, 2016[2]</td>
<td>Retrospective cohort; Inpatient, Outpatient; US; Industry, Non-govt, Non-industry; Low risk of bias</td>
<td>Sub-Study 1: Arm 1. Rivaroxaban Arm 2. Warfarin</td>
<td>Total: 30,988; Sub-Study 1: 11,411 per arm Sub-Study 2: 4083 per arm</td>
<td>Not available.</td>
<td>Sub-Study 1: Arm 1: 70.66 (SD: 10.99) Arm 2: 70.72 (SD: 11.35) Sub-Study 2: Arm 1: 71.00 (SD: 11.25) Arm 2: 71.15 (SD:11.12)</td>
<td>None</td>
<td>Intracranial hemorrhage Ischemic CVA Composite: Ischemic CVA + Intracranial hemorrhage</td>
</tr>
<tr>
<td>Coleman, 2016[3]</td>
<td>Retrospective cohort; Outpatient; Europe; Industry; Low risk of bias</td>
<td>Arm 1: Rivaroxaban Arm 2: VKA</td>
<td>Total: 2,078</td>
<td>1 year</td>
<td>Arm 1: 74.0 (SD: 10.7) Arm 2: 74.4 (SD: 9.9)</td>
<td>None</td>
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<tr>
<td>Coleman, 2017[4]</td>
<td>Retrospective; Outpatient; Europe; Industry, Non-govt; Low risk of bias</td>
<td>Arm 1: Apixaban Arm 2: VKA</td>
<td>Total: 1,670; Arm 1. 835 Arm 2. 835</td>
<td>Follow-up in person years Arm 1. 1.809 Arm 2. 2.814</td>
<td>Arm 1. 75.3 (SD: 10.6) Arm 2. 74.8 (SD: 9.2)</td>
<td>None</td>
<td>CVA TIA MI Intracerebral hemorrhage Other non-traumatic intracranial hemorrhage</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
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<tr>
<td>Connolly, 2006 ACTIVE-W</td>
<td>RCT; Unclear/NR; US, Canada, UK, Europe, S. America, Asia, Africa, Australia/NZ; Industry; Good</td>
<td>Arm 1: Clopidogrel; Aspirin Arm 2: VKA (Unspecified)</td>
<td>Total: 6,706; Arm 1: 3,335 Arm 2: 3,371</td>
<td>Total: Median 1.28 years</td>
<td>Arm 1: 70.2 (SD: 9.4) Arm 2: 70.2 (SD: 9.5)</td>
<td>None</td>
<td>Systemic embolism Myocardial infarction CV infarction/stroke Ischemic stroke Intracerebral hemorrhage HRQOL/ Functional capacity All-cause mortality CV mortality Major bleed Minor bleed Composite outcome: Systemic embolism, CV infarction/stroke, Myocardial infarction, CV mortality</td>
</tr>
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<tr>
<td>Connolly, 200913 RE-LY</td>
<td>RCT; Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Good</td>
<td>Arm 1: Dabigatran (110 mg twice daily) Arm 2: Dabigatran (150 mg twice daily) Arm 3: VKA (Warfarin)</td>
<td>Total: 18,113</td>
<td>Total: Median 2.0 years</td>
<td>Arm 1: 71.4 (SD: 8.6) Arm 2: 71.5 (SD: 8.8) Arm 3: 71.6 (SD: 8.6)</td>
<td>None</td>
<td>Compiled all together for ease: Cerebrovascular infarction Systemic embolism DVT Hemorrhagic stroke Intracerebral hemorrhage Extracranial hemorrhage Major bleed Minor bleed Mortality All-cause mortality Cardiovascular mortality Myocardial infarction Health-related quality of life Composite outcomes (include combinations of the above)</td>
</tr>
</tbody>
</table>

Companions: Oldgren, 201116 Eikelboom, 201117 Diener, 201018 Hohnloser, 201219 Nagarakanti, 201120 Hart, 201221 Healey, 201222 Ezekowitz, 200913* Verdecchia, 201724 Lauw, 201725 Brambatti, 2015126 Hijazi, 2014127 Marijon, 201317 Connolly, 2013128 Monz, 2013129 Eikelboom, 2013130

Total: Median 2.0 years | Arm 1: 71.4 (SD: 8.6) Arm 2: 71.5 (SD: 8.8) Arm 3: 71.6 (SD: 8.6) | None | Compiled all together for ease: Cerebrovascular infarction Systemic embolism DVT Hemorrhagic stroke Intracerebral hemorrhage Extracranial hemorrhage Major bleed Minor bleed Mortality All-cause mortality Cardiovascular mortality Myocardial infarction Health-related quality of life Composite outcomes (include combinations of the above) |
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<th>Special Population</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Connolly, 2009[1] ACTIVE-A</td>
<td>RCT; Outpatient; US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ; Industry; Good</td>
<td>Arm 1: Clopidogrel; Aspirin Arm 2: Aspirin</td>
<td>Total: 7,554</td>
<td>Total: 3.6 years</td>
<td>Total: 71</td>
<td>None</td>
<td>CV infarction/stroke Ischemic stroke Intracerebral hemorrhage Myocardial infarction Systemic embolism CV mortality All-cause mortality Major bleed Minor bleed Composite outcome: Systemic embolism, CV infarction/stroke, Myocardial infarction, CV mortality</td>
</tr>
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<tr>
<td>Connolly, 2011[^18]</td>
<td>RCT; Outpatient; Unclear/NR; Industry; Good</td>
<td>Arm 1: Apixaban Arm 2: Aspirin</td>
<td>Total: 5,599</td>
<td>Total: 1.1 years</td>
<td>Arm 1: 70 (SD: 9) Arm 2: 70 (SD: 10)</td>
<td>None</td>
<td>Intracerebral hemorrhage; Systemic embolism; Myocardial infarction; CV infarction/stroke; Subdural hematoma; Minor bleed; Major bleed; Ischemic stroke; All-cause mortality; Healthcare utilization - Hospital admissions Composite outcomes (include combinations of the above)</td>
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<td>Lawrence, 2012[^132] Previous stroke or TIA; No prior CVA Eikelboom, 2012[^133]; Stage III CKD O'Donnell, 2016[^135]; Apixaban group MRIs Ng, 2016[^136]; Age Coppens, 2014[^138]; Flaker, 2012[^139]</td>
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<td>Companions:</td>
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<tr>
<td>Lawrence, 2012[^132]</td>
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<tr>
<td>Eikelboom, 2012[^133]</td>
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<tr>
<td>Eikelboom, 2010[^134]</td>
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<tr>
<td>O'Donnell, 2016[^135]</td>
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<td>Ng, 2016[^136]</td>
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<tr>
<td>Lip, 2014[^137]</td>
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<td>Coppens, 2014[^138]</td>
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<tr>
<td>Flaker, 2012[^139]</td>
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<tr>
<td>Deambrosis, 2017[^140]</td>
<td>Retrospective cohort; Inpatient, Outpatient; Italy; Unclear/NR; High risk of bias</td>
<td>Arm 1. N-VKA group (did not receive any VKA treatment) Arm 2. VKA group (received 6 months of treatment)</td>
<td>Total: 6,138 Arm 1. N-VKA 3,114 Arm 2. VKA 3,024</td>
<td>Total: 37.70 months (IQR 0–85.17) Arm 1. 23.47 months (IQR 0- 85.13) Arm 2. 48.73 months (IQR 6.70- 85.17)</td>
<td>Total: 75.59 (SD: 11.51)</td>
<td>None</td>
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</table>

[^18]: AVERROES
[^132]: Lawrence, 2012
[^133]: Eikelboom, 2012
[^134]: Eikelboom, 2010
[^135]: O'Donnell, 2016
[^136]: Ng, 2016
[^137]: Lip, 2014
[^138]: Coppens, 2014
[^139]: Flaker, 2012
[^140]: Deambrosis, 2017
<table>
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<tbody>
<tr>
<td>Doucet, 2008[142]</td>
<td>Prospective cohort; Inpatient; Europe; Unclear/NR; Poor</td>
<td>Arm 1: VKA (Unspecified) Arm 2: Aspirin</td>
<td>Total: 209; Arm 1: 102 Arm 2: 107</td>
<td>Total: 3 months</td>
<td>Arm 1: 82.9 (SD: 7.1) Arm 2: 86.5 (SD: 6.5)</td>
<td>Permanent AF</td>
<td>Cerebrovascular infarction All-cause mortality Healthcare utilization - Hospital admissions Composite outcome: Major bleed, Minor bleed</td>
</tr>
<tr>
<td>Ezekowitz, 2007[143] PETRO</td>
<td>RCT; Inpatient; US, Europe; Industry; Good</td>
<td>Arm 1: Dabigatran (50 mg twice daily) Arm 2: Dabigatran (150 mg twice daily) Arm 3: Dabigatran (300 mg twice daily) Arm 4: Warfarin</td>
<td>Total: 502</td>
<td>Total: 3 months</td>
<td>Arm 1: 70 (SD: 8.8) Arm 2: 70 (SD: 8.1) Arm 3: 69.5 (SD: 8.4) Arm 4: 69 (SD: 8.3)</td>
<td>None</td>
<td>Major bleed CV infarction/stroke Composite outcome: Major or clinically relevant bleed</td>
</tr>
<tr>
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<td>Figini, 2017&lt;sup&gt;144&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient; Italy; Unclear/NR High risk of bias</td>
<td>Arm 1. Watchman Arm 2. Amplatzer Cardiac Plug (ACP)</td>
<td>Total: 165; Arm 1. 66 Arm 2. 99</td>
<td>Total: 448 days (IQR 167–793)</td>
<td>Total: 72 (SD: 9)</td>
<td>None</td>
<td>Thromboembolic stroke; Hemorrhagic stroke; Major bleeding Gastrointestinal bleeding Intracranial bleeding Other bleeding Minor bleed; Mortality</td>
</tr>
<tr>
<td>Fonseca, 2015&lt;sup&gt;143&lt;/sup&gt; IMS Health’s Charge Detail Master Database</td>
<td>Retrospective cohort; Inpatient, Outpatient; US; Industry; Low risk of bias</td>
<td>Arm 1: Warfarin Arm 2: Dabigatran</td>
<td>Arm 1: 1292; 488 for re-admission analysis Arm 2: 646; 244 for re-admission analysis</td>
<td>30 days</td>
<td>Arm 1: Warfarin= 72.1 (SD: 10.9) Arm 2: Dabigatran= 71.7 (SD: 11.4)</td>
<td>None</td>
<td>Health services utilization (e.g., hospital admissions; costs) Difference in average length of stay</td>
</tr>
<tr>
<td>Forslund, 2016&lt;sup&gt;146&lt;/sup&gt; Administrative health data register of the Stockholm Region</td>
<td>Prospective cohort; Inpatient, Outpatient; Europe; Government; High risk of bias</td>
<td>Arm 1. Warfarin Arm 2. Dabigatran Arm 3. Rivaroxaban Arm 4. Apixaban Arm 5. Aspirin</td>
<td>Total: 17,741 Arm 1. 9,969 Arm 2. 2,701 Arm 3. 2,074 Arm 4. 1,352 Arm 5. 4,540</td>
<td>Follow-up at 1 year and 2 years</td>
<td>Mean age Arm 1. 76.3 Arm 2. 73.8 Arm 3. 75.6 Arm 4. 76.1 Arm 5. 79.5</td>
<td>None</td>
<td>Long-term adherence to therapy</td>
</tr>
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<td>Forslund, 2017&lt;sup&gt;147&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient, Outpatient; Europe; Government, Non-govt, Non-industry; Low risk of bias</td>
<td>Arm 1: Warfarin Arm 2: NOAC (rivaroxaban, apixaban, dabigatran)</td>
<td>Total: 22,198; Arm 1. 12,919 Arm 2. 9,279</td>
<td>Arm 1: 1.61 years Arm 2: 1.07 years</td>
<td>Arm 1: 74.1 (SD: 11.0) Arm 2: 72.9 (SD: 11.1)</td>
<td>None</td>
<td>Ischemic CVA Death Hemorrhagic CVA GIB Hospitalized bleed Composite: TIA/Ischemic CVA+Stroke unspecified+ death; Any severe bleed (defined by: intracranial, GIB, hemothorax, hemipericardium, intraocular, anemia 2/2 to bleed, esophageal); TIA/Ischemic CVA+Stroke unspecified; Any intracranial bleed</td>
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<td>Study Author Year Acronym</td>
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<td>Frost, 2002</td>
<td>Retrospective cohort; Inpatient, Outpatient; Europe; Government, Non-govt, Non-industry; Poor</td>
<td>Arm 1: VKA (Warfarin) Arm 2: No oral anticoagulation</td>
<td>Total: 5,124; Arm 1. 1,390 Arm 2. 3,734</td>
<td>Total: 2.31 years</td>
<td>Unclear/NR</td>
<td>None</td>
<td>CV infarction/stroke</td>
</tr>
<tr>
<td>Giner-Soriano, 2017 ESC-FA (Effectiveness, Safety and Costs in Atrial Fibrillation)</td>
<td>Retrospective cohort; Inpatient, Outpatient, Europe; Government, Non-govt/non-industry, High risk of bias</td>
<td>Arm 1. No antithrombotic Arm 2. Antiplatelets Arm 3. VKAs</td>
<td>Total: 22,205; Arm 1. 5,724 Arm 2. 7,424 Arm 3. 9,057</td>
<td>The total person-time during the follow-up was 44,370.2 PY</td>
<td>Total: 72.8 (SD: 13.1) Arm 1. 69.6 (SD: 16.4) Arm 2. 74.6 (SD: 12.9) Arm 3. 73.4 (SD: 10.3)</td>
<td>None</td>
<td>Cerebral Hemorrhage, Gastrointestinal Hemorrhage, All-cause mortality, Stroke</td>
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<tr>
<td>Study Author Year Acronym</td>
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<td>Companions: Steffel, 2016; Rost, 2016; Bohula, 2016; Magnani, 2016; Gupta, 2016; Xu, 2016; Yamashita, 2016; Eisen, 2016; Geller, 2015; Ruff, 2015; O'Donoghue, 2015; Ruff, 2014; Giugliano, 2014</td>
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<td>Gloekler, 2015&lt;sup&gt;(13)&lt;/sup&gt;</td>
<td>Prospective cohort; Outpatient; Europe; Unclear/NR; High risk of bias</td>
<td>Arm 1: Amplatzer cardiac plug Arm 2: Amulet</td>
<td>Total: 100; Arm 1: 50 Arm 2: 50</td>
<td>Arm 1: 127 (SD: 46) Arm 2: 105 (SD: 48)</td>
<td>Arm 1: 72.5 (SD: 11.5) Arm 2: 75.6 (SD: 9.7)</td>
<td>None</td>
<td>Procedural success Stroke All-cause mortality Cardiac tamponade Bailout by surgery</td>
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<tr>
<td>Gorst-Rasmussen, 2016&lt;sup&gt;(164)&lt;/sup&gt; Danish National Patient Registry</td>
<td>Prospective cohort/registry; Inpatient, Outpatient; Europe, Unclear/NR; Low risk of bias</td>
<td>Arm1. Warfarin (any dose) Arm 2. Dabigatran 110mg Arm 3. Dabigatran 150mg bid Arm 4. Rivaroxaban 15mg Arm 5. Rivaroxaban 20mg qday</td>
<td>Total: 22,358; Arm 1. 11,045 Arm 2. 8,908 Arm 3. 8,908 Arm 4. 2,405 Arm 5. 2,405</td>
<td>Total: 1.08 years (IQR 0.52-1.72) Arm 1. 72.6 (SD: 11.3) Arm 2. 80.8 (SD: 8.0) Arm 3. 66.0 (SD: 8.5) Arm 4. 82.8 (SD: 8.7) Arm 5. 72.8 (SD: 9.9)</td>
<td>None</td>
<td>Ischemic stroke/systemic embolism (SE)/transient ischemic attack (TIA) any bleeding (intracranial bleeding, gastrointestinal, major bleeding events) all-cause death. intracranial bleeding gastrointestinal bleeding myocardial infarction venous thromboembolism</td>
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<td>Graham, 2015[165] Medicare database</td>
<td>Retrospective cohort; Inpatient, Outpatient; US; Government; Low risk of bias</td>
<td>Arm 1. Warfarin Arm 2. Dabigatran</td>
<td>Arm 1. 67,207 Arm 2. 67,207</td>
<td>Unclear/NR</td>
<td>Arm 1. Warfarin: 65–74 years 41% 75–84 43% ≥85 16% Arm 2. Dabigatran: 65–74 years 42% 75–84 43% ≥85 16%</td>
<td>Age ≥ 65 years old</td>
<td>Ischemic stroke, Major bleeding with specific focus on intracranial and gastrointestinal bleeding AMI All hospitalized bleeding events Mortality</td>
</tr>
<tr>
<td>Graham, 2016[166]</td>
<td>Prospective cohort; Unclear/NR, US; Government; Low risk of bias</td>
<td>Arm 1. Dabigatran 150 mg twice daily Arm 2. Rivaroxaban 20 mg once daily.</td>
<td>Arm 1: 52,240 Arm 2: 66,651</td>
<td>Arm 1. Dabigatran mean 108 days (0-969) Arm 2. Rivaroxaban mean 111 days (0-923)</td>
<td>65-74: 50% 75-84: 40% ≥85: 9%</td>
<td>Age &gt;= 65 with Medicare</td>
<td>Thromboembolic stroke Intracranial hemorrhage Major gastrointestinal bleeding Death Acute myocardial infarction</td>
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<td>Study Author Year</td>
<td>Acronym</td>
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<td>Companions: Easton, 2012</td>
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<td>Hohnloser, 2012</td>
<td>168</td>
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<tr>
<td>Lopes, 2010</td>
<td>170*</td>
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<td>Lopes, 2017</td>
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<td>Cowper, 2017</td>
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<td>Westenbrink, 2017</td>
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<td>Hu 2017</td>
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<td>Guimaraes, 2017</td>
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<td>Bahit, 2017</td>
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<td>Alexander, 2016</td>
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<td>Hijazi, 2016</td>
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<td>De Caterina, 2016</td>
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<td>Durheim, 2016</td>
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<td>Vinereanu, 2015</td>
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<td>Avezum, 2015</td>
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<td>Ezekowitz, 2015</td>
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<td>Held, 2015</td>
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<td>Hylek, 2014</td>
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<td>Halvorsen, 2014</td>
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<td>Alexander, 2014</td>
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<td>Wallentin, 2013</td>
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<td>Al-Khatib, 2013</td>
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<td>Hansen, 2010&lt;sup&gt;191&lt;/sup&gt;</td>
<td>Retrospective cohort; Outpatient; Europe; Industry; Good</td>
<td>Arm 1: VKA (Warfarin) Arm 2: Aspirin Arm 3: Clopidogrel Arm 4: Clopidogrel; Aspirin Arm 5: VKA (Warfarin); Aspirin Arm 6: VKA (Warfarin); Clopidogrel Arm 7: VKA (Warfarin); Clopidogrel; Aspirin</td>
<td>Total: 118,606; Arm 1. 50,919 Arm 2. 47,541 Arm 3. 3,717 Arm 4. 2,859 Arm 5. 18,345 Arm 6. 1,430 Arm 7. 1,281</td>
<td>Total: 3.3 years (SD: 2.6)</td>
<td>Total: 73.7 (SD: 12.3)</td>
<td>None</td>
<td>Major bleed</td>
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<td>Study Author Year</td>
<td>Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
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<td>Hart, 2008¹⁹²</td>
<td>CHARISMA</td>
<td>RCT; Unclear/NR; US; Industry; Good</td>
<td>Arm 1: Clopidogrel; Aspirin Arm 2: Aspirin</td>
<td>Total: 583; Arm 1 (298) Arm 2 (285)</td>
<td>Total: 2.3 years</td>
<td>Total: 70</td>
<td>None</td>
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<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
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<td>Johnson, 2016 Clinical Practice Research Datalink (CPRD)</td>
<td>Retrospective cohort; Primary Care; U.K. Industry; High risk of bias</td>
<td>Arm 1. Apixaban Arm 2. Rivaroxaban Arm 3. Dabigatran Arm 4. VKA</td>
<td>Total: 13,089; Arm 1. 541 Arm 2. 1,589 Arm 3. 741 Arm 4. 10,218</td>
<td>Arm 1. 4 months (IQR 2.1-7.3) Arm 2. 5.8 months (IQR 2.6-11.0) Arm 3. 9.4 months (IQR 4.2-15.6) Arm 4. 10.3 months (IQR 5.0-15.9)</td>
<td>Total: 75.0 (IQR 68.0–82.0)</td>
<td>None</td>
<td>Bleeding outcomes; Long-term adherence to therapy (Persistence)</td>
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<tr>
<td>Hohnloser, 2017 CARBOS study</td>
<td>Retrospective cohort; Unclear/NR; Europe; Industry, Non-govt, Non-industry; Low risk of bias</td>
<td>Arm 1. VKA Arm 2. Apixaban Arm 3. Dabigatran Arm 4. Rivaroxaban</td>
<td>Total: 35,013; Arm 1. 16,179 Arm 2. 3,633 Arm 3. 3,138 Arm 4. 12,083</td>
<td>Arm 1. 280 days Arm 2. 218 days Arm 3. 261 days Arm 4. 258 days</td>
<td>Arm 1. 76.1 (SD:9.1) Arm 2. 75.5 (SD: 10.8) Arm 3. 72.6 (SD: 11.2) Arm 4. 73.4 (SD: 11.3)</td>
<td>None</td>
<td>Major bleeding (ED admission) GIB Any bleeding Composite: ischemic CVA + systemic embolism +major bleeding</td>
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<tr>
<td>Study Author Year Acronym</td>
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<tr>
<td>Holmes, 2009 PROTECT-AF</td>
<td>RCT; Inpatient; US, Europe; Industry; Good</td>
<td>Arm 1: Transcatheter: WATCHMAN Arm 2: VKA (Warfarin)</td>
<td>Total: 707; Arm 1. 463 Arm 2. 244</td>
<td>Arm 1: 18 months (SD: 10) Arm 2: 18 months (SD: 10)</td>
<td>Arm 1: 71.7 (SD: 8.8) Arm 2: 72.7 (SD: 9.2)</td>
<td>None</td>
<td>Ischemic stroke CV mortality Intracerebral hemorrhage All-cause mortality Composite outcome: Systemic embolism, CV infarction/stroke, Intracerebral hemorrhage, CV mortality Composite outcome: Major bleed, Minor bleed</td>
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<tr>
<td>Holmes, 2014 PREVAIL</td>
<td>RCT; Outpatient; US; Industry; Fair</td>
<td>Arm 1: WATCHMAN device Arm 2: Warfarin (Control)</td>
<td>Total: 407</td>
<td>Total: 11.8 months (SD: 5.8)</td>
<td>Arm 1: 74 (SD: 7.4) Arm 2: 74.9 (SD: 7.2)</td>
<td>None</td>
<td>Composite outcome: Hemorrhagic or ischemic stroke, SE, and cardiovascular/ unexplained Death Composite outcome: Ischemic stroke or SE Composite outcome: All-cause death, ischemic stroke, SE, or device-procedure-related events</td>
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<td>Study Author Year Acronym</td>
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<td>Hylek, 2003 ATRIA</td>
<td>Retrospective cohort; Outpatient; US; Government; Good</td>
<td>Arm 1: No antithrombotic therapy Arm 2: Aspirin Arm 3: VKA (Warfarin)</td>
<td>Total: 596; Arm 1. 248 Arm 2. 160 Arm 3. 188</td>
<td>Unclear/NR</td>
<td>Arm 1: 79 Arm 2: 80 Arm 3: 76</td>
<td>Patients with prior stroke</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Jacobs, 2009</td>
<td>Retrospective cohort; Outpatient; US; Industry; Poor</td>
<td>Arm 1: VKA (Warfarin) Arm 2: Aspirin</td>
<td>Total: 106; Arm 1. 90 Arm 2. 16</td>
<td>Total: 12 months</td>
<td>all ≥65</td>
<td>None</td>
<td>All-cause mortality Major bleed CV infarction/stroke</td>
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<tr>
<td>Laliberte, 2014</td>
<td>Retrospective cohort; inpatient, outpatient; US; Industry, Non-govt, Non-industry; Low risk of bias</td>
<td>Arm 1: Rivaroxaban Arm 2: Warfarin</td>
<td>Total: 18,270; Arm 1. 3,654 Arm 2. 14,616</td>
<td>Arm 1: 83 Days (SD: 58) Arm 2. 113 days (SD: 70)</td>
<td>Arm 1. 73.3 (SD: 8.4) Arm 2 . 73.7 (SD: 8.3)</td>
<td>None</td>
<td>Medication persistence (gap &lt; 60D) Intracranial hemorrhage GIB Ischemic CVA Hemorrhagic CVA Systemic embolism Composite: major bleed; CVA + systemic embolism</td>
</tr>
<tr>
<td>Laliberte, 2015 Humana database</td>
<td>Retrospective cohort; Inpatient, Outpatient, Emergency Room; US; Industry; Low risk of bias</td>
<td>Arm 1. Warfarin Arm 2. Rivaroxaban</td>
<td>Arm 1. 2,253 Arm 2. 2,253</td>
<td>Arm 1. Warfarin 123.7 days (SD: 91.4) Arm 2. Rivaroxaban 114.0 days (SD: 93.9)</td>
<td>Arm 1. Warfarin 74.5 (SD: 8.7) Arm 2. Rivaroxaban 74.2 (SD: 9.0)</td>
<td>None</td>
<td>Total number of hospitalization days All-cause and afib related: Hospitalizations ED visits Outpatient visits</td>
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<tr>
<td>Study Author Year Acronym</td>
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<tr>
<td>Larsen, 2014²⁰⁷</td>
<td>Retrospective cohort; Unclear/NR; Europe; Unclear/NR; High risk of bias</td>
<td>Arm 1: VKA-naïve stratum Dabigatran 110 mg&lt;br&gt;Arm 2: VKA-naïve stratum Dabigatran 150 mg&lt;br&gt;Arm 3: VKA-naïve stratum Warfarin&lt;br&gt;Arm 4: VKA-experienced stratum Dabigatran 110mg&lt;br&gt;Arm 5: VKA-experienced Dabigatran 150 mg&lt;br&gt;Arm 6: VKA-experienced Warfarin</td>
<td>Arm 1: 3,045&lt;br&gt;Arm 2: 4,018&lt;br&gt;Arm 3: 14,126&lt;br&gt;Arm 4: 2,038&lt;br&gt;Arm 5: 2,214&lt;br&gt;Arm 6: 8,504</td>
<td>13.2 months (SD: 6.1)</td>
<td>Arm 1: 82&lt;br&gt;Arm 2: 67&lt;br&gt;Arm 3: 73&lt;br&gt;Arm 4: 82&lt;br&gt;Arm 5: 69&lt;br&gt;Arm 6: 74</td>
<td>None</td>
<td>Any bleeding&lt;br&gt;Major bleeding&lt;br&gt;Intracranial bleeding (including retinal bleeding and traumatic intracranial bleeding)&lt;br&gt;Gastrointestinal bleeding&lt;br&gt;Fatal bleeding</td>
</tr>
<tr>
<td>Larsen, 2016²⁰⁸ Danish National Patient Registry</td>
<td>Prospective cohort/registry; Inpatient, Outpatient; Europe, Non-govt, Non-industry; Low risk of bias</td>
<td>Arm 1. Warfarin&lt;br&gt;Arm 2. Dabigatran 150mg bid&lt;br&gt;Arm 3. Rivaroxaban 20mg qday&lt;br&gt;Arm 4. Apixaban 5mg bid</td>
<td>Total: 61,678;&lt;br&gt;Arm 1. 35,436&lt;br&gt;Arm 2. 12,701&lt;br&gt;Arm 3. 7,192&lt;br&gt;Arm 4. 6,349</td>
<td>Total mean: 1.9 years&lt;br&gt;Apixaban, mean: 0.9 years</td>
<td>Total: 70.9 (IQR 64.3-77.7)&lt;br&gt;Arm 1. 72.4 (IQR 64.7-79.8)&lt;br&gt;Arm 2. 67.6 (IQR 62.0-72.4)&lt;br&gt;Arm 3. 71.8 (IQR 65.7-78.9)&lt;br&gt;Arm 4. 71.3 (IQR 65.8-77.2)</td>
<td>None</td>
<td>Ischaemic stroke or systemic embolism&lt;br&gt;Ischaemic stroke&lt;br&gt;All cause mortality&lt;br&gt;Ischaemic stroke, systemic embolism, or death&lt;br&gt;Any bleeding&lt;br&gt;Major bleeding&lt;br&gt;Intracranial bleeding</td>
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<tr>
<td>Lauffenburger, 2015</td>
<td>Retrospective cohort; Inpatient, Outpatient; US Government, Non-govt, Non-industry; Low risk of bias</td>
<td>Arm 1. Warfarin Arm 2. Dabigatran</td>
<td>Arm 1. 43,865 Arm 2. 64,935</td>
<td>Total: 358 days (SD: 224)</td>
<td>Total: 69.9 (SD: 12.4)</td>
<td>None</td>
<td>Composite of the occurrence of ischemic stroke, TIA, and other thromboembolic events; Composite of intracranial hemorrhage or hemorrhagic stroke, gastrointestinal (GI) hemorrhage, or other bleeding; MI.</td>
</tr>
<tr>
<td>Lee, 2016</td>
<td>RCT; Inpatient, US; Unclear/NR; Poor</td>
<td>Arm 1: Internal ligation excision Arm 2: Stapled excision Arm 3: Surgical excision</td>
<td>Total: 28</td>
<td>Total: 0.4 years (SD: 0.1)</td>
<td>Arm 1: 69 (SD: 7.0) Arm 2: 67.9 (SD: 8.9) Arm 3: 66.9 (SD: 7.3)</td>
<td>None</td>
<td>Systemic embolism (excludes PE and DVT); Hemorrhagic stroke Major bleed Mortality</td>
</tr>
<tr>
<td>Lee, 2017</td>
<td>Prospective cohort/registry; Unclear/NR Europe; Unclear/NR High risk of bias</td>
<td>Arm 1. VKA Arm 2. ASA Arm 3. VKA + ASA</td>
<td>Total: 71,959; Arm 1. 37,539 Arm 2. 25,458 Arm 3. 8,962</td>
<td>Total median: 4.1 years</td>
<td>Total median: 75 years</td>
<td>All Danish residents hospitalized with first-time AF and without a history of CAD</td>
<td>Myocardial Infarction Stroke Bleeding</td>
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<tr>
<td>Leef, 2015</td>
<td>Retrospective cohort; Inpatient, Outpatient; US; Unclear/NR; Low risk of bias</td>
<td>Arm 1. Warfarin Arm 2. NOAC (includes Dabigatran, Rivaroxaban, and Apixaban)</td>
<td>Arm 1: 554 Arm 2: 554 (Dabigatran, n=475 Rivaroxaban, n=123 Apixaban, n=8)</td>
<td>Total median: 42.5 months</td>
<td>Arm 1. Warfarin: 63.6 (SD: 12.1) Arm 2. NOAC: 64.3 (SD: 11.4)</td>
<td>None</td>
<td>All-cause mortality; stroke (combined ischemic, hemorrhagic, and unspecified)</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
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<td>Li, 2017&lt;sup&gt;213&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient, Outpatient, Emergency Room; US; Unclear/NR; Low risk of bias</td>
<td>Arm 1. Apixaban Arm 2. Warfarin</td>
<td>Arm 1: 38,470 Arm 2: 38,470</td>
<td>Restricted to 1 year follow-up</td>
<td>Arm 1. Apixaban 70.9 (SD: 12.0) Arm 2. Warfarin 70.9 (SD: 11.9)</td>
<td>None</td>
<td>Stroke/SE, Hemorrhagic stroke, Ischemic stroke, SE, Major bleeding, ICH, GI bleeding, Other bleeding</td>
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<tr>
<td>Lin, 2017&lt;sup&gt;214&lt;/sup&gt;</td>
<td>Retrospective cohort; Inpatient, Outpatient; US; Industry, Non-govt, Non-industry; Low risk of bias</td>
<td>Sub-Study 1: Arm 1: Apixaban Arm 2: Rivaroxaban Sub-Study 2: Arm 1: Apixaban Arm 2: Dabigatran Sub-Study 3: Arm 1: Apixaban Arm 2: Warfarin</td>
<td>Total: 23,186; Sub-Study 1: 8,124 Sub-Study 2: 5,368 Sub-Study 3: 9,694</td>
<td>Sub-Study 1 Arm 1. 4.5 months (SD: 4.3) Arm 2. 4.5 months (SD: 4.5) Sub-Study 2 Arm 1. 5.2 months (SD: 5.1) Arm 2. 5.0 months (SD: 5.2) Sub-Study 3 Arm 1. 4.9 months (SD: 4.9) Arm 2. 4.8 months (SD: 4.8)</td>
<td>Sub-Study 1 Arm 1. 62.0 (SD: 8.5) Arm 2. 62.0 (SD: 8.4) Sub-Study 2 Arm 1. 63.0 (SD: 9.2) Arm 2. 63.0 (SD: 9.3) Sub-Study 3 Arm 1. 63.9 (SD: 9.5) Arm 2. 64.0 (SD: 9.4)</td>
<td>None</td>
<td>Inpatient hospitalization, Outpatient office visit, Outpatient prescription claims Major bleed (“includes GI, intracranial hemorrhage and other major bleeds”’’')</td>
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<tr>
<td>Study Author Year Acronym</td>
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<tr>
<td>Lip, 2015\textsuperscript{216} Danish Patient Registry</td>
<td>Retrospective cohort; Inpatient, Outpatient; Europe; Non-govt, Non-industry; High risk of bias</td>
<td>Arm 1: Warfarin Arm 2: Aspirin Arm 3: No Treatment</td>
<td>Total: 39,400</td>
<td>Total: 5.9 years</td>
<td>Total: 59 (51-65)</td>
<td>None</td>
<td>Stroke Intracranial bleeding All-cause mortality</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
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<tr>
<td>Lip, 2016</td>
<td>Retrospective cohort; Unclear/NR; US; Unclear/NR; Low risk of bias</td>
<td>Sub-Study 1: Arm 1. Warfarin Arm 2. Apixaban Sub-Study 2: Arm 1. Warfarin Arm 2. Dabigatran Sub-Study 3: Arm 1. Warfarin Arm 2. Rivaroxaban Sub-Study 4: Arm 1. Apixaban Arm 2. Dabigatran Sub-Study 5: Arm 1. Apixaban Arm 2. Rivaroxaban Sub-Study 6: Arm 1. Dabigatran Arm 2. Rivaroxaban</td>
<td>Sub-Study 1: 13,928 (6,964 per arm) Sub-Study 2: 9,030 (4,515 per arm) Sub-Study 3: 25,250 (12,625 per arm) Sub-Study 4: 8,814 (4,407 per arm) Sub-Study 5: 14,798 (7,399 per arm) Sub-Study 6: 9,314 (4,657 per arm)</td>
<td>In days. Sub-Study 1: Arm 1. 161.6 (SD: 159.0) Arm 2. 14.8.1 (SD: 138.0) Sub-Study 2: Arm 1. 160.5 (SD: 159.7) Arm 2. 178.1 (SD: 179.3) Sub-Study 3: Arm 1. 162.7 (SD: 160.8) Arm 2. 177.9 (SD: 171.5) Sub-Study 4: Arm 1. 145.6 (SD: 136.5) Arm 2. 179.0 (SD: 179.1) Sub-Study 5: Arm 1. 147.6 (SD: 137.6) Arm 2. 182.1 (SD: 174.9) Sub-Study 6: Arm 1. 177.3 (SD: 178.7) Arm 2. 172.5 (SD: 169.5)</td>
<td></td>
<td>None</td>
<td>Major bleeding (definition: requiring hospitalization)</td>
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<td>Study Author Year</td>
<td>Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
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<td>Lip, 2017&lt;sup&gt;219&lt;/sup&gt;</td>
<td>Danish National Prescription Registry</td>
<td>Prospective cohort/registry; Unclear/NR Europe; Unclear/NR; Low risk of bias</td>
<td>Arm 1. Apixaban 5mg bid Arm 2. Dabigatran 150mg bid Arm 3. Rivaroxaban 20mg day Arm 4. Warfarin</td>
<td>Total: 14,020; Arm 1. 1,470 Arm 2. 3,272 Arm 3. 1,604 Arm 4. 7,674</td>
<td>Total: 2.6 years (SD: 1.6)</td>
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<td>Lorenzoni, 2004&lt;sup&gt;220&lt;/sup&gt;</td>
<td>CLAAF</td>
<td>RCT; Outpatient; Europe; Industry; Fair</td>
<td>Arm 1: VKA (Warfarin) Arm 2: Clopidogrel; Aspirin</td>
<td>Total: 30; Arm 1. 14 Arm 2. 16</td>
<td>Arm 1: 3 months Arm 2: 3 months</td>
<td>Arm 1: Median 72 Arm 2: Median 68</td>
<td>None</td>
</tr>
<tr>
<td>Mant, 2007&lt;sup&gt;221&lt;/sup&gt;</td>
<td>BAFTA</td>
<td>RCT; Inpatient; UK; Non-govt, Non-industry; Good</td>
<td>Arm 1: VKA (Warfarin) Arm 2: Aspirin</td>
<td>Total: 973; Arm 1. 488 Arm 2. 485</td>
<td>Total: 2.7 years (SD: 1.2)</td>
<td>Arm 1: 81.5 (SD: 4.3) Arm 2: 81.5 (SD: 4.2)</td>
<td>None</td>
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<tr>
<td>Study Author Year Acronym</td>
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<td>Mar Contreras Muruaga, 2017</td>
<td>Cross-sectional; Unclear/NR; Europe; Industry; Low risk of bias</td>
<td>Arm 1: VKA Arm 2: DOAC (Rivaroxaban, Apixaban, Dabigatran)</td>
<td>Total: 1,337; Arm 1. 750 Arm 2. 587</td>
<td>Total: 36.7 months (SD: 48.5)</td>
<td>Arm 1. 52.28 months Arm 2. 17.07 months</td>
<td>Total: 75.0 (SD: 8.9) Arm 1. 75.3 (SD: 9.2) Arm 2. 76.1 (SD: 8.5)</td>
<td>None</td>
</tr>
<tr>
<td>Martinez, 2016</td>
<td>Prospective cohort; Outpatient, UK; Unclear/NR; Low risk of bias</td>
<td>Arm 1. VKAs: includes acenocoumarol, phenindione or warfarin Arm 2. NOACs: includes apixaban, dabigatran or rivaroxaban</td>
<td>Arm 1: 12,307 Arm 2: 914</td>
<td>Unclear/NR</td>
<td>Arm 1. VKAs: 74.4 (SD: 10.4) Arm 2. NOACs: 74.5 (SD: 11.3)</td>
<td>None, but results also stratified by risk score</td>
<td>Persistence with OAC, was estimated using competing risk survival analyses accounting for switching of type of OAC and mortality as competing risks</td>
</tr>
<tr>
<td>Monaco, 2017</td>
<td>Retrospective cohort; Patient data; Europe; Unclear/NR; High risk of bias</td>
<td>Arm 1: DOACs ROR Arm 2: Rivaroxaban Arm 3: Apixaban Arm 4: Dabigatran</td>
<td>Total: 32,972</td>
<td>Unclear/NR</td>
<td>Total: 75.6 (SD: 10.1)</td>
<td>None</td>
<td>Cerebrovascular infarction Stroke Gastrointestinal hemorrhage Intracerebral hemorrhage Muscular weakness Renal impairment</td>
</tr>
<tr>
<td>Nelson, 2014</td>
<td>Retrospective cohort; Inpatient, Outpatient; US; Industry, Non-govt, Non-industry; Low risk of bias</td>
<td>Arm 1. Rivaroxaban Arm 2. Warfarin</td>
<td>Total: 14,518; Arm 1. 7,259 Arm 2. 7,259</td>
<td>Arm 1. 184 days Arm 2. 408 days</td>
<td>Arm 1. 71.6 (SD: 11.8) Arm 2. 71.6 (SD: 11.7)</td>
<td>None</td>
<td>Medication persistence (defined as absent refill gap &gt; 60 days)</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
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<td>Nielsen, 2017\textsuperscript{229} Danish National Patient Registry, Other: Danish national prescription registry; Danish civil registration system</td>
<td>Prospective cohort/registry; Inpatient, Outpatient; Europe; Non-govt, Non-industry; Low risk of bias</td>
<td>Arm 1. Warfarin Arm 2. Dabigatran 110mg bid Arm 3. Rivaroxaban 15mg qday Arm 4. Apixaban 2.5mg bid</td>
<td>Total: 55,644; Arm 1. 38,893 Arm 2. 8,875 Arm 3. 3,476 Arm 4. 4,400 Total mean: 2.3 years</td>
<td>Apixaban mean: 1 year</td>
<td>Total: 73.9 (SD: 12.7)</td>
<td>Arm 1: 71.0 (SD: 12.6) Arm 2: 79.9 (SD: 9.0) Arm 3: 77.9 (SD: 13.5) Arm 4: 83.9 (SD: 8.2)</td>
<td>None, but more older age and renal disease given reduced dosing Ischaemic stroke/systemic embolism Ischaemic stroke All cause mortality Major bleeding Any bleeding Haemorrhagic stroke</td>
</tr>
<tr>
<td>Noseworthy, 2016\textsuperscript{230} Other: Optum Labs Data Warehouse</td>
<td>Retrospective cohort; Inpatient, Outpatient; US; Non-govt, Non-industry; Low risk of bias</td>
<td>Sub-Study 1: Arm 1. Rivaroxaban Arm 2. Dabigatran Sub-Study 2: Arm 1. Apixaban Arm 2. Dabigatran Sub-Study 3: Arm 1. Apixaban Arm 2. Rivaroxaban</td>
<td>Total: 57,788; Sub-Study 1: 31,574 (15,787 per arm) Sub-Study 2: 13,084 (6,543 per arm) Sub-Study 3: 13,130 (6565 per arm)</td>
<td>Not available</td>
<td>Sub-Study 1: Arm 1. 70 (IQR 62-78) Arm 2. 71 (IQR 62-78) Sub-Study 2: Arm 1. 73 (IQR 65-81) Arm 2. 73 (IQR 65-81) Sub-Study 3: Arm 1. 73 (IQR 65-81) Arm 2. 73 (IQR 65-81)</td>
<td>None</td>
<td>Ischemic CVA Hemorrhagic CVA Intracranial bleed Major bleed (GIB, intracranial, other) Composite: stroke + systemic embolism</td>
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<tr>
<td>Olesen, 2011\textsuperscript{15}</td>
<td>Retrospective cohort; Inpatient; Europe; Unclear/NR; Poor</td>
<td>Arm 1: Placebo Arm 2: VKA (unspecified) Arm 3: Aspirin Arm 4: VKA (unspecified); Aspirin</td>
<td>Total: 132,372; Arm 1. 58,883 Arm 2. 37,425 Arm 3. 24,984 Arm 4. 11,080 Total: Max 12 years</td>
<td>Arm 1: 72.8 (SD: 14.4) Arm 2: 70.6 (SD: 11.1) Arm 3: 78.1 (SD: 11.2) Arm 4: 73.1 (SD: 9.6)</td>
<td>None</td>
<td>Diagnostic Accuracy</td>
<td></td>
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<tr>
<td>Study Author Year Acronym</td>
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<td>Patel, 2011 ROCKET-AF</td>
<td>RCT; Outpatient; US, Canada, UK, Europe, S. America, Asia, Africa, Australia/NZ; Industry; Good</td>
<td>Arm 1: Rivaroxaban Arm 2: VKA (Warfarin)</td>
<td>Total: 14,264; Arm 1. 7,131 Arm 2. 7,133</td>
<td>Total median: 707 days</td>
<td>Total median: 73</td>
<td>None</td>
<td>Major bleed Ischemic stroke CV infarction/stroke Composite outcome (includes combinations of multiple outcomes including the above)</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
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<td>Rash, 2007²⁵¹ WASPO</td>
<td>RCT; Outpatient; UK; Unclear/NR; Good</td>
<td>Arm 1: VKA (Warfarin) Arm 2: Aspirin</td>
<td>Total: 75; Arm 1. 36 Arm 2. 39</td>
<td>Total: 12 months</td>
<td>Total: 83 (IQR 80-90) Arm 1: 83.5 (IQR 80-90) Arm 2: 82.6 (IQR 80-90)</td>
<td>Permanent AF</td>
<td>All-cause mortality TIA Composite outcome: TIA, Major bleed, Ischemic stroke</td>
</tr>
<tr>
<td>Ruiz Ortiz, 2010²⁴⁸</td>
<td>Prospective cohort; Outpatient; Europe; Non-govt, Non-industry; Fair</td>
<td>Arm 1: OAC Arm 2: Non-OAC</td>
<td>Total: 796; Arm 1. 564 Arm 2. 232</td>
<td>Total: 2.4 years (SD: 1.9)</td>
<td>Total: 73 (SD: 8)</td>
<td>Permanent AF</td>
<td>Major bleed All-cause mortality Composite outcome: TIA, Ischemic stroke Diagnostic Accuracy, Diagnostic Thinking/Therapeutic Efficacy</td>
</tr>
<tr>
<td>Sam, 2004²⁵² Framingham</td>
<td>Retrospective cohort; Outpatient; US; Government; Fair</td>
<td>Arm 1: no therapy Arm 2: Aspirin Arm 3: VKA (Warfarin)</td>
<td>Total: 393; Arm 1 231 Arm 2 82 Arm 3 80</td>
<td>Arm 1: ~ 5 years Arm 2: ~ 5 years Arm 3: ~ 5 years</td>
<td>Arm 1: 77.3 (SD: 10.6) Arm 2: 76.4 (SD: 10.6) Arm 3: 70.7 (SD: 11.4)</td>
<td>None</td>
<td>Major bleed Minor bleed Intracerebral hemorrhage</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Intervention or Tool and Comparators</td>
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<td>Schmid, 2013253</td>
<td>Prospective cohort; Inpatient; Europe Industry, Non-govt, Non-industry; High risk of bias</td>
<td>Arm 1: Amplatzer NDA Arm 2: ACP device</td>
<td>Total: 64</td>
<td>Total: 7.2 months (SD: 2.7)</td>
<td>Total: 66 (SD: 9)</td>
<td>None</td>
<td>Major bleeding Thrombus Mortality Procedural complications Device embolisation Stroke</td>
</tr>
<tr>
<td>Seeger, 2015254</td>
<td>Two commercial health insurance databases (MarketScan, Truven and Clininformatics, Optum)</td>
<td>Arm 1. Warfarin Arm 2. Dabigatran</td>
<td>Arm 1: 19,189 Arm 2: 19,189</td>
<td>Arm 1. Mean 0.34 years Arm 2. Mean 0.42 years</td>
<td>Arm 1. 68.33 (SD: 12.2) Arm 2. 68.73 (SD: 12.0)</td>
<td>None but entire cohort and by sub-groups by age, gender, and comorbidities</td>
<td>Hospitalization for Haemorrhagic or Ischaemic stroke; major bleeding, Stroke or embolism, Systemic embolism, Ischemic stroke, Hemorrhagic stroke, MI, Major intracranial bleeding, GI bleeding</td>
</tr>
<tr>
<td>Seeger, 2017255</td>
<td>Retrospective cohort; Inpatient, Outpatient; US; Industry, Non-govt, Non-industry; Low risk of bias</td>
<td>Sub-Study 1: Matched in MarketScan Arm 1: Dabigatran Arm 2: Warfarin Sub-Study 2: Matched in Clininformatics Arm 1: Dabigatran Arm 2: Warfarin</td>
<td>Total: 38,378; Sub-Study 1 Arm 1. 15,529 Arm 2. 15,529 Sub-Study 2 Arm 1. 3,660 Arm 2. 3,660</td>
<td>Unclear/NR</td>
<td>Sub-Study 1: Arm 1. 68.7 (SD: 12.0) Arm 2. 68.3 (SD: 12.2) Sub-Study 2: Arm 1. 63.4 (SD: 10.9) Arm 2. 63.1 (SD: 10.9)</td>
<td>None</td>
<td>CVA (hemorrhagic or ischemic) Major bleeding (including intracranial or extracranial)</td>
</tr>
<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Intervention or Tool and Comparators</td>
<td>Total N Interventions (N)</td>
<td>Follow-up period</td>
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<tr>
<td>Shireman, 2004\textsuperscript{256} Medicaid National Stroke Project</td>
<td>Retrospective cohort; Inpatient; US; Non-govt, Non-industry; Fair</td>
<td>Arm 1: VKA (Warfarin) Arm 2: VKA (Warfarin); Clopidogrel or Aspirin or Ticlopidine</td>
<td>Total: 10,093; Arm 1. 8,131 Arm 2. 1,962</td>
<td>Total: 90 days</td>
<td>Total: 77.2</td>
<td>None</td>
<td>Major bleed Composite outcome: Intracerebral hemorrhage, Subdural hematoma</td>
</tr>
<tr>
<td>Staerk, 2015\textsuperscript{257} Danish Patient Registry</td>
<td>Retrospective cohort; Inpatient, Outpatient; Europe; Non-govt, Non-industry; High risk of bias</td>
<td>Arm 1: OAC-naive warfarin Arm 2: OAC-naive dabigatran 110 Arm 3: OAC-naive dabigatran 150 Arm 4: OAC-experienced dabigatran 110 Arm 5: OAC-experienced dabigatran 150</td>
<td>Total: 10,437</td>
<td>Total: 244 days (IQR 105–377)</td>
<td>Total: 71.2 (SD: 11.0)</td>
<td>None</td>
<td>Dyspepsia Gastrointestinal bleeding Long-term adherence to therapy</td>
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<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Intervention or Tool and Comparators</td>
<td>Total N Interventions (N)</td>
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<td>Stellbrink, 2004 [59] ACE</td>
<td>RCT; Inpatient, Outpatient; Europe; Industry; Fair</td>
<td>Arm 1: LMWH (Enoxaparin) Arm 2: VKA (Phenprocoumon); UFH (IV Heparin)</td>
<td>Total: 496; Arm 1. 248 Arm 2. 248</td>
<td>Total: 28-49 days</td>
<td>Arm 1: 66 (SD: 11) Arm 2: 65 (SD: 11)</td>
<td>None</td>
<td>Systemic embolism Cerebrovascular infarction TIA All-cause mortality Major bleed Minor bleed CV mortality Composite outcome: Cerebrovascular infarction, TIA, Systemic embolism, Major bleed, All-cause mortality</td>
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<tr>
<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Intervention or Tool and Comparators</td>
<td>Total N Interventions (N)</td>
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<td>Tsivgoulis, 2005</td>
<td>Prospective cohort; Inpatient, Outpatient; Europe; Unclear/NR; Good</td>
<td>Arm 1: VKA (Warfarin) Arm 2: Aspirin</td>
<td>Total: 207; Arm 1. 72 Arm 2. 135</td>
<td>Total 88.4 months (IQR 3-120)</td>
<td>Arm 1: 79.9 (SD: 2.8) Arm 2: 80.7 (SD: 3.1)</td>
<td>Patients with prior stroke</td>
<td>All-cause mortality Composite outcome: Cerebrovascular infarction, Systemic embolism</td>
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<tr>
<td>Vaughan Sarrazin, 2014</td>
<td>Retrospective cohort; VA patient data; US; Government; High risk of bias</td>
<td>Arm 1: VKA (warfarin) Arm 2: Dabigatran</td>
<td>Arm 1: 83,950 Arm 2: 1,394</td>
<td>Unclear/NR</td>
<td>Arm 1: 74.4 (SD: 10.1) Arm 2: 69.7 (SD: 9.0)</td>
<td>None</td>
<td>Any bleeding Gastrointestinal hemorrhage Intracranial hemorrhage Hemorrhage – other site All cause mortality</td>
</tr>
<tr>
<td>Vemmos, 2004</td>
<td>Prospective cohort; Inpatient, Outpatient; Europe; Unclear/NR; Fair</td>
<td>Arm 1: VKA (Warfarin) Arm 2: Aspirin</td>
<td>Total: 191; Arm 1. 67 Arm 2. 124</td>
<td>Total: 50.4 months (IQR 12 to 60)</td>
<td>Arm 1: 74.6 (SD: 6.5) Arm 2: 76.2 (SD: 6.9)</td>
<td>Patients with prior stroke</td>
<td>All-cause mortality Major bleed Composite outcome: Systemic embolism, Ischemic stroke</td>
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<td>Study Author Year Acronym</td>
<td>Study Design Setting Location Funding Source Quality</td>
<td>Intervention or Tool and Comparators</td>
<td>Total N Interventions (N)</td>
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<tr>
<td>Vemmos, 2006</td>
<td>RCT; Outpatient; Europe; Unclear/NR; Fair</td>
<td>Arm 1: Aspirin Arm 2: VKA (Warfarin 1mg/day fixed dose) Arm 3: VKA (Warfarin adjusted dose)</td>
<td>Total: 45; Arm 1: 15 Arm 2: 14 Arm 3: 16</td>
<td>Total: 3.7 months (IQR 1-6)</td>
<td>Arm 1: 79.5 (SD: 2.9) Arm 2: 79.9 (SD: 1.7) Arm 3: 80.1 (SD: 2.5)</td>
<td>None</td>
<td>Ischemic stroke Systemic embolism All-cause mortality Myocardial infarction Major bleed</td>
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<td>Villines, 2015</td>
<td>DoD database Retrospective cohort; Inpatient, Outpatient; US; Industry; Low risk of bias</td>
<td>Arm 1: Warfarin Arm 2: Dabigatran</td>
<td>Arm 1: 12,793 Arm 2: 12,793</td>
<td>Arm 1. Warfarin 217.2 days (SD: 222.9) Arm 2. Dabigatran 297.3 days (258.1)</td>
<td>Arm 1. 74.0 (SD: 9.0) Arm 2. 73.8 (SD: 9.3)</td>
<td>None</td>
<td>Stroke Major bleeding Ischemic stroke Hemorrhagic stroke Major intracranial bleeding Major GI bleeding MI Death</td>
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<td>Weir, 2017</td>
<td>Optum's Integrated Claims-Clinical de-identified dataset Retrospective cohort; Inpatient; Outpatient; ER; US; Industry; Non-govt, Non-industry; Low risk of bias</td>
<td>Sub-Study 1: (eCrCl &lt; 50) Arm 1. Rivaroxaban Arm 2. Warfarin Sub-Study 2: (eCrCl 50-80) Arm 1. Rivaroxaban Arm 2. Warfarin Sub-Study 3: (eCrCl &gt;80) Arm 1. Rivaroxaban Arm 2. Warfarin</td>
<td>Total: 3,756; Sub-Study 1: Arm 1. 427 Arm 2. 447 Sub-Study 2: Arm 1. 655 Arm 2. 720 Sub-Study 3: Arm 1. 713 Arm 2. 794</td>
<td>Sub-Study 1: Arm 1. 232 days (SD: 202) Arm 2. 275 (SD: 243) Sub-Study 2: Arm 1. 222 (SD: 215) Arm 2. 257 (SD: 230) Sub-Study 3: Arm 1. 231 (SD: 222) Arm 2. 223 (SD: 226)</td>
<td>Categorized into percentages in the following groups: &lt;65, 65-75, &gt;75</td>
<td>None</td>
<td>Ischemic CVA Major bleed (defined by Cunningham et al.) Composite: VTE+MI+CVA</td>
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<td>Study Author Year</td>
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<td><strong>Abbreviations:</strong> AF = atrial fibrillation; IQR = interquartile range; N = number of patients; NR = not reported; PY = patient years; RCT = randomized controlled trial; SD = standard deviation</td>
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<td><strong>Yigit, 2003</strong></td>
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<td><strong>RCT; Inpatient, Outpatient Turkey; Unclear/NR; Fair</strong></td>
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<td>Arm 1: TEE; VKA (Warfarin); LMWH (Dalteparin)</td>
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<td>Arm 2: TEE; VKA (Warfarin); UFH (IV Heparin)</td>
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<td>Total: 170; Arm 1: 1.89 Arm 2: 2.81</td>
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<td>Total: 6 months Arm 1: 4 weeks Arm 2: 4 weeks</td>
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<td>Total: 62.6 (SD: 10.2) Arm 1: 63.4 (SD: 9.4) Arm 2: 61.9 (SD: 10.2)</td>
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<td>Persistent AF</td>
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<td><strong>Systemic embolism</strong></td>
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<td><strong>Yao, 2016</strong></td>
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<td>OptumLabs Data Warehouse (OLDW), Retrospective; Inpatient, Outpatient, US; Non-govt, Non-industry; Low risk of bias</td>
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<td>Sub-Study 1: Arm 1. Apixaban Arm 2. Warfarin</td>
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<td>Sub-Study 2: Arm 1. Dabigatran Arm 2. Wafarin</td>
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<td>Sub-Study 3: Arm 1. Rivaroxaban Arm 2. Warfarin</td>
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<td>Total: 76,354; Sub-Study 1: 15,390 (7,695 in each arm) Sub-Study 2: 28,614 (14,307 in each arm) Sub-Study 3: 32,350 (16,175 in each arm)</td>
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<td>Sub-Study 1: 0.5 years (SD: 0.6) Sub-Study 2: 0.7 years (SD: 0.8) Sub-Study 3: 0.6 years (SD: 0.7)</td>
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<td>Sub-Study 1: Arm 1. 7.3 (IQR 66-81) Arm 2. 7.3 (IQR 66-81) Sub-Study 2: Arm 1. 7.3 (IQR 62-78) Arm 2. 7.3 (IQR 61-78) Sub-Study 3: Arm 1. 7.2 (IQR 64-79) Arm 2. 7.2 (IQR 64-80)</td>
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<td>None</td>
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<td><strong>Ischemic CVA Hemorrhagic CVA Intracranial bleed GIB</strong></td>
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<td><strong>Composite:</strong> CVA + systemic embolism; Major bleed (def: GI, intracranial and other sites)</td>
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<td><strong>Weitz, 2010</strong></td>
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<td>RCT; Outpatient; Unclear/NR; Industry; Good</td>
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<td>Arm 1: Edoxaban (30mg qd) Arm 2: Edoxaban (30mg bid) Arm 3: Edoxaban (60mg qd) Arm 4: Edoxaban (60mg bid) Arm 5: VKA (Warfarin)</td>
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<td>Total: 1,143; Arm 1: 235 Arm 2: 244 Arm 3: 234 Arm 4: 180 Arm 5: 250</td>
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<td>Total: 12 weeks Arm 1: 65.2 (SD: 8.3) Arm 2: 64.8 (SD: 8.8) Arm 3: 64.9 (SD: 8.8) Arm 4: 64.7 (SD: 9.0) Arm 5: 66.0 (SD: 8.5)</td>
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<td>Arm 1: 65.2 (SD: 8.3) Arm 2: 64.8 (SD: 8.8) Arm 3: 64.9 (SD: 8.8) Arm 4: 64.7 (SD: 9.0) Arm 5: 66.0 (SD: 8.5)</td>
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<td>Persistent AF</td>
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<td>Major bleed Minor bleed Myocardial infarction CV mortality Composite outcome: Cerebrovascular infarction, TIA, Intracerebral hemorrhage, Ischemic stroke</td>
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<td><strong>Abbreviations:</strong> AF = atrial fibrillation; IQR = interquartile range; N = number of patients; NR = not reported; PY = patient years; RCT = randomized controlled trial; SD = standard deviation</td>
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References in Appendix F


Patients Not Eligible for Warfarin Use

Three studies have specifically looked at effectiveness of therapy in patients who were considered unsuitable for warfarin therapy.\(^1-3\) The ACTIVE-A trial\(^1\) was designed to determine whether the combination of clopidogrel (75mg daily) plus aspirin (75 to 100mg daily) was better than aspirin alone for prevention of stroke and cardiovascular events (non-CNS embolism, MI, or vascular death) in patients with AF and at least one additional risk factor for vascular events who were considered unsuitable for warfarin therapy. A total of 7,554 patients were enrolled in a double-blind fashion from 580 centers in 33 countries, and the median followup was 3.6 years. In the ITT analyses, the combination of clopidogrel plus aspirin compared with aspirin alone significantly reduced the primary outcome by 11 percent, primarily due to a 28 percent reduction in stroke (ischemic or unknown origin) (RR 0.72; 95% CI 0.62 to 0.83; \(p<0.001\)). MI occurred in 90 patients in the clopidogrel group (0.7% per year) and in 115 in the placebo group (0.9% per year; RR 0.78; 95% CI 0.59 to 1.03; \(p=0.08\)). Importantly, clopidogrel plus aspirin compared with aspirin alone significantly increased the rate of major bleeding, including intracranial and extracranial bleeding, from 1.3 percent to 2.0 percent per year (RR 1.57; 95% CI 1.29 to 1.92; \(p<0.001\)). The rates of bleeding in the clopidogrel plus aspirin group were very similar to those observed in the warfarin arm from the ACTIVE-W study. One should also keep in mind that among the reasons for enrolling in this trial, 50 percent of the time this was due to physician assessment that the patient was inappropriate for warfarin and therefore could be in the study, which is a subjective decision. On the other hand, it is known that this subjective decision from physicians is common in clinical practice, and the results of this trial might be applicable to daily practice. In summary, if we treat 1,000 AF patients that “cannot be put on warfarin” during 3 years, clopidogrel plus aspirin would prevent 28 strokes and 6 MIs, but it would cause 20 major bleeding events, 3 of them fatal. Thus, caution is warranted when considering clopidogrel plus aspirin for patients with AF for stroke prevention.

In the light of the ACTIVE-A results, another recent study deserves special attention. In patients with AF who failed, or were unsuitable for VKA treatment, apixaban (5mg orally twice daily) was compared with aspirin (81–324mg daily) in the AVERROES trial, a randomized, double-blind, and multicenter study.\(^3\) In a prespecified analysis of the AVERROES trial, results were consistent in the subgroup of patients who tried but failed VKA therapy. Of 5599 patients, 2216 (40%) had previously failed VKA treatment [main reasons: poor international normalized ratio (INR) control 42%, refusal 37%, bleeding on VKA 8%]. Compared with those expected to be unsuitable for VKA therapy, those who had previously failed were older, more often male, had higher body mass index, more likely to have moderate renal impairment and a history of stroke and less likely to have heart failure or to be medically undertreated. The effects of apixaban compared with aspirin were consistent in those who previously failed and those who were expected to be unsuitable, for both SSE (\(p=0.13\) for interaction) and major bleeding (\(p=0.74\) for interaction) and were also consistent among different subgroups of patients who had previously failed VKA therapy defined by reasons for unsuitability, age, sex, renal function, CHADS2 score, aspirin dose, duration, indication, and quality of INR control of prior VKA use.

A subanalysis of the AVERROES trial explored the patterns of bleeding during treatment and defined bleeding risks based on stroke risk with aspirin versus apixaban in patients with
atrial fibrillation unsuitable for warfarin. The rate of a bleeding event was 3.8% per year with aspirin and 4.5% per year with apixaban (hazard ratio with apixaban, 1.18; 95% CI 0.92-1.51; P=0.19). The anatomic site of bleeding did not differ between therapies. Risk factors for bleeding common to apixaban and aspirin were use of non-study aspirin>50% of the time and a history of daily/occasional nosebleeds. The rates of both stroke and bleeding increased with higher CHADS2 scores but apixaban compared with aspirin was associated with a similar relative risk of bleeding (p=0.21 for interaction) and a reduced relative risk of stroke (p=0.37 for interaction) irrespective of CHADS2 category.

In a multicenter prospective, nonrandomized trial the ASAP study evaluated left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation. The purpose of this study was to assess the safety and efficacy of left atrial appendage (LAA) closure in nonvalvular atrial fibrillation patients ineligible for warfarin therapy. The mean CHADS score and CHADS-VASc (CHADS score plus 2 points for age ≥75 years and 1 point for vascular disease, age 65 to 74 years, or female sex) score were 2.8 ± 1.2 and 4.4 ± 1.7, respectively. History of hemorrhagic/bleeding tendencies (93%) was the most common reason for warfarin ineligibility. Mean duration of followup was 14.4 ± 8.6 months. Serious procedure- or device-related safety events occurred in 8.7% of patients (13 of 150 patients). All-cause stroke or systemic embolism occurred in 4 patients (2.3% per year): ischemic stroke in 3 patients (1.7% per year) and hemorrhagic stroke in 1 patient (0.6% per year). This ischemic stroke rate was less than that expected (7.3% per year) based on the CHADS scores of the patient cohort.

In summary, three studies, evaluating very different interventions, included patients with nonvalvular AF who were deemed unsuitable for oral anticoagulation with warfarin; these studies found that there are alternative treatments for prevention of ischemic events in this patient population. One study found that clopidogrel plus aspirin was superior to aspirin alone for stroke prevention, but was associated with a higher risk of bleeding. One study found that apixaban compared with aspirin was associated with a lower risk of stroke and no difference in risk of bleeding. One single arm study found that use of the Watchman device was associated with a lower risk of stroke compared to the risk predicted by the CHADS scores of the participants in the study.

Patients With AF and Renal Impairment

Seven substudies from five large RCTS evaluated stroke prevention treatment in patients with AF and renal impairment. One substudy\(^4\) of the ROCKET AF study\(^5\) analyzed the efficacy results using rivaroxaban compared with warfarin in patients with renal impairment. ITT analysis showed that both medications had similar results with similar rates of stroke or systemic embolism (HR 0.86; 95% CI 0.63 to 1.17). In the per-protocol population, there were 2,950 patients (20.7%) with renal impairment (creatinine clearance 30–49 mL/min) using rivaroxaban 15mg/d (n=1,434) or warfarin (n=1,462). Among those patients, the primary outcome of stroke or systemic embolism occurred in 2.32 per 100 patient-years using rivaroxaban versus 2.77 per 100 patient-years with warfarin (HR 0.84; 95% CI 0.57 to 1.23). Rates of the principal safety outcome in the safety population (major and clinically relevant non-major bleeding: 17.82 vs. 18.28 per 100 patient-years; p=0.76) and intracranial bleeding (0.71 vs. 0.88 per 100 patient-years; p=0.54) were similar with rivaroxaban or warfarin. Fatal bleeding (0.28 vs. 0.74% per 100 patient-years; p=0.047) occurred less often with rivaroxaban. This study suggested that patients with AF and moderate renal insufficiency have higher rates of stroke and bleeding than those
with normal renal function. Rivaroxaban preserved the benefit of warfarin in preventing stroke and systemic embolus and produced lower rates while on treatment. Bleeding rates with the reduced dose of rivaroxaban were similar to those on warfarin therapy, and there were fewer fatal bleeds with rivaroxaban.

Another substudy\(^6\) of the ROCKET AF trial\(^5\) evaluated outcomes in patients with worsening renal function (WRF), as defined as >20% decline in creatinine clearance (CrCl) measurement at any point in the study. Dose of rivaroxaban was determined based on CrCl during the initial screening visit and despite changes in renal function over time, dose was not changed unless patient had two consecutive measurements of CrCl <25 mL/min at which point the medication was discontinued. Overall, patients treated with Rivaroxaban had similar screening CrCl compared to those randomized to warfarin (68 mL/min (IQR 53 to 87) vs. 68 mL/min (IQR 53 to 88); p=0.36). Patients randomized to warfarin had a larger decline in mean CrCl compared to those taking rivaroxaban (-4.3 vs. -3.5; p<0.0001). Compared to patients with stable renal function (SRF), there was no difference in stroke or systemic embolism among patients with worsening renal function (Adj HR 1.25; 95% CI 0.89 to 1.75; p=0.19). However, patients with worsening renal function had higher rates of all-cause mortality (HR 1.49; 95% CI 1.12 to 1.98; p=0.0067) and the composite outcome of stroke/systemic embolism/vascular death/MI (HR 1.40; 95% CI 1.13-1.73; p=0.0023). Among patients with worsening renal function, those randomized to treatment with rivaroxaban were less likely to have stroke/systemic embolism (WRF HR 0.50; 95% CI 0.27 to 0.93; SRF HR 0.97; 95% CI 0.76 to 1.24; p value for interaction 0.05), more likely to have a hemoglobin decrease (WRF HR 1.98; 95% CI 1.11 to 3.55; SRF HR 1.06; 95% CI 0.85 to 1.32; p value for interaction 0.047) and had no difference in major or NMCRC bleeding (HR WRF 1.06; 95% CI 0.80 to 1.39; HR SRF 0.98; 95% CI 0.89 to 1.08; p value for interaction 0.61).

One substudy\(^7\) of the AVERROES trial\(^3\) compared apixaban 5mg twice daily (2.5mg twice daily in selected patients) with aspirin 81–324mg daily in 1,697 patients with stage III chronic kidney disease (CKD). Apixaban significantly reduced primary events (stroke and systemic embolism) by 68 percent (5.6% per year on aspirin vs. 1.8% per year on apixaban; HR 0.32; 95% CI 0.18 to 0.55; p<001) for stage III CKD participants and by 43 percent (2.8% per year on aspirin vs. 1.6% per year on apixaban; HR 0.57; 95% CI 0.37 to 0.87; p=.009) for patients with an estimated glomerular filtration rate (eGFR) ≥60 mL/min per 1.73m\(^2\) (p value for interaction=0.10) in the ITT population. There was no significant difference in major bleeding in stage III CKD patients by treatment (2.2% per year with aspirin vs. 2.5% per year with apixaban; HR 1.20; 95% CI 0.65 to 2.1).

A substudy\(^8\) of the ARISTOTLE trial\(^9\) compared apixaban 5mg twice daily with warfarin (target INR 2.0–3.0) in different levels of GFR. According to baseline Cockcroft–Gault, there were 7,518 patients (42%) with an eGFR >80 mL/min, 7,587 (42%) with an eGFR between 50 and 80 mL/min, and 3,017 (15%) with an eGFR ≤50 mL/min. In the ITT population, rates of cardiovascular events and bleeding were higher at impaired renal function levels (eGFR ≤80 mL/min). Apixaban was more effective than warfarin in preventing stroke or systemic embolism and in reducing mortality irrespective of renal function, with no significant interaction between the treatment effect and the level of renal dysfunction. These results were consistent regardless of methods for GFR estimation, achieving statistical significance on the subgroup ≤50 mL/min by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (all-cause mortality and stroke/systemic embolism), subgroup Cockcroft–Gault 50-80 mL/min (stroke/systemic embolism), and subgroup cystatin C >80 mL/min (stroke/systemic embolism). Apixaban was
associated with fewer major bleeding events across all ranges of eGFRs. The relative risk reduction in major bleeding was greater in patients with an eGFR ≤50 mL/min using Cockcroft–Gault (HR 0.50; 95% CI 0.38 to 0.66; p value for interaction=0.005) or CKD-EPI equations (HR 0.48; 95% CI 0.37 to 0.64; p value for interaction=0.003]. When cystatin C was used to estimate GFR, apixaban was associated with fewer bleeding events across all ranges of eGFR, but without any significant interaction with the treatment effect on major bleeding (p value for interaction=0.54).

In sensitivity analyses, trial investigators examined whether the reduction in bleeding in patients with impaired renal function was due to the more frequent use of the lower apixaban dose (2.5mg twice daily). In both sensitivity analyses, the interaction between treatment and renal function remained statistically significant for major bleeding.

Another substudy of the ARISTOTLE trial evaluated outcomes related to change in renal function over time in patients treated with 5mg apixaban twice daily compared to warfarin. In patients with worsening renal function over 12 months of followup, apixaban showed numerically lower relative risk of stroke or systemic embolism (HR 0.80; 95% CI 0.51 to 1.24; p=0.86) as well as major bleeding (HR 0.76; 95% CI 0.54 to 1.07; p=0.73) compared to warfarin, although neither reached statistical significance. These results were similar across levels of renal dysfunction, defined as eGFR >80 mL/min, eGFR 50-80 mL/min and eGFR <50 mL/min.

In the ENGAGE AF study,11 patients randomized to the high dose edoxaban arm received 60mg daily if their CrCl was over 50 ml/min or 30mg daily if their CrCl was between 30mg/min and 50mg/min. In a substudy, no statistically significant interaction was found between treatment (edoxaban vs. warfarin) and CrCl (30-50 ml/min vs. >50 ml/min) on the primary efficacy outcome of stroke or systemic embolic event (p = 0.94 for interaction). In both renal function groups, there was no statistically significant difference between edoxaban and warfarin (HR 0.87; 95% CI 0.65 to 1.18 for CrCl >50ml/min and HR 0.87; 95% CI 0.72 to 1.04 for CrCl 30-50ml/min). There was also no statistically significant interaction between treatment and CrCl on major bleeding (p=0.62 for interaction). In exploratory analyses, there was no statistically significant interaction between CrCl subgroups (30-50 ml/min, >50-95 ml/min, and >95ml/min) and treatment on stroke or systemic embolic event, systemic embolic events, any stroke, ischemic stroke, hemorrhagic stroke, MI, any cause death, cardiovascular death, fatal bleeding, intracranial hemorrhage, or minor bleeding. There was, however, a statistically significant interaction on GI bleeding (p=0.02 for interaction) in which patients with CrCl of >50-95 ml/min had a higher risk with edoxaban vs. warfarin (HR 1.47; 95% CI 1.15 to 1.87) than the other two CrCl subgroups (HR 1.17; 95% CI 0.78 to 1.76 for CrCl 30-50ml/min and HR 0.67; 95% CI 0.40 to 1.10 for CrCl >95ml/min).

A prespecified study of the RE-LY trial investigated the outcomes of the trial in relation to renal function. Glomerular filtration rate was estimated with the Cockcroft-Gault, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Modification of Diet in Renal Disease (MDRD) equations in all randomized patients with available creatinine at baseline (n=17 951), and cystatin C-based glomerular filtration rate was estimated in a subpopulation with measurements available (n=6190). A glomerular filtration rate ≥80, 50 to <80, and <50mL/min was estimated in 32.6%, 47.6%, and 19.8% and in 21.6%, 59.6%, and 18.8% of patients based on Cockcroft-Gault and CKD-EPI, respectively. Rates of stroke or systemic embolism, major bleeding, and all-cause mortality increased as renal function decreased. The rates of stroke or systemic embolism were lower with dabigatran 150mg and similar with 110mg twice daily compared with warfarin, without significant heterogeneity in subgroups defined by renal
function (interaction $P>0.1$ for all). For the outcome of major bleeding, there were significant interactions between treatment and renal function according to CKD-EPI and MDRD equations, respectively ($P<0.05$). The relative reduction in major bleeding with either dabigatran dose compared with warfarin was greater in patients with glomerular filtration rate $\geq 80$ mL/min.

In summary, sub-studies of 5 large RCTs evaluated the effects of DOACs compared to either warfarin or aspirin in patients with some degree of renal disease. These studies demonstrated that compared to participants with normal renal function, participants with renal disease had increased risk of ischemic events, bleeding, and all-cause mortality. In all 5 sub-studies, among participants with renal disease, use of the DOACs were consistently similar to or better than warfarin in the prevention of stroke/SE and bleeding events. One sub-study demonstrated that in patients with stage 3 CKD, compared to aspirin, apixaban was associated with lower risk of stroke and no difference in bleeding.

Patients With Paroxysmal Versus Sustained AF

One substudy$^{14}$ of the ACTIVE W RCT$^{15}$ analyzed the results in patients with paroxysmal AF ($n=1,202$) as compared with those who had sustained (persistent or permanent) AF ($n=5,495$). Patients with paroxysmal AF were younger, had a shorter AF history, more hypertension, and less valvular disease, heart failure, and diabetes mellitus than patients with sustained AF. Irrespective of type of AF, the incidence of stroke and non-CNS embolism was lower for patients treated with oral anticoagulation. There were more bleedings of any type in patients receiving clopidogrel plus aspirin, irrespective of the type of AF, but major bleeding events were similar in all groups (paroxysmal vs. sustained, and oral anticoagulants vs. clopidogrel+aspirin).

A secondary analysis$^{16}$ of the ARISTOTLE trial$^{9}$ evaluated treatment with apixaban 5mg twice daily compared to warfarin in patients with paroxysmal or persistent AF. Overall, patients with paroxysmal atrial fibrillation were less likely to have stroke or systemic embolism (HR 0.65; 95% CI 0.48 to 0.87; $p=0.003$) and all-cause mortality was also significantly less (HR 0.72; 95% CI 0.61 to 0.85; $p=0.0002$). There was no significant interaction with regard to stroke or systemic embolism by type of AF and treatment type (HR Paroxysmal 0.72; 95% CI 0.41 to 1.25; HR Persistent 0.80; 95% CI 0.66 to 0.97; $p$ value for interaction 0.71), all-cause mortality (HR Paroxysmal 0.99; 95% CI 0.72 to 1.37; HR Persistent 0.88; 95% CI 0.78 to 0.99; $p$ value for interaction 0.50) and major bleeding (HR Paroxysmal 0.73; 95% CI 0.49 to 1.08; HR Persistent 0.68; 95% CI 0.59 to 0.80; $p$ value for interaction 0.75) in patients treated with apixaban compared with warfarin.

In summary, analysis of two large RCTs evaluated for differences in treatment effects (clopidogrel plus aspirin vs warfarin or apixaban vs warfarin) for stroke prevention/bleeding by type of AF (paroxysmal or persistent). In neither study was there a difference in treatment effect by type of AF.

Patients with Recently Diagnosed AF

One substudy$^{17}$ of the ARISTOTLE RCT$^{9}$ evaluated patients with AF first diagnosed within 30 days prior to randomization. Regardless of timing of diagnosis, apixaban had similar benefits on prevention of stroke or systemic embolism and major bleeding compared to warfarin (interaction $p$ values 0.94 and 0.78 respectively).
Patients With AF After Stroke

Eight studies explored stroke prevention treatment in patients with AF who had previously suffered a stroke.\(^\text{18-25}\)

The Heparin in Acute Embolic Stroke Trial (HAEST)\(^\text{20}\) was a multicenter RCT on the effect of LMWH (dalteparin 100 IU/kg subcutaneously twice a day) or aspirin (160mg every day) for the treatment of 449 patients with acute ischemic stroke and AF. The primary aim was to test whether treatment with LMWH, started within 30 hours of stroke onset, is superior to aspirin for the prevention of recurrent stroke during the first 14 days. The frequency of recurrent ischemic stroke during the first 14 days was 19/244 (8.5%) in dalteparin-allocated patients versus 17/225 (7.5%) in aspirin-allocated patients (OR 1.13; 95% CI 0.57 to 2.24). In the ITT analyses, the OR remained unchanged after adjusting for sex in logistic-regression analysis (1.19; 95% CI 0.60 to 2.36). The secondary events during the first 14 days also revealed no benefit of dalteparin compared with aspirin. There were no significant differences in functional outcome or death at 14 days or 3 months.

A prespecified subgroup analysis\(^\text{21}\) of the ROCKET AF study\(^\text{5}\) investigated whether the efficacy and safety of rivaroxaban compared with warfarin was consistent among patients with and without previous stroke or TIA. A total of 14,264 patients from 1,178 centers in 45 countries were included. Patients with AF who were at increased risk of stroke (CHADS\(_2\) score \(>2\)) were randomly assigned (1:1) in a double-blind manner to rivaroxaban 20mg daily or adjusted dose warfarin (to maintain INR 2.0–3.0). Patients and investigators were masked to treatment allocation. The primary outcome was the composite of stroke or non-CNS systemic embolism as a safety outcome. The treatment effects of rivaroxaban and warfarin were compared among patients with and without previous stroke or TIA. The safety analyses were done in the on-treatment population. Efficacy analyses were analyzed by ITT, and 7,468 (52%) patients had a previous stroke (n=4,907) or TIA (n=2,561). The number of events per 100 person-years for the primary outcome in patients treated with rivaroxaban compared with warfarin was consistent among patients with previous stroke or TIA (2.79% rivaroxaban vs. 2.96% warfarin; HR 0.94; 95% CI 0.77 to 1.16) and those without (1.44% vs. 1.88%; HR 0.77; 95% CI 0.58 to 1.01; comparison interaction \(p=0.23\)). Similarly, the number of major and non-major clinically relevant bleeding events per 100 person-years in patients treated with rivaroxaban compared with warfarin was consistent among patients with previous stroke or TIA (13.31% rivaroxaban vs. 13.87% warfarin; HR 0.96; 95% CI 0.87 to 1.07) and those without (16.69% vs. 15.19%; HR 1.10; 95% CI 0.99 to 1.21; comparison interaction \(p=0.08\)).

One observational study\(^\text{18}\) followed a consecutive series of AF patients with first-ever ischemic stroke and evaluated prospectively those with moderate to severe disability (grade 4–5 on the modified Rankin Scale) who were treated during a 5-year followup period with either warfarin or aspirin. Death and recurrent vascular events were documented. Out of a pool of 438 AF patients, 191 were prospectively assessed. During a mean followup of 50.4 months, the cumulative 5-year mortality was 76.7% (95% CI 69.0 to 84.3), and the 5-year recurrence rate was 33.7% (95% CI 23.3 to 44.1). Additionally, two non-cerebral major bleeding events requiring hospital admission and blood transfusion were recorded in the warfarin group. Only one non-cerebral bleeding event was documented in the aspirin group. The annual event rates for all major bleeding complications in aspirin and warfarin groups were 0.7 and 3.3 percent, respectively. Aspirin versus warfarin was an independent predictor of mortality. Prior TIA and aspirin versus warfarin were predictors of vascular recurrence. Anticoagulation was associated with a decreased risk of death (HR 0.44; 95% CI 0.27 to 0.70; \(p<0.001\)) and recurrent...
thromboembolism (HR 0.36; 95% CI 0.17 to 0.77; p<0.01). The results of this observational study suggest that chronic anticoagulation therapy may be effective in lengthening survival and preventing recurrent thromboembolism in AF patients who have suffered a severely disabling ischemic stroke.

An observational study analyzed recurrent cerebral and non-cerebral ischemic vascular events, major intracerebral and extracerebral bleeding, and vascular death in 401 consecutive patients with ischemic stroke or TIA and AF who were discharged with oral anticoagulation, antiplatelet agents, or heparin only in a clinical routine setting. Patients on oral anticoagulation at time of discharge were significantly younger and had suffered a major stroke less often than patients who received antiplatelet agents or heparin at discharge. One year after discharge, adherence to therapy was higher in patients discharged on oral anticoagulation (72%) than in those on antiplatelet agents (46%; p<0.001). The majority of patients discharged on heparin were subsequently treated with oral anticoagulation. During a median followup of 25 months (IQR, 15–38), 103 (26%) patients experienced a complication: 91 (88%) patients an ischemic complication and 12 (12%) a bleeding complication. The rate of ischemic complications and the overall rate of complications were lowest in patients discharged on oral anticoagulation. Patients on antiplatelet agents at discharge suffered from ischemic complications significantly more often during the followup period than patients on oral anticoagulation or heparin at discharge (30% vs. 16% vs. 23%; p=0.031). Patients on antiplatelet agents suffered their first vascular complication significantly sooner after discharge than patients on oral anticoagulation. Safety outcomes showed that three percent of the patients on antiplatelet agents and four percent of those on oral anticoagulation suffered from major bleeding complications during followup (p=0.028). The rate of intracranial bleeding was higher in patients on oral anticoagulation (3% vs. 1%), but the total numbers were too small to allow a valid statistical comparison. Total mortality was lowest in patients discharged on oral anticoagulation, and vascular mortality also seemed somewhat lower in this group but the difference was not significant.

A predefined analysis was conducted of the outcomes of the RE-LY trial in subgroups of patients with or without previous stroke or transient ischemic attack. The primary efficacy outcome was stroke or systemic embolism, and the primary safety outcome was major hemorrhage. Within the subgroup of patients with previous stroke or TIA, 1,195 patients were from the 110mg dabigatran group, 1,233 from the 150mg dabigatran group, and 1,195 from the warfarin group. Stroke or systemic embolism occurred in 65 patients (2.78% per year) on warfarin compared with 55 (2.32% per year) on 110mg dabigatran (relative risk [RR] 0.84; 95% CI 0.58 to 1.20) and 51 (2.07% per year) on 150mg dabigatran (RR 0.75, 95% CI 0.52 to 1.08). The rate of major bleeding was significantly lower in patients on 110mg dabigatran (RR 0.66; 95% CI 0.48 to 0.90) and similar in those on 150mg dabigatran (RR 1.01; 95% CI 0.77 to 1.34) compared with those on warfarin. The effects of both doses of dabigatran compared with warfarin were not significantly different between patients with previous stroke or TIA and those without for any of the outcomes from RE-LY apart from vascular death (110mg group compared with warfarin group, interaction p=0.038). By these results, the effects of 110mg dabigatran and 150mg dabigatran twice daily in patients with previous stroke or TIA are consistent with those of other patients in RE-LY, for whom, compared with warfarin, 150mg dabigatran reduced stroke or systemic embolism and 110mg dabigatran was noninferior.

A prespecified subgroup analysis of AVERROES included 5,599 patients (mean age 70 years) with AF who were at increased risk of stroke and unsuitable for warfarin therapy. These patients were randomly assigned to receive apixaban 5mg twice daily (n=2,808) or aspirin 81–
324 mg per day (n=2,791). The primary efficacy outcome was stroke or systemic embolism in the ITT population; the primary safety outcome was major bleeding. In this subanalysis of patients with previous stroke or TIA, the effects of apixaban in patients with and without previous stroke or TIA were compared. The cumulative HR for stroke or systemic embolism at 1 year was 5.73% (95% CI 4.10 to 8.02) in patients with previous stroke or TIA and 2.36% (1.93 to 2.89) in those without. In patients with previous stroke or TIA treated with apixaban, the rates of stroke or systemic embolism, ischemic stroke, and disabling or fatal stroke were consistently lower than those in patients treated with aspirin. In patients with previous stroke or TIA, 10 events of stroke or systemic embolism occurred in the apixaban group (n=390), cumulative hazard 2.39% per year) compared with 33 in the aspirin group (n=374). This resulted in a cumulative hazard of 2.39 percent in the apixaban group and 9.16 percent per year in the aspirin group (HR 0.29; 95% CI 0.15 to 0.60). In those without previous stroke or TIA, 41 events (n=2,417, 1.68% per year) and 80 events (n=2,415, 3.06% per year) occurred in the apixaban and aspirin groups, respectively (HR 0.51; 95% CI 0.35 to 0.74). Compared with those treated with aspirin, the 1-year risk of stroke or systemic embolism decreased by 73 percent in patients treated with apixaban and with previous stroke or TIA (1-year absolute risk reduction of 6.4%; 95% CI 2.8 to 10.0) and by 45 percent in patients treated with apixaban and without previous stroke or TIA (1-year absolute risk reduction of 1.4%, 95% CI 0.4 to 2.3). The p values for interaction between history of previous stroke or TIA and treatment were not significant, indicating that the results in the subgroups were consistent with the overall result of the study. Major bleeding, the primary safety outcome, was more frequent in patients with history of previous stroke or TIA than in patients without this history (HR 2.88; 95% CI 1.77 to 4.55), but risk of this event did not differ between treatment groups. The effect of apixaban versus aspirin for bleeding complications was consistent in the two subgroups, with nonsignificant interaction p values.

A prespecified subgroup analysis from the ARISTOTLE trial evaluated the efficacy and safety of apixaban compared with warfarin in subgroups of patients with and without previous stroke or TIA. The primary efficacy outcome was stroke or systemic embolism, analyzed by intention to treat. The primary safety outcome was major bleeding in the on-treatment population. Outcomes in patients with and without previous stroke or TIA were compared. Of the trial population, 3,436 (19%) had a previous stroke or TIA. In the subgroup of patients with previous stroke or TIA, the rate of stroke or systemic embolism was 2.46 per 100 patient-years of followup in the apixaban group and 3.24 in the warfarin group (HR 0.76; 95% CI 0.56 to 1.03); in the subgroup of patients without previous stroke or TIA, the rate of stroke or systemic embolism was 1.01 per 100 patient-years of followup with apixaban and 1.23 with warfarin (HR 0.82; 95% CI 0.65 to 1.03). The relative risk reduction of stroke or systemic embolism with apixaban versus warfarin was similar among patients with and those without previous stroke or TIA (p for interaction=0.71). The reduction in rates of cardiovascular death, disabling or fatal stroke, and all-cause mortality with apixaban versus warfarin was similar in patients with and without previous stroke or TIA (p for interaction=0.53, 0.18, and 0.89, respectively). Compared with patients without previous stroke or TIA, patients with previous stroke or TIA were more likely to have major bleeding (HR 1.37; 95% CI 1.17 to 1.62) and intracranial bleeding (2.15, 95% CI 1.57 to 2.96). The relative risk reductions in major bleeding and total bleeding with apixaban versus warfarin were similar in both groups (p for interaction=0.69 and 0.0, respectively). Intracranial bleeding was reduced in the apixaban groups from 1.49 per 100 patient-years of followup on warfarin to 0.55 per 100 patient-years on apixaban in those with previous stroke or TIA (HR 0.37; 95% CI 0.21 to 0.67) and from 0.65 per 100 patient-years of
followup on warfarin to 0.29 per 100 patient-years on apixaban in those without previous stroke or TIA (0.44, 95% CI 0.30 to 0.66). Based on these results, the effects of apixaban versus warfarin were consistent in patients with AF with and without previous stroke or TIA.

In a substudy of the ENGAGE AF study\(^2\), in which with prior ischemic stroke or TIA were compared with patients without prior ischemic stroke or TIA, no statistically significant interaction was found between prior stroke/TIA and treatment (high dose edoxaban vs. warfarin) for stroke or systemic embolic event, any stroke, hemorrhagic stroke, ischemic stroke, any cause death, or cardiovascular death.

Studies were inconsistent in terms of the interventions evaluated and their findings. Three studies compared anticoagulation to aspirin therapy.\(^1\),\(^8\),\(^2\),\(^3\) Anticoagulation with either apixaban or warfarin was superior to aspirin therapy in preventing recurrent thromboembolism.\(^1\),\(^8\),\(^2\),\(^3\) Four studies compared direct oral anticoagulants to warfarin therapy.\(^2\),\(^1\),\(^2\),\(^4\),\(^5\) These studies demonstrated that there was no difference in risk of stroke or systemic embolism when comparing direct oral anticoagulants (edoxaban, rivaroxaban, apixaban, dabigatran 110mg BID) to warfarin therapy. The only exception was the dabigatran 150mg BID dose showed reduced risk of stroke or systemic embolism compared to warfarin therapy.

**Patients With AF and Different Thromboembolic Risks**

Six studies explored the comparative safety and effectiveness of stroke prevention therapy in patients with different thromboembolic risks.\(^1\),\(^5\),\(^2\),\(^7\),\(^3\),\(^1\)

An observational study\(^2\) sought to determine the efficacy and safety of warfarin and aspirin in patients with nonvalvular AF, with separate analyses according to predicted thromboembolic and bleeding risk. Nationwide registries allowed the identification of all patients discharged with nonvalvular AF in Denmark (n=132,372). For every patient, the risk of stroke and bleeding was calculated by CHADS\(_2\), CHA\(_2\)DS\(_2\)-VASc, and HAS-BLED. In different groups according to thromboembolic risks, warfarin consistently lowered the risk of thromboembolism compared with aspirin; the combination of warfarin+aspirin did not yield any additional benefit. In patients at high thromboembolic risk, HRs (95% CIs) for thromboembolism were (adjusted for all baseline characteristics): CHA\(_2\)DS\(_2\)-VASc \(\geq\) 2: HR 1.81 (1.73 to 1.90), 1.14 (1.06 to 1.23) for aspirin and warfarin+aspirin, respectively, compared with warfarin; CHADS\(_2\) \(\geq\) 2: HR 1.73 (1.64 to 1.83), 1.05 (0.96 to 1.15), for aspirin and warfarin+aspirin, respectively, compared with warfarin. The risk of bleeding was increased with warfarin, aspirin, and warfarin+aspirin compared with no treatment; the HRs were 1.0 (warfarin; reference), 0.93 (aspirin; 0.89–0.97), 1.64 (warfarin+aspirin; 1.55–1.74), and 0.84 (no treatment; 0.81–0.88), respectively. This large cohort study corroborates the effectiveness of warfarin and no effect of aspirin treatment on the risk of stroke/thromboembolism. Also, the risk of bleeding was increased with both warfarin and aspirin treatment, but the net clinical benefit was clearly positive, in favor of warfarin in patients with increased risk of stroke/thromboembolism.

A prospective cohort study\(^2\) analyzed the effectiveness and safety of oral anticoagulants in 796 outpatients with nonvalvular AF in daily clinical practice, according to embolic risk evaluated by means of CHADS\(_2\) score. Oral anticoagulation was prescribed to 564 (71%) patients. After 2.4 ± 1.9 years of followup, the embolic event (TIA, ischemic stroke, peripheral embolism) rates (per 100 patient-years) for each stratum of the CHADS\(_2\) score for patients with/without oral anticoagulants were: 1/4.1; p=0.23 (CHADS\(_2\)=0); 0.6/7.1; p=0.0018 (CHADS\(_2\)=1); 0.5/5.1; p=0.0014 (CHADS\(_2\)=2); 2.4/12.5; p=0.0017 (CHADS\(_2\)=3) and 2.9/20; p=0.013 (CHADS\(_2\)=4). The severe bleeding rates for the same CHADS\(_2\) score strata were 3/0.8,
0.8/0.7, 1.3/0.7, 0.4/0, and 2.9/5 in patients with/without oral anticoagulants (nonsignificant). This study demonstrated that oral anticoagulants appeared safe and effective in patients with CHADS$_2$≥1.

In ACTIVE W, oral anticoagulation was more efficacious than combined clopidogrel plus aspirin in preventing vascular events in patients with AF. A subanalysis of ACTIVE W evaluated the findings according to risk stratification using the CHADS$_2$ score. Treatment-specific rates of stroke and major bleeding were calculated for patients with a CHADS$_2$=1 and compared with those with a CHADS$_2$ >1. The ACTIVE W primary outcome (stroke, noncentral nervous system systemic embolism, all-cause mortality, and MI) occurred more frequently in patients on clopidogrel+aspirin, both with CHADS$_2$=1 (3.28% per year versus 1.92% per year, RR=1.72; p=0.01) and with CHADS$_2$ >1 (7.14% per year versus 5.18% per year, RR 1.40; p=0.0035). CHADS$_2$ status did not significantly affect the relative benefit of oral anticoagulants for this outcome (P for interaction=0.41). Observed stroke rates for those with a CHADS$_2$=1 were 1.25 percent per year on clopidogrel+aspirin and 0.43 percent per year on oral anticoagulants (RR 2.96; 95% CI 1.26 to 6.98; p=0.01). Among patients with a CHADS$_2$=1, the stroke rates were 3.15 percent per year on clopidogrel+aspirin and 2.01 percent per year on oral anticoagulants (RR 1.58; 95% CI 1.11 to 2.24; p=0.01; p for interaction between stroke risk category and efficacy of oral anticoagulants=0.19). The risk of major bleeding during oral anticoagulants was significantly lower among patients with CHADS$_2$=1 (1.36% per year) compared with CHADS$_2$>1 (2.75% per year) (RR 0.49; 95% CI 0.30 to 0.79; p=0.003). For patients with CHADS$_2$=1, the rate of major bleeding was 2.09 percent per year on clopidogrel+aspirin, which was higher than the rate of 1.36 percent per year on oral anticoagulants (RR 1.55; 95% CI 0.91 to 2.64; p=0.11). For patients with CHADS$_2$>1, major bleeding occurred at a rate of 2.63 percent per year on clopidogrel+aspirin and 2.75 percent per year on oral anticoagulants (RR 0.97; 95% CI 0.69 to 1.35; p=0.84). The relative risk of major bleeding with clopidogrel+aspirin, compared with oral anticoagulants was not significantly different between patients with high and low CHADS$_2$ scores (p for interaction=0.15); however, the absolute risk of major bleeding on oral anticoagulants was significantly lower among patients with CHADS$_2$=1 compared with CHADS$_2$>1 (RR=0.49; 95% CI 0.30 to 0.79; p=0.0003). Based on these results, patients with a CHADS$_2$=1 had a low risk of stroke, yet still derived a modest (<1% per year) but statistically significant absolute reduction in stroke with oral anticoagulants compared with clopidogrel+aspirin and had low rates of major hemorrhage on oral anticoagulants.

A subgroup analysis of the RE-LY trial evaluated the prognostic importance of CHADS$_2$ risk score in patients with AF receiving oral anticoagulants, including warfarin and the direct thrombin inhibitor dabigatran. Of the 18,112 patients, the distribution of CHADS$_2$ scores were as follows: 0–1, 5,775 patients; 2, 6,455 patients; and 3–6, 5,882 patients. Annual rates of the primary outcome of stroke or systemic embolism among all participants were 0.93, 1.22, and 2.24 percent in patients with a CHADS$_2$ score of 0–1, 2, and 3–6 respectively. Annual rates of other outcomes among all participants with CHADS$_2$ scores of 0–1, 2, and 3–6, respectively, were 2.26, 3.11, and 4.42 percent (major bleeding); 0.31, 0.40, and 0.61 percent (intracranial bleeding); and 1.35, 2.39, and 3.68 percent (vascular mortality) (p <0.001 for all comparisons). Rates of stroke or systemic embolism, major and intracranial bleeding, and vascular and total mortality each increased in the warfarin and dabigatran groups with increasing CHADS$_2$ score. The reduction in stroke or systemic embolism with dabigatran 150mg twice daily versus warfarin was consistent across the CHADS$_2$ risk groups. Across CHADS$_2$ risk groups, the rates of stroke
or systemic embolism were similar with dabigatran 110mg twice daily and warfarin. The rates of intracranial bleeding with dabigatran 150mg or 110mg twice daily were lower than those with warfarin; there was no significant heterogeneity in subgroups defined by CHADS₂ scores.

A fair-quality observational study³⁰ that included 8,962 patients with AF and a CHA₂DS₂-VASc score=0 showed that among untreated patients, the rates of stroke/thromboembolism, major bleeding, and mortality were 0.64 percent, 1.12 percent, and 1.08 percent per year, respectively. Use of oral anticoagulation and/or antiplatelet therapy was not associated with a reduction in stroke/thromboembolism (RR 0.99; 95% CI 0.25 to 3.99; p=0.99) and was not associated with a different prognosis in terms of bleeding events, improved survival, or a composite outcome of stroke/thromboembolism, bleeding, and death (RR 0.80; 95% CI 0.40 to1.61; p=0.53).

Finally, a secondary analysis³¹ of the ARISTOTLE trial⁹ compared apixaban 5mg twice daily versus warfarin (target INR 2·0–3·0) in patients with different levels of risk of stroke and of bleeding in AF, according to patients’ CHADS₂, CHA₂DS₂-VASc, and HAS-BLED scores. Irrespective of CHADS₂ score, patients assigned to apixaban had significantly lower rates of stroke or systemic embolism, mortality, International Society on Thrombosis and Haemostasis (ISTH) major bleeding, intracranial bleeding, and any bleeding than did those assigned warfarin, with no evidence of statistical heterogeneity. The benefits of apixaban compared with warfarin for all outcomes (including events during treatment only) across CHA₂DS₂-VASc categories were similar to those seen across CHADS₂ score categories. No difference was recorded for MI. Irrespective of HAS-BLED score, patients assigned to apixaban had lower rates of stroke or systemic embolism, mortality, ISTH major bleeding, Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding, Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe or moderate bleeding, and any bleeding, including events during treatment only, than did those assigned to warfarin. The reduction in intracranial bleeding with apixaban compared with warfarin was greater in patients with a HAS-BLED score of 3 or higher (HR 0·22; 95% CI 0·10 to 0·48) than was the reduction seen in those with a HAS-BLED score of 0–1 (HR 0·66; 95% CI 0·39 to 1·12), but not significantly so (p value for interaction=0·0604). Finally, regardless of CHADS₂, CHA₂DS₂-VASc, and HAS-BLED score, patients who received apixaban had fewer events than did patients who received warfarin, with lower rates of the composite of stroke, systemic embolism, ISTH major bleeding, and all-cause mortality.

The studies were inconsistent in terms of the comparisons evaluated and the findings. Two studies showed a decrease in risk of thromboembolism when comparing warfarin therapy to aspirin and clopidogrel regardless of calculated risk.¹⁵,²⁷ When comparing direct oral anticoagulants (apixaban or dabigatran) to warfarin therapy, a decrease in risk of thromboembolism was seen with direct oral anticoagulant agents.³⁰,³¹ Lastly, one study looking at only patients with CHA₂DS₂-VASc score=0 showed no different in risk of thromboembolism between those using oral anticoagulation and/or antiplatelet therapy.³⁰

**Patients With AF According to INR Control**

Four studies evaluated treatment safety and effectiveness according to center-based INR control.³³⁻³⁶ In the first study,³³ incident ischemic strokes were evaluated in a cohort of 13,559 patients with nonvalvular AF. Of 596 ischemic strokes, 32 percent occurred during warfarin therapy, 27 percent during aspirin therapy, and 42 percent during neither type of therapy. Among patients who were taking warfarin, an INR of <2.0 at admission, as compared with an INR of ≥2.0, independently increased the odds of a severe stroke in a proportional odds logistic-
regression model (OR 1.9; 95% CI 1.1 to 3.4) across three severity categories of stroke and the risk of death within 30 days (HR 3.4; 95% CI 1.1 to 10.1). The proportion of patients who had a severe or fatal stroke did not differ significantly between those with an admission INR of 1.5–1.9 and those with an INR of <1.5. After adjustment for potential confounders in the proportional odds model, the medication group remained an independent risk factor for the severity of stroke when patients who had an INR ≥2.0 were compared with those who had an INR of <2.0 or those who were taking neither aspirin nor warfarin. An INR of 1.5–1.9 at admission was associated with a mortality rate similar to that for an INR of <1.5 (18% and 15%, respectively). The 30-day mortality rate among patients who were taking aspirin at the time of the stroke was similar to that among patients who were taking warfarin and who had an INR <2.0. The rate of ischemic stroke was highest at INR values <2.0, especially values <1.5. By contrast, there was no marked absolute increase in the rate of intracranial hemorrhage at INR values <4.0. Based on these results, anticoagulation that results in an INR ≥2.0 in patients with nonvalvular AF reduces the frequency of ischemic stroke, its severity, and the risk of death from stroke.

A second observational study included an analysis of warfarin subgroups according to INR control compared with no therapy. Ischemic stroke rate relative risk (RR) was 0.93 (95% CI 0.71 to 1.22) in patients below therapeutic range (INR <2), 0.69 (0.57 to 0.83) in the group within therapeutic range (INR 2–3), 0.82 (0.57 to 1.20) in patients above therapeutic range (INR >3), and 0.62 (0.56 to 0.69) in the group with unknown therapeutic range. Intracranial hemorrhage RR was 1.16 (95% CI 0.62 to 2.16) in patients below therapeutic range (INR <2), 1.13 (0.74 to 1.72) in the group within therapeutic range (INR 2–3), 3.26 (1.67 to 6.38) in patients above therapeutic range (INR >3), and 1.29 (0.98 to 1.69) in the group of unknown therapeutic range. A post-hoc analysis of the ARISTOTLE trial evaluated apixaban 5mg twice daily compared to warfarin treatment with differing times in therapeutic range. Overall, apixaban significantly reduced the rate of stroke or systemic embolism compared to warfarin (HR 0.79; 95% CI 0.66–0.95). The treatment benefit of apixaban was similar across the lowest and highest quartiles of individual time in therapeutic range (iTTR) without interaction between quality of INR control and frequency of events (iTTR 24.3-60.5 HR 0.70; 95% CI 0.52 to 0.94; iTTR 71.2-83.2 HR 0.87; 95% CI 0.57 to 1.33; p value for interaction 0.060). There were also similar treatment effects with regards to all cause death in the lowest (HR 0.87; 95% CI 0.71 to 1.06) and highest quartiles of iTTR (HR 0.89; 95% CI 0.67 to 1.16; p value for interaction 0.67). Additionally, the same benefit of apixaban with regards to bleeding outcomes was observed across the lowest and highest quartiles of iTTR.

A substudy of the ROCKET AF trial examined rivaroxaban once daily versus warfarin treatment with differing times in therapeutic range. For all patients randomized to warfarin, the mean time in therapeutic range (TTR) was 55%. Patients treated with rivaroxaban were compared to those treated with warfarin, across four quartiles of TTR: Q1=0 to 50.6%; Q2=50.7 to 58.5%; Q3=58.6 to 65.7%; Q4=65.7 to 100%. There was no significant difference in the primary outcomes of stroke or systemic embolism in patients treated with rivaroxaban across center TTR (cTTR) for warfarin (HR Q1 0.70; 95% CI 0.47 to 1.04; HR Q2 0.90; 95% CI 0.64 to 1.26; HR Q3 0.88; 95% CI 0.62 to 1.25; HR Q4 0.73; 95% CI 0.50 to 1.06; p value for interaction 0.71). However, patients treated with rivaroxaban did have lower risk of major or NMCR bleeding compared to patients in the lowest quartile of warfarin cTTR with a significant interaction between treatment and time in therapeutic range (Q1 HR 0.80; 95% CI 0.66 to 0.98;
Q2 HR 0.96; 95% CI 0.81 to 1.14; Q3 HR 1.03; 95% CI 0.87 to 1.22; Q4 HR 1.25; 95% CI 1.10 to 1.41; p value for interaction 0.001).

The first two studies from this group suggest that compared to aspirin or no therapy, an INR ≥ 2 lowers the risk of ischemic stroke. However, INR values above the therapeutic range may lead to higher rates of hemorrhagic stroke. The second two studies compared treatment with warfarin to a factor Xa inhibitor and showed that there was no difference in the treatment effect of rivaroxaban and apixaban across the ranges of INR values examined with regards to stroke or systemic embolism outcomes. There is mixed data regarding the interaction between INR control and treatment with regards to bleeding outcomes.

**Elderly Patients With AF**

Fourteen studies specifically explored the safety and effectiveness of stroke prevention therapies in the elderly. A single-center, retrospective, observational study included data from patients aged ≥65 years with chronic nonvalvular AF treated at an urban academic geriatrics practice over a 1-year period. Eligible patients were receiving noninvasive management of AF with warfarin or aspirin. A total of 112 patients (mean age, 82 years) were identified; 106 were included in this analysis (80 women, 26 men). Warfarin was prescribed in 85 percent (90 patients); aspirin in 15 percent (16). The distributions of both the CHADS2 and Outpatient Bleeding Risk Index scores were not significantly different between the warfarin and aspirin groups. The proportions of patients treated with warfarin were not significantly different between the groups with a high risk for hemorrhage and the groups at lower risk. At 12 months in the 90 patients initially treated with warfarin, the rate of stroke was 2 percent (2 patients); major hemorrhage, 6 percent (5); and death, 20 percent (18). The number of patients who received aspirin was too small to provide sufficient power to detect significant treatment differences.

A prospective clinical study of four clinical services of geriatric medicine included 209 inpatients, (mean age 84.7±7 years; women 60.8%) with chronic AF. The patients were distributed into two groups (anticoagulant or aspirin) according to medical decision. The evolution of the patients was recorded after 3 months. One hundred and two patients (48.8%) received anticoagulant and 107 patients received aspirin. Patients in the aspirin group were significantly older (86.5±6.5 vs. 82.9±7.1 years), had more frequent social isolation, had higher systolic blood pressure, and had more important subjective bleeding risk and risk of falls. After 3 months, the two groups did not significantly differ for death, bleeding, or ischemic events.

A prospective RCT included 973 patients aged 75 years or over (mean age 81·5 years, SD 4·2) with AF from primary care who were randomly assigned to warfarin (target INR 2–3) or aspirin (75mg per day). The primary outcome was fatal or disabling stroke (ischemic or hemorrhagic), intracranial hemorrhage, or clinically significant arterial embolism. Analysis was by intention to treat. There were 24 primary events (21 strokes, 2 other intracranial hemorrhages, and 1 systemic embolus) in people assigned to warfarin, and 48 primary events (44 strokes, 1 other intracranial hemorrhage, and 3 systemic emboli) in people assigned to aspirin in the ITT population (yearly risk 1.8% vs. 3.8%, relative risk 0.48; 95% CI 0.28 to 0.80; p=0·003). Yearly risk of extracranial hemorrhage was 1.4 percent (warfarin) versus 1.6 percent (aspirin) (relative risk 0.87, 95% CI 0.43 to 1.73).

An RCT of primary thromboprophylaxis for AF included patients aged >80 and <90 randomized to receive dose-adjusted warfarin (INR 2.0–3.0) or aspirin 300mg. The primary outcome measure was a comparative frequency of combined outcomes comprising death,
thromboembolism, serious bleeding, and withdrawal from the study. Seventy-five patients (aspirin 39; warfarin 36) were entered (mean age 83.9, 47% male). Patients on aspirin had significantly more adverse events (13/39; 33%) than patients on warfarin (2/36; 6%; p=0.002). Ten of 13 aspirin adverse events were caused by side effects and serious bleeding; there were three deaths (two aspirin, one warfarin).

Another RCT recruited patients over 75 years of age without previous stroke or systemic embolism. Patients were randomized into three groups, (A) aspirin 100mg/day, (B) fixed-dose warfarin 1mg/day; and (C) adjusted-dose warfarin with a target range of INR between 1.6 and 2.5. The study was discontinued 6 months after the enrollment of the first patient for safety reasons. Over a mean followup period of 3.7 months, two patients from group B (n=14) developed a dangerous prolongation of the INR (7.0 and 4.2), which led to the discontinuation of fixed-dose warfarin. Another patient from the same group experienced a major bleeding event 1 month after enrollment in the study (INR 5.5). The percentage of INR measurements within the target range was significantly lower in group B (48.7%) than in group C (83.7%) (p<0.001).

A prospective observational study included 207 older people (>75 years) with AF and first ever ischemic stroke. During the followup period (mean 88.4 months, range 3–120), the study population was under either oral anticoagulants (n=72) or aspirin (n=135). The cumulative 10-year mortality and recurrence rates were 92.5 percent (95% CI 85.7 to 99.3) and 66.1 percent (95% CI 43.1 to 89.1), respectively. Increasing age, functional dependency at hospital discharge, and antiplatelet versus anticoagulation therapy were independent determinants of mortality. Antiplatelet versus anticoagulation therapy was the sole determinant of vascular recurrence. Anticoagulation was associated with decreased risk of death (HR 0.47; 95% CI 0.31 to 0.72; p=0.001)) and recurrent thromboembolism (HR 0.31; 95% CI 0.16 to 0.62; p=0.002). These results suggest that the benefits of anticoagulation for secondary stroke prevention in AF patients extend to elderly.

A retrospective cohort analysis evaluated persons discharged on warfarin after an AF admission using data from Medicare’s National Stroke Project. It examined antiplatelet therapy among warfarin users and the impact on major bleeding rates. Prediction of concurrent antiplatelet use and hospitalization with a major acute bleed within 90 days after discharge from the index AF admission was assessed. A total of 10,093 warfarin patients met inclusion criteria with a mean age of 77 years; 19.4 percent received antiplatelet therapy. Antiplatelet use was less common among women, older persons, and persons with cancer, terminal diagnoses, dementia, and bleeding history. Persons with coronary disease were more likely to receive an antiplatelet agent. Antiplatelets increased major bleeding rates from 1.3 percent to 1.9 percent (P=0.052). In the multivariate analysis, factors associated with bleeding events included age (OR, 1.03; 95% CI 1.002 to 1.05), anemia (OR, 2.52; 95% CI 1.64 to 3.88), a history of bleeding (OR, 2.40; 95% CI 1.71 to 3.38), and concurrent antiplatelet therapy (OR, 1.53; 95% CI 1.05 to 2.22).

A substudy of the BAFTA trial evaluated 665 patients aged 75 or over with AF based in the community who were randomized within the BAFTA trial and were not taking warfarin throughout or for part of the study period. A total of 54 (8%) patients had an ischemic stroke, four (0.6%) had a systemic embolism, and 13 (2%) had a TIA. Based on this single trial population, current risk stratification schemes in older people with AF have only limited ability to predict the risk of stroke.

Another study examined the effectiveness of oral anticoagulation on risk of stroke of any nature (fatal and nonfatal ischemic and/or hemorrhagic stroke) in patients with nonvalvular AF or flutter living in the County of North Jutland, Denmark. This study used the Hospital
Discharge Registry covering the county (490,000 inhabitants) from 1991 to 1998 to identify 2,699 men and 2,425 women with AF or flutter, aged 60–89 years. The risk of stroke associated with use of oral anticoagulation compared with no use was estimated, after adjustment for age, diabetes and underlying cardiovascular diseases. A total of 838 of 2,699 men (31%) and 552 of 2,425 women (23%) with AF had one or more recorded prescriptions of oral anticoagulation. The incidence rates of stroke were 31 per 1000 person-years of followup in men, and 30 per 1000 person-years of followup in women. The adjusted relative risks of stroke during anticoagulation were 0.6 (95% CI 0.4 to 1.0) in men, and 1.0 (95% CI 0.7 to 1.6) in women compared with nonuse periods. The adjusted relative risks of stroke associated with use of oral anticoagulation compared with no use varied by age in men, but not in women. In men aged 60–74 years the adjusted relative risk associated with use of oral anticoagulation compared with no use was 0.5 (95% CI 0.3 to 0.9), and in men aged 75–89 years the adjusted relative risk of stroke associated with oral anticoagulation compared with no use was 0.9 (95% CI 0.4 to 1.8). The adjusted relative risk of stroke increased with age. In men and women, the risk of stroke amongst patients aged 80–89 years was increased by a factor of 2.0 and 2.9 relative to the stroke risk amongst patients aged 60–69 years.

The RE-LY trial\textsuperscript{26} randomized 18,113 patients to receive dabigatran 110 or 150mg twice a day or warfarin dose adjusted to an INR of 2.0–3.0 for a median followup of 2.0 years. A substudy of this trial\textsuperscript{46} assessed the impact of age on the findings and found that there was a significant treatment-by-age interaction, such that dabigatran 110mg twice a day compared with warfarin was associated with a lower risk of major bleeding in patients aged <75 years (1.89% vs. 3.04%; \(p<0.001\)) and a similar risk in those aged \(\geq 75\) years (4.43% vs. 4.37%; \(p=0.89\); \(p\) for interaction <0.001), whereas dabigatran 150mg twice a day compared with warfarin was associated with a lower risk of major bleeding in those aged <75 years (2.12% vs. 3.04%; \(p<0.001\)) and a trend toward higher risk of major bleeding in those aged \(\geq 75\) years (5.10% vs. 4.37%; \(p=0.07\); \(p\) for interaction <0.001). The interaction with age was evident for extracranial bleeding, but not for intracranial bleeding, with the risk of the latter being consistently reduced with dabigatran compared with warfarin irrespective of age. Based on these results, patients with AF at risk for stroke, both doses of dabigatran compared with warfarin have lower risks of both intracranial and extracranial bleeding in patients aged <75 years. In those aged \(\geq 75\) years, intracranial bleeding risk is lower but extracranial bleeding risk is similar or higher with both doses of dabigatran compared with warfarin.

A subgroup analysis of the RE-LY trial\textsuperscript{51}, attempted to estimate effects of dabigatran, compared with warfarin, on stroke, bleeding and mortality in patients with AF in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial according to age and analyzed treatment effects using age as a continuous variable and using age categories. The results showed that the benefits of dabigatran versus warfarin regarding stroke (HR range 0.63 (95% CI 0.46 to 0.86) to 0.70 (0.31 to 1.57) for dabigatran 150 mg twice daily), HR range 0.52 (0.21 to 1.29) to 1.08 (0.73 to 1.60) for dabigatran 110 mg twice daily) and intracranial bleeding were maintained across all age groups (interaction \(p\) values all not significant). There was a highly significant interaction (\(p\) value interaction <0.001) between age and treatment for extracranial major bleeding, with lower rates with both doses of dabigatran compared with warfarin in younger patients (HR 0.78 (0.62 to 0.97) for 150 mg twice daily, HR 0.72 (0.57 to 0.90) for 110 mg twice daily) but similar (HR 1.50 (1.03 to 2.18) for 110 mg twice daily) or higher rates (HR 1.68 (1.18 to 2.41) for 150 mg twice daily) in older patients (\(\geq 80\) years).
A subgroup analysis of the AVERROES trial looked at the efficacy and safety of apixaban compared with aspirin in elderly patients. Compared with aspirin, apixaban was more efficacious for preventing strokes and systemic embolism in patients ≥85 years (absolute rate [AR] 1% per year on apixaban versus 7.5% per year on aspirin; hazard ratio [HR] 0.14, 95% confidence interval [CI] 0.02-0.48) compared with younger patients (AR 1.7% per year on apixaban versus 3.4% per year on aspirin; HR 0.50, 95% CI 0.35-0.69) (P-value for interaction = 0.05). Major hemorrhage was higher in patients ≥85 years compared with younger patients but similar with apixaban versus aspirin in both young and older individuals (4.9% per year versus 1.0% per year on aspirin and 4.7% per year versus 1.2% per year on apixaban) with no significant treatment-by-age interaction (P-value = 0.65).

Two substudies of the ARISTOTLE RCT examined the treatment effects of apixaban 5mg twice daily versus warfarin in elderly patients. In the study by Halvorsen, older patients were at higher overall risk for all cardiovascular events. Risk for events increased in a step-wise manner with age (age <65 vs. age 65-74 vs. age ≥ 75) for stroke or systemic embolism (adj HR age 65-74 1.47; 95% CI 1.11 to 1.94; Adj HR age ≥ 75 1.62; 95% CI 1.18 to 2.22; adjusted p=0.10), all-cause mortality (adj HR age 65-74 1.01; CI 0.84 to 1.21; adj HR age ≥ 75 1.53; 95% CI 1.26 to 1.85; adjusted p<0.0001) and major bleeding (adj HR age 65-74 1.52; 95% CI 1.20 to 1.92; adj HR age ≥75 2.18; 95% CI 1.69 to 2.81; adjusted p<0.0001). Across older age groups, patients treated with apixaban had lower rates of stroke or systemic embolism (HR age 65-74 0.72; 95% CI 0.54 to 0.96; HR age ≥ 75 0.71; 95% CI 0.53 to 0.95; interaction with continuous age p=0.11). Similarly, apixaban reduced the risk of major bleeding compared to treatment with warfarin, across older age groups (HR age 65-74 0.71; 95% CI 0.56 to 0.89; HR age ≥75 0.64; 95% CI 0.52 to 0.79; interaction with continuous age p=0.63). There was no significant difference between treatment groups in stroke or systemic embolism or major bleed in patients <65. Further analysis of patients ≥ 75 years old showed a trend toward increasing benefit of apixaban compared to warfarin therapy with regards to bleeding in patients as renal function worsened (HR eGFR >80 0.60; 95% CI 0.28 to 1.32; HR eGFR >50-80 0.79; 95% CI 0.37 to 1.06; HR eGFR >30-50 0.53; 95% CI 0.37 to 0.76; HR eGFR ≤ 30 0.35; 95% CI 0.14 to 0.86; interaction p value 0.16).

The study by Alexander evaluated patients with one criteria for dose reduction (at least two were required to reduce dose to 2.5mg twice daily): 80 years or older, weight ≤60 kg and creatinine level of at least 1.5mg/dL. Among patients with weight ≤60 kg, those receiving apixaban had a statistically significant decreased risk of major bleeding event (HR 0.6; 95% CI 0.4 to 0.9). Patients 80 years or older and those with creatinine level of at least 1.5mg/dL, were numerically less likely to have a major bleeding event with apixaban, although this did not reach statistical significance (HR 0.7; 95% CI 0.5-1.1 and HR 0.7; 95% CI 0.5 to 1.2 respectively).

Finally, a substudy of the ROCKET AF RCT evaluated once daily rivaroxaban versus warfarin in elderly patients with AF. Outcomes in patients <75 were compared with those in patients ≥75. Patients 75 or older had lower BMI (27.3 vs. 29.0; p<0.0001), had higher mean CHADS2 score (3.69 vs. 3.30; p<0.0001) and lower rates of congestive heart failure (58.6% vs. 65.5%; p<0.0001) and diabetes (33.8% vs. 45.1%; p<0.0001). Compared to patients treated with warfarin, those randomized to treatment with rivaroxaban had similar rates of stroke/systemic embolism (HR Age ≥75 0.80; 95% CI 0.63 to 1.02; HR Age<75 0.95; 95% CI 0.76 to 1.19; p
value for interaction 0.31) and major bleeding (HR Age ≥75 1.11; 95% CI 0.92 to 1.34; HR Age <75 0.96; CI 0.78 to 1.19; p value for interaction 0.34), regardless of age. The only significant observed difference between treatment groups was in risk of hemorrhagic stroke for patients <75 years old (HR 0.47; 95% CI 0.25 to 0.88).

Fourteen studies including observational, small RCTs, and sub-studies of large RCTs compared the effect of different strategies to prevent stroke and bleeding in elderly participants with AF. Of 7 studies comparing the effects of warfarin vs aspirin in older adults, compared to aspirin, warfarin was generally found to be associated with lower risk of stroke/SE/bleeding for both primary and secondary prevention. In studies comparing the effects of DOACs vs warfarin, the DOACs were generally found to be associated with similar or decreased risk of stroke/SE/bleeding compared with warfarin among older adults.

**Patients With AF and Myocardial Infarction**

One substudy of the RE-LY trial evaluated the use of therapies for stroke prevention in AF patients with MI. In this analysis, the relative effects of dabigatran versus warfarin on myocardial ischemic events were consistent in patients with or without a baseline history of MI or coronary artery disease. Patients with a baseline history of coronary artery disease (CAD) or previous MI are at risk for recurrent ischemic events. There were 1,886 (31%) CAD/MI patients in the dabigatran 110mg group, 1,915 (31%) in the dabigatran 150mg group, and 1,849 (31%) in the warfarin group. The relative effects of dabigatran compared with warfarin were highly consistent between patients with prior CAD/MI compared with those without (all probability values for interaction were nonsignificant).

**Elderly Patients With AF and Myocardial Infarction**

One observational study evaluated the effects of a combination of antithrombotics in 7,619 NSTEMI patients aged ≥65 years with AF. Relative to aspirin alone, antithrombotics were associated with increased bleeding risk (adj HR 1.22; 95% CI 1.03 to 1.46 for aspirin+clopidogrel vs. aspirin alone; adj HR 1.46; 95% CI 1.21 to 1.80 for warfarin+aspirin vs. aspirin alone). Patients treated with triple therapy of aspirin+clopidogrel+warfarin had the greatest bleeding risk (HR 1.65; 95% CI 1.30 to 2.10). The rates of major cardiac outcomes (death, readmission for MI, or stroke) were similar between groups, although relative to aspirin alone, there was a trend toward lower risk for the warfarin+aspirin group (HR 0.88; 95% CI 0.78 to 1.00).

**Patients With AF and Peripheral Arterial Disease**

One secondary analysis of the ARISTOTLE trial evaluated outcomes in patients with AF and peripheral arterial disease (PAD), treated with apixaban versus warfarin. Compared to those without PAD, patients with PAD had similar prevention of stroke and systemic embolism with apixaban versus warfarin (PAD HR 0.63; 95% CI 0.32 to 1.25; No PAD HR 0.80; 95% CI 0.66 to 0.96; interaction p value for PAD versus no PAD 0.52). There was similarly no significant interaction between presence of PAD and treatment group on major bleeding (interaction p value 0.58). While data is only available from one study, this suggests that patients with PAD had similar benefit from treatment with apixaban as compared to those without.

**Patients With AF and Underlying Anemia**
One analysis\textsuperscript{55} of the ARISTOTLE RCT\textsuperscript{9} examined patients with anemia treated with apixaban versus warfarin. There was no difference in the benefits of reduced stroke or systemic embolization events (Anemia HR 0.56; 95% CI 0.34 to 0.95; No Anemia HR 0.84; 95% CI 0.68 to 1.01; interaction p value for anemia versus no anemia 0.17) with apixaban in patients with anemia. The incidence of new anemia during treatment was lower in patients with apixaban (HR 0.91; 95% CI 0.84 to 0.98; p=0.037) and there was no significant interaction between underlying anemia and treatment group on any of the bleeding outcomes. This single analysis suggests that the same benefits of apixaban, including decreased risk of stroke or systemic embolism, extend to patients with underlying anemia without differential change in bleeding risk.

**Patients With AF and History of Bleeding**

A secondary analysis\textsuperscript{56} of the ARISTOTLE RCT\textsuperscript{9} evaluated clinical outcomes in patients with history of bleeding treated with 5mg twice daily of apixaban versus warfarin. Patients treated with apixaban had consistently lower rates of bleeding overall and this extended to patients with prior history of bleeding. The only p value for interaction that was significant for apixaban versus warfarin was for major or clinically relevant non-major bleeding (History of bleeding HR 0.82; 95% CI 0.66-1.00; No History of Bleeding HR 0.64; 95% CI 0.57 to 0.72; p value for interaction 0.046). While only informed by one study, this suggests that the lower rates of bleeding observed with treatment with apixaban compared to warfarin are generally similar for patients with a history of bleeding. This benefit may not include lower rates of major or clinically relevant non-major bleeding; further data is necessary to clarify this borderline result.

**Patients With AF and Chronic Obstructive Pulmonary Disease**

Another analysis\textsuperscript{57} of the ARISTOTLE trial\textsuperscript{9} evaluated the treatment effects of apixaban versus warfarin in patients with chronic obstructive pulmonary disease (COPD). Overall, all-cause mortality was higher in patients with a diagnosis of COPD (adj HR 1.60; 95% CI 1.36 to 1.88; p<0.001) while there was no significant difference in major bleeding. There was no significant difference in the effect of apixaban on all-cause mortality (COPD HR 0.80, 95% CI 0.62 to 1.04; No COPD HR 0.92; 95% CI 0.82 to 1.04; p value for interaction 0.35), stroke or systemic embolism (COPD HR 0.92; 95% CI 0.52 to 1.63; No COPD HR 0.78; 95% CI 0.65 to 0.95; p value for interaction 0.62), or major bleeding (COPD HR 0.83; 95% CI 0.57 to 1.02; No COPD HR 0.67; 95% CI 0.60 to 0.75; p value for interaction 0.42) in patients with and without COPD. This single analysis from the ARISTOTLE trial gives data to suggest that there is no treatment difference in the benefits observed with apixaban in patients with or without COPD.

**Patients With AF by Sex**

One secondary analysis\textsuperscript{58} of the ARISTOTLE trial\textsuperscript{9} evaluated the treatment of men versus women with apixaban 5mg twice daily or warfarin. After adjustment, there was no difference between women and men with regard to stroke or systemic embolism (Adj HR 0.91; 95% CI 0.74 to 1.12; p=0.38) but women had significantly less all-cause mortality and cardiovascular death (adjusted HR 0.63; 95% CI 0.55 to 0.73; p<0.001). When evaluated by treatment, there was no significant interaction with sex (women HR 0.73; 95% CI 0.54 to 0.97; men HR 0.84; 95% CI 0.66 to 1.05; p value for interaction 0.45), and major bleeding (women HR 0.56; 95% CI 0.44 to 0.72; men HR 0.88; 95% CI 0.64 to 0.90; p value for interaction 0.06).

In a secondary analysis of the AVERROES study\textsuperscript{59} the effect of treatment with aspirin compared with apixaban on ischemic stroke and major bleeding was assessed in women
compared with men. Female patients with atrial fibrillation are at increased stroke risk compared with male patients, and the underlying reasons for higher risk are uncertain. Women compared with men tended to be older (aspirin, 71.8 versus 68.8 years; apixaban, 71.4 versus 68.6 years), with a higher proportion of those aged ≥75 years. Also, women had less peripheral artery disease (aspirin, 2.4% versus 3.7%; apixaban, 1.4% versus 3.0%), more heart failure, and higher mean CHADS2 (congestive heart failure, hypertension, age of 75 years or older, diabetes [1 point each], stroke or transient ischemic attack [2 points]) scores (aspirin, 2.2 versus 2.0; apixaban, 2.1 versus 2.0). Women compared with men had higher ischemic stroke rates (aspirin, 3.99% versus 2.28%; apixaban, 1.55% versus 0.82%) but similar bleeding rates (aspirin, 1.29% versus 1.22%; apixaban, 1.15% versus 1.36%). The relative effect of apixaban compared with aspirin was similar in men and women for both ischemic stroke (women, 1.55 % versus 3.99%; hazard ratio, 0.39; 95% confidence interval, 0.23-0.64; men, 0.82 % versus 2.28%; hazard ratio, 0.36; 95% confidence interval, 0.19-0.63; p value for interaction 0.84) and major bleeding (women, 1.15 % versus 1.29%; hazard ratio, 1.15; 95% confidence interval, 0.59-2.23; men, 1.36% versus 1.22%; hazard ratio, 1.13; 95% confidence interval, 0.64-2.02; p value for interaction 0.97).

In only two studies assessing potentially differences in treatment effect by sex both included apixaban but the comparators were different – one was warfarin and one was aspirin. No interaction between sex and treatment was found for major bleeding (for either comparator, warfarin or aspirin) or for ischemic stroke (as compared to aspirin).

**Patients With AF and Diabetes**

A substudy\textsuperscript{60} of the ARISTOTLE RCT\textsuperscript{9} analyzed the treatment effect of apixaban 5mg twice daily versus warfarin in patients with and without diabetes. Overall, patients with diabetes were younger, had higher weights, were more likely to have hypertension and prior stroke or systemic embolism, and had higher CHA2DS2-VASc Scores. Compared with warfarin, patients with diabetes and who received apixaban were numerically less likely to have stroke or systemic embolism (HR 0.75; 95% CI 0.53 to 1.05) or death from any cause (HR 0.89; 95% CI 0.66 to 1.20). There were no significant interactions related to diabetes for the efficacy endpoints. All-cause bleeding was significantly lower in patients with diabetes who received apixaban (HR 0.73; 95% CI 0.66 to 0.81). While ISTH major bleeding was not significantly lower in patients with diabetes who were treated with apixaban, it was significantly lower in those without diabetes (diabetes HR 0.96; 95% CI 0.74 to 1.25; no diabetes HR 0.60; 95% CI 0.51 to 0.52; p value for interaction 0.0034). This interaction remained after adjustment.

A substudy\textsuperscript{61} of the ROCKET AF Trial\textsuperscript{5} evaluated treatment effect of rivaroxaban daily versus warfarin in patients with and without diabetes. Overall, 5,695 (39.9%) of patients enrolled in the ROCKET AF trial had diabetes. Patients with diabetes had higher rates of vascular death (3.24 vs. 2.63; p=0.0001) and myocardial infarction (1.35 vs. 0.75; p<0.0001). There was not significant interaction between treatment and diabetes status for the outcomes of stroke/SE (HR diabetes 0.82; 95% CI 0.63 to 1.08; HR no diabetes 0.92; 95% CI 0.75 to 1.13; p value for interaction 0.53) and major/NMCR bleeding (HR diabetes 0.98; 95% CI 0.88 to 1.10; HR no diabetes 1.09; 95% CI 0.99 to 1.20; p value for interaction 0.17). However, in a composite endpoint of stroke/systemic embolism/vascular death/MI, patients with diabetes who were treated with rivaroxaban had slightly lower risk (HR diabetes 0.84; 95% CI 0.72 to 0.99; HR no diabetes 1.01; 95% CI 0.88 to 1.17; p value for interaction 0.097), although the interaction was not significant.
In a supplemental analysis of RE-LY trial.\textsuperscript{62} Of 18,113 patients in RE-LY, 4221 patients (23.3\%) had DM. Patients with DM were younger (70.9 vs. 71.7 years), more likely to have hypertension (86.6\% vs. 76.5\%), coronary artery disease (37.4\% vs. 24.9\%) and peripheral vascular disease (5.6\% vs. 3.2\%); (all \(p < 0.01\)). Time in therapeutic range for warfarin-treated patients was 65\% for diabetic versus 68\% for non-diabetic patients (\(p < 0.001\)). Regardless of assigned treatment, stroke or systemic embolism was more common among patients with DM (1.9\% per year vs. 1.3\% per year; \(p<0.001\)). DM was also associated with an increased risk of death (5.1\% per year vs. 3.5\% per year; \(p=0.001\)) and major bleeding (4.2\% per year vs. 3.0\% per year; \(p<0.001\)). The absolute reduction in stroke or systemic embolism with dabigatran compared to warfarin was greater among patients with DM than those without DM (dabigatran 110mg: 0.59\% per year vs. 0.05\% per year; dabigatran 150mg: 0.89\% per year vs. 0.51\% per year). There was however, no statistically significant interaction between treatment (dabigatran 110mg or dabigatran 150 mg vs. warfarin) and diabetes for stroke or systemic embolism, ischemic stroke, hemorrhagic stroke, death, major bleeding, or intracranial bleeding.

The results from three studies assessing the potential impact of diabetes on treatment effect were inconsistent; no impact on treatment effect was seen between dabigatran and warfarin on any of the included efficacy or safety outcomes; a statistically significant interaction between treatment (apixaban vs warfarin) was found only for major bleeding (diabetics did not have the same statistically significant reduction in major bleeding as non-diabetics); and a statistically significant interaction between treatment (rivaroxaban vs warfarin) was found only for a composite endpoint of stroke/systemic embolism/vascular death/MI (diabetics had a statistically significant reduction that was not seen in non-diabetics).

**Patients With AF and Aspirin Treatment**

A secondary analysis\textsuperscript{63} of the ARISTOTLE trial,\textsuperscript{9} evaluated the use of apixaban 5mg twice daily compared to warfarin in patients with concomitant aspirin therapy. Overall, patients treated with aspirin were more likely to be male, have a history of MI, PCI, CABG or PAD and to have diabetes or hypertension. After adjustment for baseline confounders and variables associated with aspirin use, patients treated with aspirin had higher rates of thromboembolic events (stroke or systemic embolism, ischemic stroke, myocardial infarction) and higher rates of bleeding. Apixaban treatment led to similar reductions in stroke or systemic embolism (Aspirin HR 0.58; 95\% CI 0.39 to 0.85; No Aspirin HR 0.84; 95\% CI 0.66 to 1.07; \(p\) value for interaction 0.10) and consistent reductions in major bleeding (aspirin HR 0.77; 95\% CI 0.60 to 0.99; no aspirin HR 0.65; 95\% CI 0.55 to 0.78; \(p\) value for interaction 0.29) in patients treated with and without aspirin.

One study\textsuperscript{64} also evaluated the use of aspirin by treatment group in the ROCKET-AF trial.\textsuperscript{5} Overall, 5,205 (46.5\%) of patients had chronic aspirin use at baseline. Patients on aspirin were younger (median age 72 versus 73 years old) and had slightly higher CHADS\(_2\) scores (mean 3.5 versus 3.4). Among all patients, those with baseline aspirin use had higher risk of all-cause death (HR 1.27; 95\% CI 1.13 to 1.42; \(p<0.0001\)) and vascular death (HR 1.29; 95\% CI 1.11 to 1.49; \(p=0.0006\)) as well as major or NMCR bleeding (HR 1.32; 95\% CI 1.21 to 1.43; \(p<0.0001\)) or major bleeding (HR 1.46, 95\% CI 1.25 to 1.71; \(p<0.0001\)). There was no significant interaction between treatment and use of aspirin versus none on any of the efficacy or safety outcomes (stroke/SE, stroke/SE/vascular death, all-cause death, vascular death, stroke, SE, MI, major/NMCR bleeding, major bleeding, ICH, fatal major bleeding, hemorrhagic stroke).
In an ENGAGE AF substudy, patients who received a single antiplatelet drug during the study at the discretion of their physician were compared to those who did not receive a single antiplatelet drug during the study. A total of 4,912 patients received a single antiplatelet drug during the study of which 92.5% were aspirin. In the high dose edoxaban vs. warfarin comparisons, there were no statistically significant interactions between treatment and use of single antiplatelet drug vs. none on stroke or systemic embolic events, ischemic stroke, hemorrhagic stroke, MI, cardiovascular death, major bleeding, intracranial bleeding, or any bleeding. Similar results were seen for the low dose edoxaban vs. warfarin comparisons and for the large subset of aspirin only users. From a total of three studies, no impact on treatment effect between apixaban, rivaroxaban, low dose endoxaban or high dose endoxaban vs warfarin was seen in patients with concomitant aspirin administration.

**Patients With AF and Hypertension**

One secondary analysis of the ROCKET AF RCT evaluated outcomes based on screening systolic blood pressure and hypertension. At baseline, 12,902 patients had a history of controlled or uncontrolled hypertension (HTN). Compared to patients without hypertension, those with hypertension had a trend toward higher risk for stroke or systemic embolism (HTN HR 1.22; 95% CI 0.89 to 1.66; uncontrolled HTN HR 1.42; 95% CI 1.03 to 1.95; p value 0.06). There was no significant interaction between treatment and HTN status (no HTN versus controlled hypertension versus uncontrolled hypertension) on all ischemic/thrombotic or bleeding outcomes. While there is only data from one study available, this suggests that there is no difference in the observed treatment effects of rivaroxaban and warfarin among patients with varying degrees of HTN.

**Patients With AF and Heart Failure**

In an ENGAGE AF substudy, the 8145 patients in the ENGAGE AF study in either the warfarin or high dose edoxaban treatment groups who had heart failure (6344 with NYHA I-II and 1801 with NYHA III-IV) were compared to the 5926 who did not have heart failure. There was no statistically significant interaction between heart failure groups (no heart failure, NYHA I-II, and NYHA III-IV) and treatment for stroke or systemic embolic events, ischemic stroke, hemorrhagic stroke, any cause death, cardiovascular death, cardiovascular hospitalization, major bleeding, intracranial hemorrhage, or GI bleeding.

A secondary analysis of the ROCKET AF RCT evaluated treatment with rivaroxaban once daily versus warfarin in patients with heart failure. Overall, 9033 (63.7%) of patients in the ROCKET AF trial had heart failure diagnosis (clinical HF or EF <40%) at the time of randomization. Patients with heart failure were significantly more likely to have stroke/systemic embolism/vascular death (HR 1.28; 95% CI 1.11 to 1.47; p=0.0006) as well as all-cause death (HR 1.34; 95% CI 1.37 to 1.98; p<0.0001) and vascular death (HR 1.65; 95% CI 1.37 to 1.98; p<0.0001). There was no significant interaction with regards to heart failure status for efficacy or safety outcome between treatment groups. However, patients with heart failure who were treated with rivaroxaban were significantly less likely to experience hemorrhagic stroke (HR 0.38; 95% CI 0.19 to 0.76).

Data from these two studies give similar findings and suggest that patients had similar ischemic and bleeding outcomes based on the treatment received regardless of heart failure status.
Patients With AF and Left Ventricular Hypertrophy

In a post-hoc analysis of the Randomized Evaluation of Long-term anticoagulation therapy (RE-LY) Study, the hypothesis that left ventricular hypertrophy (LVH) interferes with the antithrombotic effects of dabigatran and warfarin in patients with atrial fibrillation (AF) was tested. LVH was defined by electrocardiography (ECG) and included patients with AF on the ECG tracing at entry. LVH was present in 2353 (22.7%) out of 10,372 patients. In patients without LVH, the rates of primary outcome (composite of stroke and systemic embolism) were 1.59% per year with warfarin, 1.60% with dabigatran 110 mg (HR vs. warfarin 1.01, 95% confidence interval (CI) 0.75-1.36) and 1.08% with dabigatran 150 mg (HR vs. warfarin 0.68, 95% CI 0.49-0.95). In patients with LVH, the rates of primary outcome were 3.21% per year with warfarin, 1.69% with dabigatran 110 mg (HR vs. warfarin 0.52, 95% CI 0.32-0.84) and 1.55% with 150 mg (HR vs. warfarin 0.48, 95% CI 0.29-0.78). The interaction between LVH status and dabigatran 110 mg vs. warfarin was significant for the primary outcome (P = 0.021) and stroke (P = 0.016), but not for major bleeding (p=0.235). However, there was no statistically significant interaction between LVH status and dabigatran 150 mg vs. warfarin for the primary outcome (p=0.244), any stroke (P=0.147) or major bleeding (p=0.888).

In this single study, the treatment effect (reduced risk of stroke or systemic embolism, reduced risk of any stroke and no difference in major bleeding) between the FDA approved 150 mg dose of dabigatran and warfarin was not statistically significantly impacted by LVH.
References in Appendix G


# Appendix H. PCORI Methodology Standards Checklist

<table>
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<tr>
<th>PCORI Methodology Standards Checklist: SER Update</th>
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<tbody>
<tr>
<td><strong>Contract No.</strong></td>
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<td><strong>Task Order No.</strong></td>
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<tr>
<td><strong>EPC</strong></td>
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<tr>
<td><strong>Project Title</strong></td>
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<tr>
<th>Standard Category</th>
<th>Abbrev</th>
<th>Standard</th>
<th>Is this standard applicable to this SER update?</th>
<th>List sections and pages of the SER report where you address this standard</th>
<th>If applicable, describe how and why the SER update deviated from this standard?</th>
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<tbody>
<tr>
<td><strong>Cross-Cutting Standards</strong></td>
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<tr>
<td>Standards for Formulating Research Questions</td>
<td>RQ-1</td>
<td>Identify Gaps in Evidence</td>
<td>Yes</td>
<td>ES6, 5, 198</td>
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<td>RQ-2</td>
<td>Develop a Formal Study Protocol</td>
<td>Yes</td>
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<td>RQ-3</td>
<td>Identify Specific Populations and Health Decision(s) Affected by the Research</td>
<td>Yes</td>
<td>11, 116, 161-181</td>
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<td>RQ-4</td>
<td>Identify and Assess Participant Subgroups</td>
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<td>Standards Associated with Patient-Centeredness</td>
<td>PC-1</td>
<td>Engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context.</td>
<td>Yes</td>
<td>5-6, 9, 20</td>
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<td>RQ-5</td>
<td>Select Appropriate Interventions and Comparators</td>
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<td>RQ-6</td>
<td>Measure Outcomes that People Representing the Population of Interest Notice and Care About</td>
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<td>PC-2</td>
<td>Identify, Select, Recruit, and Retain Study Participants Representative of the Spectrum of the Population of Interest and Ensure that Data Are Collected Thoroughly and Systematically from All Study Participants</td>
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<td>PC-3</td>
<td>Use Patient-Reported Outcomes When Patients or People at Risk of a Condition Are the Best Source of Information</td>
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<td>PC-4</td>
<td>Support dissemination and implementation of study results</td>
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<td>Standards for Data Integrity and Rigorous Analyses</td>
<td>Assess Data Source Adequacy</td>
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<td>IR-2</td>
<td>Describe Data Linkage Plans, if Applicable</td>
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<td>IR-3</td>
<td>A priori, Specify Plans for Data Analysis that Correspond to Major Aims</td>
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<td>IR-4</td>
<td>Document Validated Scales and Tests</td>
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<td>16-17</td>
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<td>IR-5</td>
<td>Use Sensitivity Analyses to Determine the Impact of Key Assumptions</td>
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<td>Forest Plots</td>
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<td>IR-6</td>
<td>Provide Sufficient Information in Reports to Allow for Assessments of the Study’s Internal and External Validity</td>
<td>Yes</td>
<td>9-20, Appendixes</td>
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<td>MD-1</td>
<td>Describe in Protocol Methods to Prevent and Monitor Missing Data</td>
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<td>MD-2</td>
<td>Describe Statistical Methods to Handle Missing Data in Protocol</td>
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<td>Standards for Heterogeneity of Treatment Effect (HTE)</td>
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<td>State the Goals of HTE Analyses</td>
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<td>HT-2</td>
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<td>For all HTE Analyses, Pre-specify the analysis plan; for Hypothesis driven HTE Analyses, Pre-specify Hypotheses and supporting evidence base</td>
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<td>HT-3</td>
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<td>All HTE claims must be based on appropriate statistical contrasts among groups being compared, such as interaction tests or estimates of differences in treatment effect</td>
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### PCORI Methodology Standards Checklist: SER Update

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#### Standards for Specific Study Designs and Methods

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<th>Requirements for the Design and Features of Registries</th>
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<td>Standards for Selection and Use of Registries</td>
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<td>DR-3</td>
<td>Robust Analysis of Confounding Factors</td>
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<th>Standards for Data Networks as Research-Facilitating Structures</th>
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| Causal Inference Standards | CI-1 | Define Analysis Population Using Covariate Histories | N/A |

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H-5
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<td>Standards for Studies of Diagnostic Tests</td>
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<table>
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<tr>
<th>AT-3</th>
<th>Specify Structure and Analysis Plan for Bayesian Adaptive Randomized Clinical Trial Designs</th>
<th>N/A</th>
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<tr>
<td>AT-4</td>
<td>Ensure Clinical Trial Infrastructure Is Adequate to Support Planned Adaptation(s)</td>
<td>N/A</td>
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<td>AT-5</td>
<td>Use the CONSORT statement, with Modifications, to Report Adaptive Randomized Clinical Trials</td>
<td>N/A</td>
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<tr>
<td>Standards for Systematic Reviews</td>
<td>SR-1</td>
<td>Adopt the Institute of Medicine (IOM) standards for systematic reviews of comparative effectiveness research, with some qualifications.</td>
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Appendix I. Expert Guidance and Review

Stakeholder Input in Formulating the Research Protocol
To be provided in the Final Report

Peer Reviewers
To be provided in the Final Report