
# Special Assessment to Inform CMS Drug Price Negotiation: Eliquis and Xarelto

# Supplemental Materials

## Table of Contents

# A. Background and Prescribing Information: Supplemental Information

## A1. Definitions

**Atrial fibrillation (AF)** is an irregular heart rhythm (arrhythmia) that can lead to blood clots in the heart and increase the risk of stroke. During AF, the heart's lower chambers beat irregularly.

**Non-valvular atrial fibrillation (NVAF)** originates in the upper chambers of the heart and is not caused by a problem with one's heart valve.

**Valvular atrial fibrillation (VAF)** refers to patients with atrial fibrillation in the setting of mitral stenosis or artificial heart valves.

**Anticoagulants** are medications that help prevent blood clots. They work by interrupting the process involved forming blood clots and are otherwise known as blood thinners.

**Warfarin** is a specific type of anticoagulant prescribed to people who have had a condition caused by a blood clot, such as a stroke, heart attack, deep vein thrombosis. Warfarin aims to prevent clotting tendency but not prevent clotting completely. Thus, warfarin dose must be carefully monitored by blood tests and the prescribing physician may alter the dose depending on the results of the blood test.

**International normalized ratio (INR)** is a standardized guideline that measures the time it takes for a clot to form. It is standardized based upon the prothrombin time. INR for warfarin when used to prevent clots in atrial fibrillation should be between 2-3.

**Direct oral anticoagulants (DOACs)** are anticoagulants that help prevent blood clots from forming. DOACs work by interrupting the system that forms blood clots, causing the blood to take longer to clot and reducing risk of stroke. Traditional anticoagulants, such as warfarin, require monthly blood tests, dietary considerations, and attention to uncontrolled bleeding. DOACs, however, do not require regular blood tests or specific diets and begin to work quicker than warfarin. DOACs were previously known as NOACs: new/novel oral anticoagulants. DOACs can be used in the prevention of stroke for people with NVAF and management of venous thromboembolism. DOACs include apixaban, rivaroxaban, dabigatran, and edoxaban.[1,2]

**$CHADS_2$** is a tool used to estimate risk of stroke in patients with AF and guide treatment decisions. $CHADS_2$ was designed to identify patients at high risk of stroke to target for warfarin treatment based on risk factors (e.g., congestive heart failure, hypertension/high blood pressure, age [75 years], diabetes, and prior stroke/TIA).[3]

**$CHA_2DS_2$-VASc** is an updated tool from $CHADS_2$ to estimate risk of stroke in patients with AF. $CHA_2DS_2$-VASc was developed from $CHADS_2$ score to include more stroke risk factors in the calculation (e.g., vascular disease, age [65-74 years], and female sex). Low risk patients are those with a $CHA_2DS_2$-VASc of 0 (male) and 1 (female). It is recommended that oral anticoagulants are given to those with $\geq$1 additional stroke factors.[4]

**HAS-BLED** is a tool used to estimate risk of major bleeding for patients with AF on anticoagulation to inform treatment decisions. HAS-BLED was developed to complement the $CHA_2DS_2$-VASc assessment that assesses stroke risk. HAS-BLED should be used as an "alarm bell" to assist in minimizing risk of bleeding by identifying risk factors that can be avoided or reversed (e.g., current systolic blood pressure).[5]

**Ablation** is a medical procedure used to treat atrial fibrillation by burning or freezing a small area of the heart, using radiofrequency energy, to cause scarring which helps to break electrical signals that cause irregular heartbeats.

**Percutaneous coronary intervention (PCI)** is a non-surgical procedure used to treat the blockages in a coronary artery. During this procedure, a small tube (sheath) is placed into a blood vessel. A catheter (small tube) is placed within the sheath and guided to the heart and the affected coronary artery. Once the affected artery is located, a second catheter with a balloon is positioned within the narrowed/blocked section of the artery, inflated, and this opens the artery. A stent may be placed into the newly opened artery to hold the artery open. This procedure opens narrowed or blocked sections of the artery to restore blood flow. This can be used to in those with coronary artery disease, where plaque deposits within the walls of the arteries cause them to narrow, reduce blood flow, and lead to chest pain or heart attack.[6]

**Coronary artery bypass grafting (CABG)** is a surgical procedure that restores blood flow to the heart when coronary arteries may be blocked or narrowed. During this procedure, a healthy vein/artery from elsewhere in the body is used and one end is attached to the end of the largest artery in the body and the other end is attached to the blocked/narrowed artery. This allows for blood to flow through the newly created blood vessel bypassing the narrowed section of the artery and into the heart. CABG is also called heart bypass surgery.[7]

Definitions of safety and efficacy outcomes are described in Table A1.1 below.

**Table A1.1 Definitions of Outcomes Across the Main Trials.**

| Outcome | Description |
|---|---|
| **All stroke** | Focal neurologic deficit, from a nontraumatic cause, lasting ≥24 hours and was categorized as ischemic (with or without hemorrhagic transformation), hemorrhagic, or of uncertain type (in the case of patients who did not undergo brain imaging or in whom an autopsy was not performed).[8-10] |
| **Major stroke** | Strokes (any type) that result in death, long-term paralysis, or coma. |
| **Transient ischemic attack** | A transient ischemic attack (TIA) is defined as a nontraumatic abrupt onset of a focal neurologic deficit lasting <24 hours.[9,10] |
| **Ischemic stroke** | Stroke without focal collections of intracranial blood.[10] Ischemic stroke can include ischemic stroke with hemorrhagic conversion (occurs when peripheral blood extravasates across a disrupted blood brain barrier into the brain following ischemic stroke), stroke of uncertain type, and retinal ischemic event (embolism, infarction).<br><br>Strokes were categorized as ischemic or hemorrhagic or cause unknown (based on computed tomographic or magnetic resonance scanning or autopsy).[8] |
| **Hemorrhagic stroke** | Stroke with focal collections of intracerebral blood.[10] This occurs when an artery in the brain leaks blood or ruptures and places too much pressure on brain cells.[11] |
| **Systemic embolism** | Clinical history consistent with an acute loss of blood flow to a peripheral artery (vascular occlusion), supported by evidence of embolism (arterial occlusion) from surgical specimens, autopsy, angiography, vascular imaging, or other objective testing.[9]<br>In the absence of other likely mechanisms, (e.g., trauma, atherosclerosis, instrumentation).[10]<br>In ROCKET AF, they noted that, in the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities should be made with caution and requires angiographic demonstration of abrupt arterial occlusion.[10] |
| **Myocardial infarction** | In the absence of a PCI or CABG, myocardial infarction was defined as: Clinical symptoms consistent with myocardial ischemia and cardiac biomarker elevation (Troponin I or T, creatine kinase-muscle and brain subunit [CK-MB]) greater than ULN (or, if no CK-MB or troponin values are available[9], if a total CK ≥ 2×ULN) or development of new pathological Q waves in at least 2 contiguous leads on the electrocardiogram or autopsy confirmation.[8-10]<br>The ROCKET AF trial included additional guidance for participants having PCI or after coronary artery bypass graft surgery:<br>For participants having a PCI, a myocardial infarction was defined as: CK-MB (or CK in the absence of CK-MB) >3 x ULN for samples obtained within 24 hours of the procedure if the baseline values were normal or at least a 50% increase over elevated baseline values that were stable or decreasing or development of new pathological Q waves in at least 2 contiguous leads on the electrocardiogram. Symptoms of cardiac ischemia were not required.<br>After coronary artery bypass graft surgery, a myocardial infarction was defined as either: |

| | |
|---|---|
| | • CK-MB (or CK in the absence of CK-MB) >5 x ULN for samples obtained within 24 hours of the procedure with development of new pathological Q waves in at least 2 contiguous leads on the electrocardiogram; OR<br>• CK-MB (or CK in the absence of CK-MB) >10 x ULN for samples obtained within 24 hours of the procedure with or without development of new pathological Q waves in at least 2 contiguous leads on the electrocardiogram.[10] |
| **All-cause mortality** | Death by any cause. |
| **Cardiovascular deaths** | Deaths due to ischemic and hemorrhagic stroke, SE, myocardial infarction (MI), sudden death, heart failure, other cardiovascular, and unobserved deaths.[9] |
| **Fatal stroke** | Fatal stroke is defined as death from any cause within 30 days of stroke.[8] |
| **Fatal bleeding** | Bleeding event that is the primary cause of death or contributes directly to death. |
| **Minor bleeding** | All acute clinically overt bleeding events not meeting the criteria for either major bleeding or clinically relevant non-major bleeding are classified as minor bleeding.[8,12] Reported as "minimal" bleeding in ROCKET AF: all other overt bleeding episodes not meeting the criteria for major or non-major clinically relevant bleeding will be classified as minimal bleeding.[10] |
| **Major bleeding** | Major bleeding was defined as defined as clinically overt bleeding that is associated with at least 1 of the following criteria: a reduction in hemoglobin of 2.0 g/dL or more; or a transfusion of 2 or more units of packed red blood cells or whole blood; or symptomatic bleeding in a critical area or organ such as: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or a fatal outcome (or the RE-LY considered life-threatening bleeding: fatal, symptomatic intracranial bleed; reduction in hemoglobin level of at least 5.0 g/L; transfusion of at least 4 U of blood or packed cells; associated with hypotension requiring the use of intravenous inotropic agents; or necessitated surgical intervention).[8-10]<br>Major bleeding in all the trials included fatal bleeding. |
| **Intracranial bleeding (ICB)** | Any bleeding within the intracranial vault, including brain parenchyma and surrounding meningeal spaces.[13] ICB can be difficult to distinguish from ischemic stroke. Symptoms may include headache, nausea, seizures and focal or generalized neurologic symptoms. |
| **Major gastrointestinal (GI) bleeding** | Major bleeding starting in GI tract. |
| **GI bleeding** | Any type of bleeding that starts in GI tract. |
| **Clinically relevant bleeding** | Clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to hospital admission, physician-guided medical or surgical treatment, or a change in antithrombotic therapy.[9] |
| **PE/DVT** | Deep-vein thrombosis (DVT) occurs when a blood clot forms in one or more of the deep veins in the body, usually in the legs. DVT itself is not life-threatening but the blood clots may break free and travel through your bloodstream; potentially leading to a Pulmonary embolism (PE). A PE is a sudden blockage in your pulmonary arteries, the blood vessels that send blood to your lungs.<br><br>No study reported how they measured PE/DVT. In this report, we report the data of these two outcomes combined, given their association. In the RE-LY trial, only PE is reported and thus used as a proxy for PE/DVT. |

# B. Unmet Need: Supplemental Information

## B1. Methods

### *B1.1 Qualitative Methods*

We sought input from three practicing cardiologists in the treatment of NVAF to ensure that our report included all relevant evidence and reflected current practice. We also sought input from three patients with NVAF to ensure that our analyses considered the outcomes that are most important to them, to accurately reflect their experience of NVAF and its treatment, and to understand the degree of remaining unmet need. We conducted 30-minute semi-structured phone interviews with each of the aforementioned individuals in the early stages of this assessment to gather this information.

# C. Clinical Guidelines

Both US and European Guidelines are consistent in recommending anticoagulation with either a DOAC or warfarin for patients with non-valvular atrial fibrillation who are at elevated risk for stroke as assessed by a clinical prediction rule like $CHADS_2$. They generally recommend a DOAC over warfarin in patients without contraindications to a DOAC. Based on a lack of direct trial comparisons, no guideline recommends one DOAC over another DOAC.

## ACC/AHA/HRS 2019 Update of 2014 Guidelines[14]

Oral anticoagulation is recommended for patients with atrial fibrillation and a history of a prior stroke, a prior transient ischemic attack, or a $CHA_2DS_2$- VASc score of 2 or greater in men or 3 or greater in women. Options include warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban. DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in DOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve.)

For patients with AF who have a $CHA_2DS_2$- VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation.

## AAFP 2017[15]

Chronic anticoagulation is recommended for patients who have atrial fibrillation unless they are at low risk of stroke ($CHADS_2$ <2) or have specific contraindications (strong recommendation, high quality evidence). Choice of anticoagulation therapy should be based on patient preferences and patient history. Options for anticoagulation therapy may include warfarin, apixaban, dabigatran, edoxaban, or rivaroxaban. Currently, the evidence base does not support a recommendation for one anticoagulant over another. The choice of anticoagulant should be based on shared decision making between the patient and physician. Individuals on warfarin not consistently in the therapeutic range, and those who do not have cost constraints, should consider the direct oral anticoagulants.

## ACCP 2018[16]

The CHEST guidelines on antithrombotic therapy for atrial fibrillation recommend the use of the $CHA_2DS_2$-VASc in patients with AF to estimate the risk of ischemic stroke and SE. For patients with NVAF who are at low risk of stroke ($CHA_2DS_2$-VASc of 0 in men and 1 in women), they suggest no antithrombotic therapy. For patients with NVAF and one or more $CHA_2DS_2$-VASc risk factors, they

suggest oral anticoagulation. When selecting the anticoagulant, they recommend using a DOAC rather than dose-adjusted vitamin K antagonist. For patients with prior unprovoked bleeding, bleeding on warfarin therapy, or at high risk for bleeding, they suggest apixaban, edoxaban, or dabigatran. When using a dose-adjusted vitamin K antagonist, they recommend aiming for an INR of 2-3. If the quality of the vitamin K antagonist is poor (defined as time in therapeutic range <65%), they recommend interventions to improve the control, such as more frequent INR testing, reviewing adherence or potential drug interactions, and further education.

## AGS 2023[17]

The American Geriatrics Beers Criteria 2023 recommends that patients ≥65 years of age do not initiate warfarin for NVAF unless there are substantial barriers or contraindications to using a DOAC. Among DOACs, apixaban and edoxaban are considered the safest. Individuals who have been using warfarin long term with good INR control may reasonably continue warfarin. The criteria recommend avoiding rivaroxaban for long-term treatment of NVAF in favor of a safety alternative, and avoiding use of rivaroxaban when CrCl < 15 mL/min. The criteria also caution in using dabigatran over other DOACs, and avoiding use when CrCl <30 mL/min.

## European Society of Cardiology 2020[18]

For stroke prevention in non-valvular AF patients who are eligible for anticoagulation, DOACs are recommended in preference to vitamin K antagonists (warfarin). Anticoagulation is recommended for stroke prevention in AF patients with $CHA_2DS_2$-VASc score >_2 in men or >_3 in women. Anticoagulation should be considered for stroke prevention in AF patients with a CHA2DS2-VASc score of 1 in men or 2 in women. Treatment should be individualized based on net clinical benefit and consideration of patient values and preferences.

## NICE 2021[19]

A direct-acting oral anticoagulant is recommended for patients with atrial fibrillation and a $CHA_2DS_2$-VASc score of 2 or above, taking into account the risk of bleeding. Apixaban, dabigatran, edoxaban and rivaroxaban are all recommended as options.

Consider anticoagulation with a direct-acting oral anticoagulant for men with atrial fibrillation and a $CHA_2DS_2$-VASc score of 1, taking into account the risk of bleeding. Apixaban, dabigatran, edoxaban and rivaroxaban are all recommended as options.

If direct-acting oral anticoagulants are contraindicated, not tolerated or not suitable in people with atrial fibrillation, offer a vitamin K antagonist (warfarin).

# D. Comparative Clinical Effectiveness: Supplemental Information

## D1. Detailed Methods

### PICOTS

***Population***

The population of focus for the review was adults (≥ 18 years) with nonvalvular atrial fibrillation (NVAF).

Data permitting, we evaluated the evidence for subpopulations defined by:

- Those who are disabled
- Those who are terminally ill
- Those with end-stage renal disease
- Pediatric population
- Older adults (<65, 65-74 years, and ≥75 years)
- Other subpopulations, as relevant

***Interventions***

The interventions of interest for this review were:

- Apixaban
- Rivaroxaban

***Comparators***

Data permitting, we compared apixaban and rivaroxaban to dabigatran and warfarin (target international normalized ratio [INR]: 2-3).

***Outcomes***

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - All-cause mortality
    - Quality of life
    - Stroke
        - Major stroke
        - Minor stroke
        - Ischemic stroke
        - Hemorrhagic stroke
    - Systemic embolism
    - Transient ischemic attack
    - Myocardial infarction (MI)
    - Adverse events including
        - All bleeding
            - Minor bleeding
            - Major bleeding
            - Intracranial bleeding
            - Major gastrointestinal (GI) bleeding
            - GI bleeding
            - Clinically relevant bleeding

***Timing***

Evidence on intervention effectiveness and safety were derived from studies of at least one year.

***Settings***

All relevant settings were considered, including inpatient, outpatient/clinical, office, and home settings in the United States.

## Study Design

Evidence was abstracted from Phase III and beyond randomized controlled trials as well as high-quality systematic reviews; high-quality observational studies that met our PICOTS criteria and had a sample size > 100,000 were considered for long-term outcomes and low frequency adverse events. Our evidence review included input from patients and other grey literature when the evidence met ICER standards (for more information, see ICER's grey literature policy).

**Table D1.1. PRISMA 2020 Checklist**

| Section and Topic | Item # | Checklist item |
|---|---|---|
| TITLE | | |
| Title | 1 | Identify the report as a systematic review. |
| ABSTRACT | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. |
| INTRODUCTION | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. |
| METHODS | | |
| Eligibility Criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. |
| Information Sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. |
| Search Strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. |
| Selection Process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. |
| Data Collection Process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. |
| Data Items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. |
| Study Risk of Bias Assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. |
| Effect Measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. |

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|---|---|---|
| Synthesis Methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. |
| Reporting Bias Assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). |
| Certainty Assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. |
| RESULTS | | |
| Study Selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. |
| Study Characteristics | 17 | Cite each included study and present its characteristics. |
| Risk of Bias in Studies | 18 | Present assessments of risk of bias for each included study. |
| Results of Individual Studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. |
| Results of Syntheses | 20a | For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies. |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. |
| Reporting Biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. |
| Certainty of Evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. |

| | | |
|---|---|---|
| DISCUSSION | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. |
| | 23b | Discuss any limitations of the evidence included in the review. |
| | 23c | Discuss any limitations of the review processes used. |
| | 23d | Discuss implications of the results for practice, policy, and future research. |
| OTHER INFORMATION | | |
| Registration and Protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. |
| Competing Interests | 26 | Declare any competing interests of review authors. |
| Availability of Data, Code, and Other Materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. |

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

## Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on rivaroxaban and apixaban for nonvalvular atrial fibrillation followed established best research methods.[20,21] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for relevant Phase III trials. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables D1.2-1.3. We also conducted a targeted search for relevant high-quality observational studies with N > 100,000 that examined long-term outcomes and low frequency adverse events for the interventions and comparators.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews).

**Table D1.2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials for Phase III RCTs**

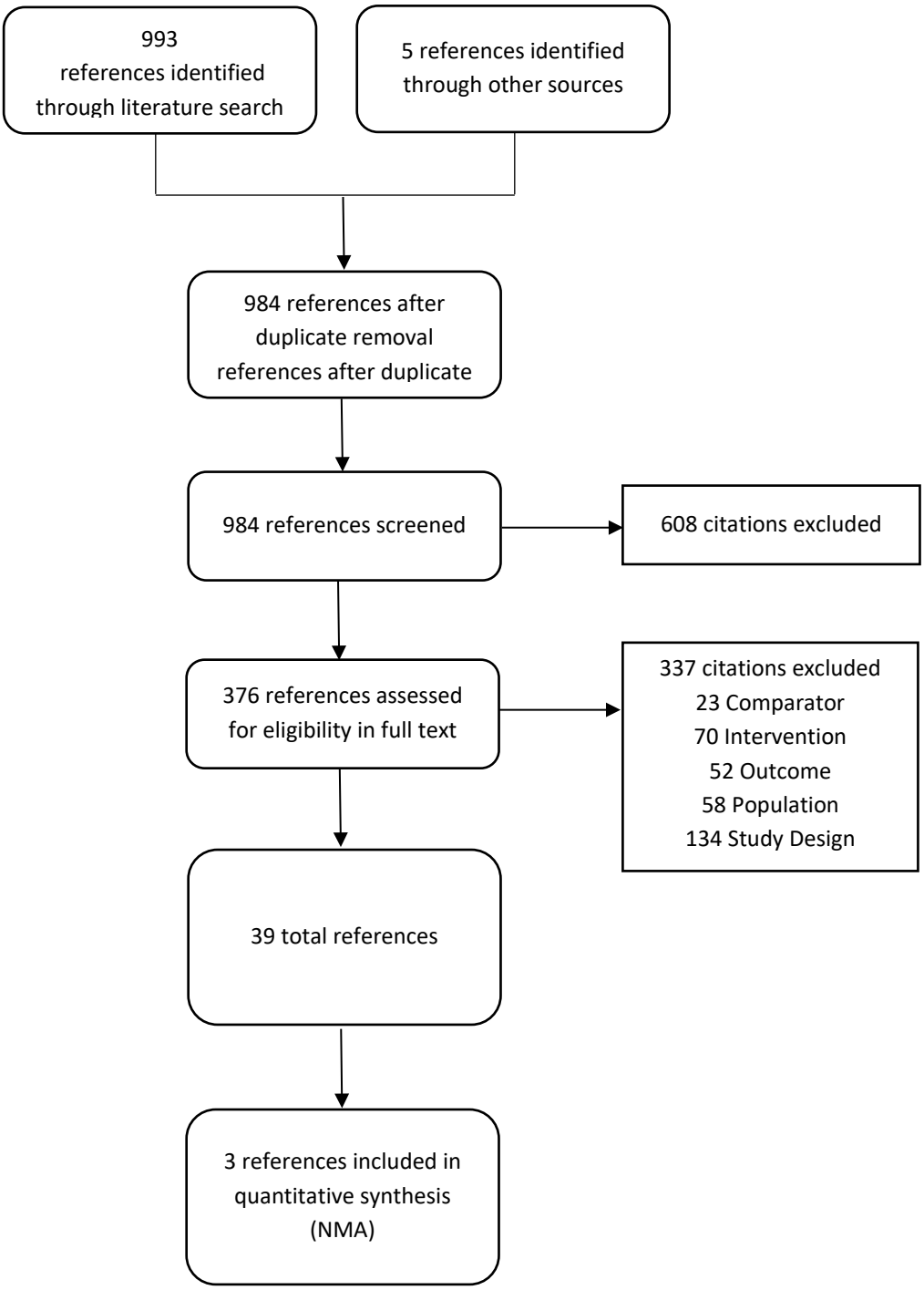
| # | Search Term |
|---|---|
| 1 | exp atrial fibrillation/ |
| 2 | 'atrial fibrillation*'.ti,ab. |
| 3 | 1 or 2 |
| 4 | exp rivaroxaban/ |
| 5 | ('xarleto' or 'bay 59-7939' or 'bay 59-7939' or 'bay597939' or 'rivaroxaban').ti,ab. |
| 6 | 4 or 5 |
| 7 | exp dabigatran/ |
| 8 | ('BIBR 1048' or 'Pradaxa' or 'Dabigatran Etexilate' or 'Etexilate' or 'Dabigatran').ti,ab. |
| 9 | 7 or 8 |
| 10 | exp warfarin/ |
| 11 | ('Apo-Warfarin' or 'Gen-Warfarin' or 'Warfarin Potassium' or 'Coumadin' or 'Coumadine' 'Warfarin Sodium' or 'Warfarin').ti,ab. |

| | |
|---|---|
| 12 | 10 or 11 |
| 13 | ('Apixaban' or 'Eliquis' or 'BMS 562247' or 'BMS562247' or 'BMS-562247-01' or 'BMS-562247').ti,ab. |
| 14 | 3 and (12 or 9 or 6 or 13) |
| 15 | 14 and ('stroke' or 'bleeding').ti,ab. |
| 16 | (clinical trial, phase iii or clinical trial, phase iv or randomized controlled trial).pt. |
| 17 | 15 and 16 |
| 18 | (animals not (humans and animals)).sh. |
| 19 | 17 not 18 |
| 20 | limit 19 to english language |
| 21 | remove duplicates from 20 |

**Table D1.3. Search Strategy of EMBASE SEARCH for Phase III RCTs**

| # | Search Term |
|---|---|
| 1 | 'atrial fibrillation'/exp |
| 2 | 'rivaroxaban'/exp |
| 3 | 'bay 59 7939':ti,ab OR 'bay59-7939':ti,ab OR 'bs 112':ti,ab OR 'bs112':ti,ab OR 'rivarolto':ti,ab OR 'xarelto':ti,ab OR 'rivaroxaban':ti,ab OR 'dst 8294':ti,ab OR 'dst8294':ti,ab OR 'jnj 39039039':ti,ab OR 'jnj39039039':ti,ab |
| 4 | #2 OR #3 |
| 5 | 'dabigatran'/exp |
| 6 | 'bibr 953':ti,ab OR 'bibr953':ti,ab OR 'dabigatran':ti,ab |
| 7 | #5 OR #6 |
| 8 | 'warfarin'/exp |
| 9 | 'warfarin':ti,ab OR 'jantoven':ti,ab OR 'bms 56793':ti,ab OR 'bms56793':ti,ab OR 'befarin':ti,ab OR 'coumadan':ti,ab OR 'coumadan sodico':ti,ab OR 'coumadin':ti,ab OR 'coumadin sodium':ti,ab OR 'coumadine':ti,ab OR 'warfarin potassium':ti,ab OR 'warfarin sodium':ti,ab |
| 10 | #8 OR #9 |
| 11 | 'apixaban'/exp |
| 12 | 'apixaben':ti,ab OR 'apixaban':ti,ab OR 'bms 562247':ti,ab OR 'bms562247':ti,ab OR 'eliques':ti,ab OR 'tah 3311':ti,ab OR 'tah3311':ti,ab OR 'eliquis':ti,ab OR 'pf 0465257':ti,ab OR 'pf0465257':ti,ab |
| 13 | #11 OR #12 |
| 14 | #1 AND (#4 OR #7 OR #10 OR #13) |
| 15 | ('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp |
| 16 | #14 NOT #15 |
| 17 | #16 AND [english]/lim |
| 18 | #17 AND [medline]/lim |
| 19 | #17 NOT #18 |
| 20 | #19 AND ('cohort analysis'/de OR 'cross sectional study'/de OR 'observational study'/de OR 'retrospective study'/de OR 'chapter' OR 'editorial'/de OR 'letter'/de OR 'note'/de OR 'review'/de OR 'short survey'/de OR 'case report'/de OR 'conference abstract'/de) |
| 21 | #19 NOT #20 |
| 22 | #21 AND ('phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de) |

**Figure D1.1. PRISMA flow Chart Showing Results of Literature Search for Apixaban, Rivaroxaban, Dabigatran, and Warfarin.**



## Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, MN); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal.

## Data Extraction

Data were extracted into Microsoft Word and Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

## Risk of Bias Assessment

We examined the risk of bias for each randomized control trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[21,23] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: "low risk of bias," "some concerns," or "high risk of bias." Guidance for risk of bias ratings using these criteria is presented below:

***Low risk of bias****: The study is judged to be at low risk of bias for all domains for this result.*

***Some concerns**: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

***High risk of bias**: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the following outcomes: Stroke/SE and Major Bleeding. See Table D1.4-5.

**Table D1.4. Risk of Bias Assessment (Stroke/Systemic Embolism)**

| Studies (Author, Year) | Randomization process | Deviation from the intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall Risk of Bias |
|---|---|---|---|---|---|---|
| ARISTOTLE (Granger et al. 2011) | Low | Low | Low | Low | Low | Low |
| ROCKET AF (Patel et al. 2011) | Low | Low | Low | Low | Low | Low |
| RE-LY (Connolly et al. 2009) | Low | Low | Low | Low | Low | Low |
| RENAL-AF (Pokorney et al. 2022) | Low | Some concerns | Some concerns | Low | Some concerns | High |
| Valkyrie (De Vriese et al. 2020) | Low | Some concerns | Low | Low | Some concerns | Some concerns |

**Table D1.5. Risk of Bias Assessment (Major Bleeding)**

| Studies (Author, Year) | Randomization process | Deviation from the intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall Risk of Bias |
|---|---|---|---|---|---|---|
| ARISTOTLE (Granger et al. 2011) | Low | Low | Low | Low | Low | Low |
| ROCKET AF (Patel et al. 2011) | Low | Low | Low | Low | Low | Low |
| RE-LY (Connolly et al. 2009) | Low | Low | Low | Low | Low | Low |
| RENAL-AF (Pokorney et al. 2022) | Low | Some concerns | Some concerns | Low | Some concerns | High |
| Valkyrie (De Vriese et al. 2020) | Low | Some concerns | Low | Low | Some concerns | Some concerns |

### Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[24,25]

### Assessment of Bias

Given the emerging nature of the evidence base for these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include non-valvular atrial fibrillation, atrial fibrillations, rivaroxaban, XARELTO™, bay 59 7939, bay59-7939, rivarolto, Xarelto, apixaban, ELIQUIS™, apixaben, bms 562247, bms562247, eliques, tah 3311, tah3311, eliquis, pf 0465257, pf0465257, warfarin, JANTOVEN™, bms 56793, bms56793, befarin, dabigatran, PRADAXA™, bibr 953, bibr953. We selected studies which would have met our inclusion criteria, and for which no findings have been published.

### Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in Tables D3.1-D3.41 and synthesized qualitatively below. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality were noted in the text of the report.

## D2. Additional Clinical Information

### Evidence Base

#### *Apixaban versus warfarin*

*ARISTOTLE*

ARISTOTLE was a Phase III RCT that evaluated the efficacy of oral apixaban 5 mg twice daily (2.5 mg twice daily if >1 of the following criteria: ≥ 80 years, ≤ 60kg, or creatinine level ≥ 1.5 mg per deciliter) versus warfarin (target international normalized ratio [INR] 2-3) in adults with AF and at least one risk factor for stroke.[9] Baseline characteristics and risk scores for all trials are outlined in Table D3.2. Of note, a greater proportion of patients were younger (30% were <65 years of age) and were taking blood pressure medication (e.g., ACE inhibitors or ARB) (70%) compared to the two other pivotal trials comparing DOACs to warfarin: ROCKET AF and RE-LY.

Patients were included if they had AF and at least one risk factor for stroke: at least 75 years old, previous stroke, transient ischemic attack, or systemic embolism, symptomatic heart failure within the previous 3 months or left ventricular ejection fraction of no more than 40%, diabetes mellitus,

or uncontrolled hypertension. Patients were excluded if they had AF due to a reversible cause, moderate or severe mitral stenosis, other conditions that required anticoagulation, stroke in the last seven days, a need for aspirin (> 165 mg a day), and severe renal insufficiency. See Table D3.1. If individuals were receiving a vitamin K antagonist (VKA), they were asked to discontinue the drug three days before randomization. Patients were stratified based on whether they had previously received warfarin and according to the clinical site.[9]

Patients in both groups received two sets of tablets each day and had INR testing every month to maintain blinding. Patients in the warfarin group would receive the true INR value along with dosage recommendation and the apixaban group would receive a sham INR value. Patients in the warfarin group had INR in therapeutic range for 66% (median) of the time.[9] To manage temporary discontinuation (e.g., for elective surgical procedures), sham INR values were provided to maintain concealment of group assignment. Possible reasons for permanent discontinuation are noted in Table D3.1 and discontinuations due to bleeding are reported in Table D3.14. When individuals discontinued the drug at the end of the trial, guidance was provided in making the transition to open-label warfarin (or other VKA) while maintaining concealment of group assignment.

At the start of the trial, patients were required to attend visits to monitor INR and complete assessments of clinical outcomes and adverse events every three months.[9] An independent, blinded, clinical events committee adjudicated all strokes, TIAs, systemic emboli, bleeding, MIA, and cause of death. Patients were not required to stop the study drug due to an event.

The trial was designed to test for noninferiority on the primary efficacy: stroke/SE, and test for superiority for primary safety outcome: and major bleeding and secondary outcomes, such as non-major bleeding, all-cause mortality, and composite outcomes. Patients were followed for a median of 1.8 years. The study aimed to recruit 18,000 participants, based upon the primary noninferiority hypothesis that apixaban would preserve at least 50% of the relative reduction in the risk of stroke/SE associated with warfarin. The hypothesis led to a lower 95% confidence interval of 1.88 for the relative risk with placebo as compared with warfarin; with two additional noninferiority tests: 1) the 95% CI should not include ≥ 1.38 and 99% CI should not include > 1.44 to declare noninferiority.[12] The occurrence of the primary occurrence was estimated to occur in 448 participants and, with the hypothesis above, this led to the planned recruitment number and period of two years. The primary and secondary analyses were conducted with Cox proportional-hazards model, stratified by previous warfarin status and geographic location. The primary and secondary analyses using intention-to-treat population, and bleeding outcomes used safety population (i.e., patients who received at least one dose of the drug). A modified intention-to-treat analysis was used to review bleeding events and composite outcomes.

***Rivaroxaban versus warfarin***

*ROCKET AF*

ROCKET AF was a Phase III RCT that evaluated the efficacy of oral rivaroxaban 20 mg once daily (15 mg once daily in those with moderate renal impairment) versus warfarin (INR 2-3) in adults with NVAF who were at moderate-to-high risk of stroke.[10] Moderate-to-high risk of stroke was determined by history of stroke, TIA, or SE, had a CHA2DS2-VASc score of ≥ 2, or two of the following risk factors: heart failure or left ventricular ejection fraction of ≤ 35%, hypertension, ≥ 75 years old, or diabetes. Patients were excluded if they had significant mitral stenosis, AF caused by a reversible disorder, active internal bleeding, recent stroke, history of intracranial bleeding, or a hemorrhagic disorder. Patients were also excluded if they had a need for aspirin of > 100 mg per day or had recent use of IV antiplatelets, fibrinolytics, or treatment with a strong inhibitor or inducer of cytochrome P450 3A4. Of note, the study investigators aimed to recruit fewer than 10% of participants who had not had a previous ischemic stroke, TIA, or SE, and who had no more than two risk factors.[10] Compared to the two other trials, patients were more likely to have diabetes (40%) and have had a prior stroke, TIA, or SE (54% vs. 20%); as reflected in the higher $CHADS_2$ scores or $CHA_2DS_2$-VASc scores (an estimate of stroke risk in patients with AF; See Supplement A1) and HAS-BLED scores (an estimate of major bleed risk). Although no patients in this trial were under 65 years of age, the median and IQR for age suggest no notable differences in age compared to the ARISTOTLE and RE-LY trials.

Patients in both groups received one tablet each day and all patients had INR testing every month to maintain blinding. Patients in the warfarin group would receive the true INR value and the rivaroxaban group would receive a sham INR value. Patients in the warfarin group had INR in therapeutic range for 55% (mean) of the time.[10]

Patients were engaged in the double-blind treatment period with an end-of-study visit. Patients returned for visits at Week 1, 2, 4, and then every 4 weeks thereafter. An independent, blinded, clinical events committee adjudicated all strokes, systemic emboli, death, MI, TIA, bleeding. Investigators were instructed to stop study drug permanently when a primary end point was suspected. After the end-of-study visit or when individuals discontinued the study drug, they were moved to a posttreatment observation period for approximately 30 days where they transitioned to open-label VKA or another appropriate therapy and were followed for events.

The trial was designed to test for noninferiority on the primary efficacy: stroke/SE and in the per-protocol population, and test for superiority for the primary safety outcome: major and nonmajor clinically relevant bleeding and secondary outcomes in the safety population and intention-to-treat population, such as cardiovascular death, MI, among others. Patients were exposed to treatment for a median of 590 days and followed for a median of 707 days. The study aimed to recruit 14,000 participants based upon a minimum of 364 events to provide statistical power to calculate the

noninferiority margin of 1.46 with a one-side alpha of 0.025. Hazards ratio, confidence intervals, and p values were calculated with Cox proportional-hazards models. There was a violation of GCP guidelines that led to an exclusion of 93 participants and additional quality issues at another site, although these quality issues did not lead to the exclusion of any additional participants. The duration of the treatment period depended on the time required to recruit enough participants and time on study drug varied across participants. In this report, we were interested in the time on-treatment. Thus, we used data from the time on-treatment in the ITT population for the primary outcome, and the time on-treatment in the safety population for all other outcomes, where ITT population data was unavailable. Hazard ratios were near identical for the primary outcome for the ITT and safety populations supporting our approach.

***Dabigatran versus warfarin***

*RE-LY*

RE-LY was a Phase III RCT that evaluated the efficacy of oral dabigatran 110 mg and 150 mg twice daily versus warfarin (INR 2-3) in adults with AF and increased risk of stroke.[26] Patients were blinded to the two doses of dabigatran, but unblinded to the assignment of warfarin or dabigatran. In this report, we only present data from the 150 mg dose as this is the approved dose for NVAF. Patients in the warfarin group had INR in therapeutic range for 64% (mean) of the time. Patients were included if they had AF and at least one of the following: previous ischemic stroke, TIA, or systemic embolism, left ventricular dysfunction, age >=75 years, age >=65 with either diabetes mellitus, history of coronary artery disease or hypertension. Patients were excluded if they had a stroke in the past 14 days, conditions associated with increased risk of bleeding, severe renal impairment (estimated creatinine clearance ≤ 30 mL/min), active liver disease, infective endocarditis, or anemia or thrombocytopenia. If patients were receiving warfarin, they were asked to discontinue warfarin on the day of randomization. Use of aspirin was permitted if < 100 mg per day. In terms of baseline characteristics, this trial recruited around 16% of those under the age of 65 and had comparable proportion of patients over 75 years as ROCKET AF.

The trial was designed to test for noninferiority on the primary outcome: stroke or systemic embolism and superiority for the primary safety outcome: major bleeding and secondary outcomes, such as stroke, death, MI, and composite outcomes. A blinded endpoint methodology was implemented in this trial. Patients were followed for a median of 2 years. The study initially aimed to recruit 15,000 participants (increased to 18,000 to maintain statistical power in case of low event rate), based upon the primary noninferiority hypothesis that the upper bound of one-sided 97.5% CI for the relative risk of an outcome with dabigatran as compared to warfarin fall below 1.46, assuming one year of follow-up, and event rate of 1.6% per year.

There were two protocol changes during the trial. First, participants were balanced for enrollment based upon whether they had received long-term therapy with VKA. Second, there was an increase in sample size to 18,000 to maintain statistical power if there were a low event rate.

Patients completed follow-up assessments every 3 months for the first year, then every 4 months until the end of the study.[26] Each outcome was adjudicated by two blinded independent investigators. From the methods, it was not clear whether patients had to discontinue due to experiencing an outcome event but, of note, 2-3% discontinued due to an outcome event. Patients receiving warfarin underwent INR testing at least once every four weeks. For individuals assigned warfarin who had to temporarily discontinue the study drug during the trial, due to an elective surgical procedure, they were recommended to stop warfarin 5 days prior to the procedure and resume when clinically feasible with or without bridging therapy. For those assigned dabigatran, they were recommended to stop the study drug 24 hours before procedure and resume when clinically feasible. Possible reasons for permanent discontinuation are noted in Table D3.1. When individuals discontinued dabigatran due to adverse events, there was no specific protocol for prescribing, and it was left up to clinical judgement as to whether these individuals were instead prescribed warfarin or another anticoagulant medication. The analyses were conducted with Cox proportional-hazards modelling. Analyses used the intention-to-treat population.

***End-Stage Renal Disease Trials***

*RENAL AF*

RENAL AF was a Phase IV randomized, open-label, blinded-outcome RCT that evaluated the efficacy of oral apixaban 5 mg twice daily versus warfarin (INR 2-3) in those with AF and end-stage renal disease (ESRD) in the US.[27] A subset of patients (29%) in the apixaban group were given apixaban 2.5 mg twice daily if they had a target weight ≤ 60 kg or age ≥ 80 years; higher compared to the ARISTOTLE trial (4.7%). Treatment was planned for up to 15 months but, as the study was terminated early, patients were only followed for a median of 330 (apixaban) or 340 (warfarin) days. AF is common in those with ESRD and there have been noted concerns about bleeding rates and calcific uremic arteriolopathy in those with ESRD who use warfarin. The primary outcome was major or clinically relevant nonmajor bleeding, and secondary outcomes included stroke/SE and death. Patients were included if they had AF, as defined as AF on ECG at enrollment or two or more reports of AF from separate monitoring events at least 2 weeks apart, CHA2DS2-VASc score of ≥ 2, and ESRD treated with hemodialysis for ≥ 3 months. Patients were excluded if they had other conditions that required anticoagulation, moderate or severe mitral stenosis, need for aspirin (> 81 mg a day), life expectancy < 3 months, or kidney transplant expected in < 3 months. Patients could continue IV heparin at the start or during hemodialysis. Patients were stratified based on whether they had previously received warfarin and according to the clinical site. Patients in the warfarin group had INR in therapeutic range for 44% (median) of the time; lower than the other trials described in this report (55-66%).[27]

RENAL-AF was designed to test for noninferiority on the primary outcome: major or clinically relevant nonmajor bleeding and test for superiority for primary and secondary outcomes, including stroke/SE and death. RENAL-AF trial initially planned to recruit 762 participants, based on testing the noninferiority hypothesis. However, there were issues with recruitment of these participants and this study was ultimately terminated early. The study investigators noted that this was in part due to patients with ESRD receiving hemodialysis were deemed not suitable for anticoagulants by their physician and the high mortality rate in this group meant that it was challenging to enroll and maintain patients in ESRD trials.[27] As a result, the study recruited 154 participants overall and results were considering exploratory.

*Valkyrie*

Valkyrie study was a Phase IV randomized, open-label trial that evaluated the efficacy of oral rivaroxaban 10 mg once daily versus warfarin (INR 2-3) in those with NVAF on chronic hemodialysis.[28] There was an additional group who received rivaroxaban and menquinone-7. As this intervention was not one of our interventions of interest, we did not include the results of this group in our report. Patients were included if they had NVAF, ESRD with chronic hemodialysis, and had a CHA2DS2-VAS2 score of ≥ 2. Patients were excluded if they had known intestinal malabsorption, life expectancy < 1 year, prosthetic mechanical heart valve, or had liver dysfunction. Patients in the warfarin group had INR in therapeutic range for 55% (mean) of the time.[28]

The study was designed to examine whether the replacement of warfarin by rivaroxaban can slow progression of vascular calcification. Thus, the primary outcome was the absolute and relative change in coronary artery calcification score. Secondary outcomes included a composite of non-fatal stroke and cardiovascular events, death, and bleeding. Participants were followed for 18 months. This study was underpowered to detect comparative benefit of rivaroxaban and warfarin on stroke and bleeding.

***Observational Data***

Lau et al. (2022)[29] was a multinational, active-comparator cohort study of 527,226 new users of DOACs across four countries. We only report data from apixaban, dabigatran, and rivaroxaban. All participants had adults with AF, had not previously used a DOAC, and had at least one year of observation data before the index date. Baseline characteristics for all observational studies are reported in Tables D3.33-34. The primary outcomes were a composite of ischemic stroke/SE, intracranial hemorrhage, gastrointestinal bleeding, and all-cause mortality. The follow-up duration for each DOAC ranged from 534 to 1612 days.

Chan et al. (2022)[30] was a nationwide retrospective cohort study that used the Taiwan National Health Insurance Research Database to examine the risk of interstitial lung disease (ILD) in patients who received dabigatran, apixaban, or rivaroxaban compared to those who received warfarin. The

study noted that there were previous cases of ILD associated with apixaban, especially in Asian patients, but no large observational study had examined this relationship. All patients were adults with AF diagnosed between 2010 and 2017. The primary outcome was new-onset idiopathic ILD and secondary efficacy outcomes included major bleeding, stroke, SE, among others. Patients were followed from the drug index date to first occurrence of ILD, death, or until the end of the study.

Graham et al. (2015)[31] was a retrospective cohort study that examined the efficacy and safety of dabigatran and warfarin in a real-world setting of Medicare patients who were new users of dabigatran or warfarin. All participants had AF or atrial flutter and had filled a new prescription between October 2010 and December 2012. Patients were prescribed dabigatran 75mg, dabigatran 150mg, or warfarin. The primary outcomes were ischemic stroke, major, GI, intracranial, or intracerebral bleeding, and MI. Patients were followed until they reached an outcome event, had a gap in anticoagulant supply, transferred to nursing home or hospice care, or until the end of the study period. We only report data from the dabigatran 150 mg dose as this is the FDA-approved dose for NVAF.

## NMA Methods

As direct evidence for the comparative efficacy of apixaban and rivaroxaban versus dabigatran was unavailable, we evaluated the feasibility of conducting quantitative synthesis for the outcomes of interest. We explored any differences in study populations, study design, analytic methods, and outcome assessment for each outcome of interest in the RCTs evaluating the interventions/comparators of interest. Trials deemed sufficiently similar in terms of population, intervention type, and outcome definitions were included in the NMAs. We did not include the two ESRD trials in the NMA due to differences in study design, baseline characteristics, and study quality.

All three trials were conducted in patients with NVAF. Outcome definitions for the trials were sufficiently similar, see Table A1.1. Patients in the ARISTOTLE trial were younger and patients in the ROCKET AF were more likely to have had a prior stroke, TIA, or SE; as reflected in the higher CHADS2 scores. However, there was no consistent effect modification for age or CHADS2 scores for stroke/SE or major bleeding across the trials. Based on this, we assumed that the populations were similar enough to conduct the NMAs. We conducted 13 NMAs using data from the three trials described above; 6 are reported in the main report (stroke/SE, MI, all-cause mortality, major bleeding, all discontinuation, and discontinuation due to AEs) and 7 are reported below in Supplement D. See Figure D2.1 for the NMA figure.

The NMAs combined data from trials comparing apixaban, rivaroxaban, or dabigatran with warfarin using a Bayesian Markov Chain Monte Carlo method to estimate the hazard ratio for apixaban or rivaroxaban versus dabigatran and warfarin. We used noninformative prior distributions for all model parameters for all analyses. We initially discarded the first 40,000 iterations as "burn-in" and

base inferences on an additional 40,000 iterations using three chains. Convergence of chains were assessed with the Gelman-Rubin statistic and visually using trace plots. We assumed a priori that the fixed-effect model would be more appropriate because it is standard practice within a Bayesian environment when the network is entirely made up of single study connections. We did conduct random-effects model and we report the results from random effects models with noninformative prior distributions for all model parameters in Tables D2.10-12. The credible intervals from the random effects NMA are many orders of magnitude wider than those of the original trial results, which reflects the poor accuracy of random effects models when there are only single study connections in the network. Posterior mean residual deviance and deviance information criterion values were calculated to assess the goodness of fit of the models to the data. All models had very good fit to the data. See Table D2.9.

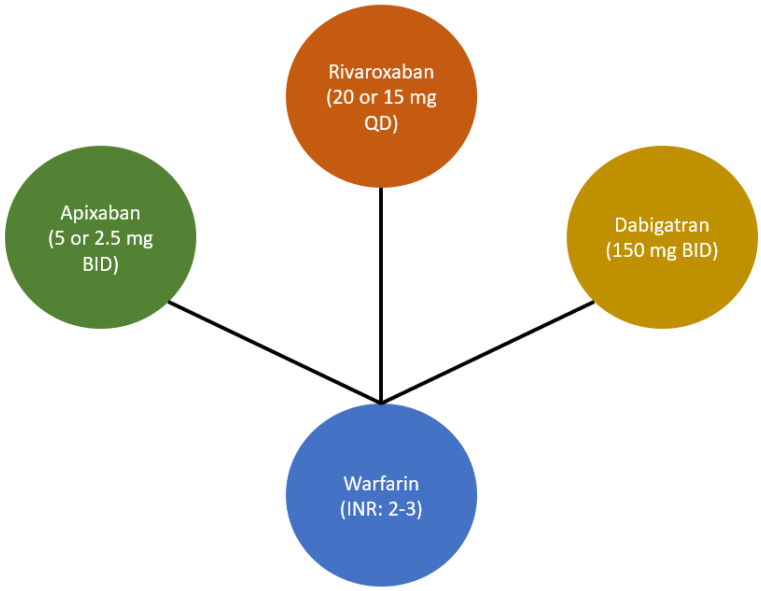
We analyzed the mean difference in hazard ratio (HR) using a generalized linear model. The primary inputs to the models were the Log-HR and the associated standard error, derived from the mean HR for the various outcomes and their associated 95% CIs that were reported in the studies. The Log-HR was calculated by taking the natural log of the mean HR. The standard error was derived from the width of the log of the 95% CIs divided by 3.92 (1.96 x 2). In two of the three trials, HRs were reported. In one trial (RE-LY), risk ratios (RR) were reported. We assumed that the risk ratio could be used to approximate a hazard ratio as the duration of the trial was comparable to the two trials reporting HR and the risk of the outcome, e.g., stroke/SE, major bleeding etc., were unlikely to change over the duration of the trial. In situations where only the number of events per group were reported (i.e., HR or RR were not provided), we estimated the risk ratio and 95% CI. For the PE/DVT outcome, the ARISTOTLE trial only reported PE. We used data from the ROCKET AF trial that separated data by PE and DVT and estimated the RR for these outcomes. The number of patients with an event were similar and the RR were similar with overlapping confidence intervals. From this, we assumed that the rates of DVT in the ARISTOTLE trial would be similar to PE and used DVT as a proxy for PE/DVT. Input data for each NMA are provided in Tables D3.3-3.4.

***NMA Limitations***

Our NMAs have certain limitations. First, we had a small network of trials and the evidence plot was a star network with no head-to-head comparisons of the interventions of interest. As the trials were sufficiently similar, we were able to analyze the data using a fixed-effect model. Additional trials and data would enable more precise estimates to be calculated and to be able to assess inconsistency across the trials. Second, due to the presentation of the data across the trials, we assumed that the RR was comparable to HR in order to conduct the NMA. We acknowledge RR and HR are different measures, with RR measuring the ratio of an outcome in an exposed group versus a non-exposed group and HR measuring the ratio of the hazard rate of an outcome between the two groups at a given time period. We also acknowledge that using RR to estimate HR may lead to biases in estimating the absolute risk difference when event rate is low and follow-up time is short.

However, all studies were at least one year duration, and we did not expect the risk of the event to change over the duration of the trials. Thus, we used either HR or RR as input for the NMAs. Third, one of the trials (ARISTOTLE) reported data for only PE, not DVT, unlike the two other clinical trials. While PE and DVT are two separate conditions, a PE occurs of the DVT clot breaks off and travels to the lungs. The ROCKET AF trial reported PE and DVT separately, both of which occurred at low frequency in the trial. We estimated the RR for PE and DVT for this trial separately and the RRs were similar with overlapping confidence intervals. From this, we assumed that we could use PE alone as a proxy for PE/DVT in the ARISTOTLE trial. The NMA reported no effects between treatments and thus the economic model did not model differential effects for this outcome. Finally, we compared our results to prior NMAs and the magnitude of effectiveness were generally similar for all analyses. See Section D4 and Table D4.1.

**Figure D2.1. Diagram for All NMA Outcomes**.




## NMA Results

### *Apixaban*

*Direct Evidence: Apixaban versus warfarin*

In the ARISTOTLE trial, patients who received apixaban had a lower rate of all stroke (HR: 0.79; 95% CI: 0.65 to 0.95; p=0.01) and hemorrhagic stroke (HR: 0.51; 95% CI: 0.35 to 0.75; p<0.001) compared

to those who received warfarin, but a similar rate of ischemic stroke (HR: 0.92; 95% CI: 0.74 to 1.13; p=0.42). The rate of PE/DVT was low overall and similar between the two groups (apixaban:0.04% per year and warfarin: 0.05%) (HR: 0.78; 95% CI: 0.74 to 1.13, p=0.42). In terms of safety, patients receiving apixaban had a lower rate of intracranial bleeding (0.33% per year) compared to those in the warfarin group (0.8%) (HR: 0.42; 95% CI: 0.30 to 0.58). The risk of major gastrointestinal (GI) bleed and cardiovascular death were not statistically significantly different, but point estimates favored apixaban (GI bleed HR: 0.89; 95% CI: 0.70 to 1.15; cardiovascular death HR: 0.89; 95% CI: 0.76 to 1.04).[9] See Table D3.3.

*Indirect Evidence: Apixaban versus dabigatran*

The risk of all stroke and ischemic stroke were not statistically significantly different between the groups, but the point estimates favored dabigatran (all stroke HR: 1.23; 95% CrI: 0.92 to 1.67; ischemic stroke HR: 1.21; 95% CrI: 0.87 to 1.68). The risk of hemorrhagic stroke and PE/DVT were not statistically significantly different between the groups, but the point estimates favored apixaban (hemorrhagic stroke HR: 0.87; 95% CrI: 0.48 to 1.57; PE/DVT HR: 0.49; 95% CrI: 0.14 to 1.68). In terms of safety, fewer major GI bleeds were seen with apixaban (HR: 0.59; 95% CrI: 0.42 to 0.84), but there was no difference in intracranial bleeding (HR: 1.05; 95% CrI: 0.63 to 1.77) and cardiovascular death (HR: 1.05; 95% CrI: 0.84 to 1.30). As noted in the main report, apixaban had lower total discontinuation compared to dabigatran See Tables D2.1-D2.10.

***Rivaroxaban***

*Direct Evidence: Rivaroxaban versus warfarin*

In the ROCKET AF trial, the rate of all stroke and ischemic stroke were not statistically significantly different between the groups but favored rivaroxaban (all stroke: HR: 0.85; 95% CI: 0.70 to 1.03; p=0.09; ischemic stroke: HR: 0.94; 95% CI: 0.75 to 1.17; p=0.58). Patients receiving rivaroxaban had a lower rate of hemorrhagic stroke (HR: 0.59; 95% CI: 0.37 to 0.93; p=0.02). The rate of PE/DVT was higher in the ROCKET AF trial compared to the ARISTOTLE and RE-LY trials, and rates were similar in the two groups. In terms of safety, patients receiving rivaroxaban had a lower rate of intracranial bleeding (0.5% per year) compared to those in the warfarin group (0.7%) (HR: 0.67; 95% CI: 0.47 to 0.93). The rate of cardiovascular death was not statistically significantly different between the groups but favored rivaroxaban (HR: 0.89; 95% CI: 0.73 to 1.10). In contrast, patients receiving rivaroxaban had a higher rate of major GI bleeding (3.15% per year) compared to warfarin (2.16%).[10] See Table D3.3.

*Indirect Evidence: Rivaroxaban versus dabigatran*

The risk of all stroke, hemorrhagic stroke, and ischemic stroke were not statistically significantly different between the groups, but the point estimates favored dabigatran (all stroke HR: 1.33; 95% CrI: 0.98 to 1.80; hemorrhagic stroke HR: 1.24; 95% CrI: 0.88 to 1.73; ischemic stroke HR: 1.24; 95%

CrI: 0.88 to 1.73). The risk of PE/DVT was not statistically significantly different between the groups, but the point estimate favored rivaroxaban (HR: 0.53; 95% CrI: 0.21 to 1.31). In terms of safety, the risk of intracranial bleeding was not statistically significantly different between the groups and credible intervals were large (HR: 1.67; 95% CrI: 0.99 to 2.82). There were no clear differences in major GI bleed (HR: 0.97; 95% CrI: 0.72 to 1.32) and cardiovascular death (HR: 1.05; 95% CrI: 0.81-1.36). As noted in the main report, rivaroxaban had lower rates of total discontinuation compared to dabigatran. See Tables D2.1-D2.10.

**Table D2.1. Network Meta-Analysis Results for <u>All Stroke</u>.**

| | | | |
|---|---|---|---|
| Apixaban (5 mg or 2.5 mg BID) | | | |
| 0.93<br>(0.93, 1.21) | Rivaroxaban (20 mg or 15 mg QD) | | |
| 1.23<br>(0.92, 1.66) | 1.33<br>(0.98, 1.8) | Dabigatran (150 mg BID) | |
| **0.79**<br>**(0.66, 0.95)** | 0.89<br>(0.70, 1.03) | **0.64**<br>**(0.51, 0.81)** | Warfarin (INR: 2-3) |

BID: twice a day, QD: once a day.

**Legend**: Each box represents the estimated hazard ratio and 95% credible interval for the direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.0.

**Table D2.2. Network Meta-Analysis Results for Hemorrhagic Stroke.**

| | | | |
|---|---|---|---|
| Apixaban (5 mg or 2.5 mg BID) | | | |
| 0.87<br>(0.48, 1.57) | Rivaroxaban (20 mg or 15 mg QD) | | |
| 1.96<br>(0.93, 4.11) | **2.27**<br>**(1.04, 4.97)** | Dabigatran (150 mg BID) | |
| **0.51**<br>**(0.35, 0.75)** | **0.59**<br>**(0.37, 0.93)** | **0.26**<br>**(0.14, 0.49)** | Warfarin (INR: 2-3) |

BID: twice a day, QD: once a day.

**Legend**: Each box represents the estimated hazard ratio and 95% credible interval for the direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.0.

**Table D2.3. Network Meta-Analysis Results for Ischemic Stroke.**

| | | | |
|---|---|---|---|
| Apixaban (5 mg or 2.5 mg BID) | | | |
| 0.98<br>(0.72, 1.32) | Rivaroxaban (20 mg or 15 mg QD) | | |
| 1.21<br>(0.87, 1.68) | 1.24<br>(0.88, 1.73) | Dabigatran (150 mg BID) | |
| 0.92<br>(0.75, 1.13) | 0.94<br>(0.75, 1.17) | **0.76**<br>**(0.59, 0.98)** | Warfarin (INR: 2-3) |

BID: twice a day, QD: once a day.

**Legend**: Each box represents the estimated hazard ratio and 95% credible interval for the direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.0.

**Table D2.4. Network Meta-Analysis Results for Pulmonary Embolism/ Deep-Vein Thrombosis (PE/DVT).**

| | | | |
|---|---|---|---|
| Apixaban (5 mg or 2.5 mg BID) | | | |
| 0.92 (0.3, 2.78) | Rivaroxaban (20 mg or 15 mg) | | |
| 0.49 (0.14, 1.68) | 0.53 (0.21, 1.31) | Dabigatran (150 mg) | |
| 0.78 (0.29, 2.09) | 0.85 (0.51, 1.41) | 1.61 (0.76, 3.42) | Warfarin (INR: 2-3) |

BID: twice a day, QD: once a day.

**Legend**: Each box represents the estimated hazard ratio and 95% credible interval for the direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.0.

**Table D2.5. Network Meta-Analysis Results for Intracranial Bleeding.**

| | | | |
|---|---|---|---|
| Apixaban (5 mg or 2.5 mg BID) | | | |
| **0.63 (0.4, 0.99)** | Rivaroxaban (20 mg or 15 mg) | | |
| 1.05 (0.63, 1.77) | 1.67 (0.99, 2.82) | Dabigatran (150 mg) | |
| **0.42 (0.3, 0.58)** | 0.67 (0.48, 0.93) | 0.4 (0.27, 0.6) | Warfarin (INR: 2-3) |

BID: twice a day, QD: once a day.

**Legend**: Each box represents the estimated hazard ratio and 95% credible interval for the direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.0.

**Table D2.6. Network Meta-Analysis Results for Major GI Bleeding.**

| | | | |
|---|---|---|---|
| Apixaban (5 mg or 2.5 mg BID) | | | |
| 0.61<br>(0.44, 0.84) | Rivaroxaban (20 mg or 15 mg) | | |
| **0.59**<br>**(0.42, 0.84)** | 0.97<br>(0.72, 1.32) | Dabigatran (150 mg) | |
| 0.89<br>(0.69, 1.15) | **1.46**<br>**(1.2, 1.78)** | **1.5**<br>**(1.19, 1.89)** | Warfarin (INR: 2-3) |

BID: twice a day, QD: once a day.

**Legend**: Each box represents the estimated hazard ratio and 95% credible interval for the direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.0.

**Table D2.7. Network Meta-Analysis Results for Cardiovascular Death.**

| | | | |
|---|---|---|---|
| Apixaban (5 mg or 2.5 mg BID) | | | |
| 1<br>(0.77, 1.3) | Rivaroxaban (20 mg or 15 mg) | | |
| 1.05<br>(0.84, 1.3) | 1.05<br>(0.81, 1.36) | Dabigatran (150 mg) | |
| 0.89<br>(0.76, 1.04) | 0.89<br>(0.72, 1.1) | **0.85**<br>**(0.73, 0.99)** | Warfarin (INR: 2-3) |

BID: twice a day, QD: once a day.

**Legend**: Each box represents the estimated hazard ratio and 95% credible interval for the direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.0.

**Table D2.8. Network Meta-Analysis Results for All-Cause Mortality.**

| | | | |
|---|---|---|---|
| Apixaban (5 mg or 2.5 mg BID) | | | |
| 1.05<br>(0.84, 1.3) | Rivaroxaban (20 mg or 15 mg QD) | | |
| 1.01<br>(0.85, 1.2) | 0.97<br>(0.77, 1.21) | Dabigatran (150 mg BID) | |
| 0.89<br>0.89 (0.79, 1) | 0.85<br>(0.71, 1.02) | 0.88<br>(0.77, 1) | Warfarin (INR: 2-3) |

BID: twice a day, QD: once a day.

**Legend**: Each box represents the estimated hazard ratio and 95% credible interval for the direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.0.

**Table D2.9. Network Meta-Analysis Results for Discontinuation Due to Adverse Events.**

| | | | |
|---|---|---|---|
| Apixaban (5 mg or 2.5 mg BID) | | | |
| **0.76**<br>**(0.65, 0.89)** | Rivaroxaban (20 mg or 15 mg QD) | | |
| **0.48**<br>**(0.39, 0.58)** | **0.63**<br>**(0.51, 0.77)** | Dabigatran (150 mg BID) | |
| 0.9<br>(0.81, 1) | **1.19**<br>**(1.06, 1.34)** | **1.89**<br>**(1.6, 2.24)** | Warfarin (INR: 2-3) |

BID: twice a day, QD: once a day.

**Legend**: Each box represents the estimated hazard ratio and 95% credible interval for the direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.0.

**Table D2.10. Network Meta-Analysis Results for Discontinuation (All).***

| | | | |
|---|---|---|---|
| Apixaban (5 mg or 2.5 mg BID) | | | |
| **0.84 (0.77, 0.92)** | Rivaroxaban (20 mg or 15 mg QD) | | |
| **0.63 (0.56, 0.7)** | **0.74 (0.67, 0.82)** | Dabigatran (150 mg BID) | |
| **0.9 (0.84, 0.96)** | **1.07 (1.01, 1.13)** | **1.44 (1.32, 1.57)** | Warfarin (INR: 2-3) |

BID: twice a day, QD: once a day.

*Excluding those with an outcome event.

**Legend**: Each box represents the estimated hazard ratio and 95% credible interval for the direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.0.

**Table D2.11. Model Fit for Fixed-Effects Models.**

| | Resdev | DIC |
|---|---|---|
| **Stroke/SE** | 3.003 | 6.006 |
| **All stroke** | 2.997 | 5.99 |
| **Hemorrhagic stroke** | 3.000 | 6.002 |
| **Ischemic stroke** | 2.993 | 5.986 |
| **MI** | 2.990 | 5.981 |
| **PE/DVT** | 2.988 | 5.975 |
| **Major bleeding** | 2.997 | 5.994 |
| **Intracranial bleeding** | 3.004 | 6.008 |
| **Major GI bleeding** | 3.001 | 6.002 |
| **All-cause mortality** | 2.997 | 5.995 |
| **Cardiovascular death** | 3.000 | 6.000 |
| **Discontinuation (all)** | 3.008 | 6.02 |
| **Discontinuation due to AEs** | 3.001 | 6.002 |

DIC: Deviance information criterion, DVT: Deep-vein thrombosis, GI: Gastrointestinal, MI: Myocardial infarction, PE: Pulmonary embolism, Resdev: residual deviance

**Table D2.12. Comparison of Fixed-Effects and Random-Effects Models for NMA.**

| | HR (95% credible intervals) | | | |
|---|---|---|---|---|
| | Fixed-effects model | | Random-effects model | |
| | Apixaban vs. warfarin | Apixaban vs. dabigatran | Apixaban vs. warfarin | Apixaban vs. dabigatran |
| **Stroke/SE** | 0.79 (0.66, 0.95) | 1.2 (0.9, 1.59) | 0.79 (0.46, 1.37) | 1.2 (0.55, 2.61) |
| **All stroke** | 0.79 (0.66, 0.95) | 1.23 (0.92, 1.66) | 0.79 (0.44, 1.41) | 1.23 (0.54, 2.84) |
| **Hemorrhagic stroke** | 0.51 (0.35, 0.75) | 1.96 (0.93, 4.11) | 0.51 (0.09, 2.89) | 1.96 (0.16, 23.41) |
| **Ischemic stroke** | 0.92 (0.75, 1.13) | 1.21 (0.87, 1.68) | 0.92 (0.62, 1.36) | 1.21 (0.69, 2.13) |
| **MI** | 0.88 (0.66, 1.17) | 0.64 (0.41, 0.98) | 0.88 (0.55, 1.42) | 0.64 (0.32, 1.28) |
| **PE/DVT** | 0.78 (0.29, 2.09) | 0.49 (0.14, 1.68) | 0.78 (0.25, 2.4) | 0.49 (0.11, 2.1) |
| **Major bleeding** | 0.69 (0.6, 0.8) | 0.74 (0.61, 0.91) | 0.69 (0.43, 1.12) | 0.74 (0.38, 1.47) |
| **Intracranial bleeding** | 0.42 (0.3, 0.58) | 1.05 (0.63, 1.77) | 0.42 (0.13, 1.37) | 1.05 (0.19, 5.64) |
| **Major GI bleeding** | 0.89 (0.69, 1.15) | 0.59 (0.42, 0.84) | 0.89 (0.51, 1.55) | 0.59 (0.27, 1.3) |
| **All-cause mortality** | 0.89 (0.79, 1) | 1.01 (0.85, 1.2) | 0.89 (0.71, 1.12) | 1.01 (0.73, 1.4) |
| **Cardiovascular death** | 0.89 (0.76, 1.04) | 1.05 (0.84, 1.3) | 0.89 (0.69, 1.14) | 1.05 (0.74, 1.49) |
| **Discontinuation (all)** | 0.9 (0.84, 0.96) | 0.63 (0.56, 0.7) | 0.9 (0.57, 1.43) | 0.63 (0.33, 1.2) |
| **Discontinuation due to AEs** | 0.9 (0.81, 1) | 0.48 (0.39, 0.58) | 0.9 (0.4, 2.02) | 0.48 (0.15, 1.49) |

AEs: adverse events, DVT: Deep-vein thrombosis, GI: Gastrointestinal, MI: Myocardial infarction, PE: Pulmonary embolism.

**Table D2.13. Comparison of Fixed-Effects and Random-Effects Models for NMA.**

| | HR (95% credible intervals) | | | |
|---|---|---|---|---|
| | Fixed-effects model | | Random-effects model | |
| | Rivaroxaban vs. warfarin | Rivaroxaban vs. dabigatran | Rivaroxaban vs. warfarin | Rivaroxaban vs. dabigatran |
| **Stroke/SE** | 0.79 (0.65, 0.96) | 1.2 (0.89, 1.6) | 0.79 (0.46, 1.37) | 1.2 (0.55, 2.61) |
| **All stroke** | 0.85 (0.7, 1.03) | 1.33 (0.98, 1.8) | 0.85 (0.48, 1.52) | 1.33 (0.58, 3.07) |
| **Hemorrhagic stroke** | 0.59 (0.37, 0.93) | 2.27 (1.04, 4.97) | 0.59 (0.1, 3.36) | 2.27 (0.19, 27.13) |
| **Ischemic stroke** | 0.94 (0.75, 1.17) | 1.24 (0.88, 1.73) | 0.94 (0.63, 1.4) | 1.24 (0.7, 2.19) |
| **MI** | 0.81 (0.62, 1.06) | 0.59 (0.38, 0.9) | 0.81 (0.51, 1.3) | 0.59 (0.3, 1.17) |
| **PE/DVT** | 0.85 (0.51, 1.41) | 0.53 (0.21, 1.31) | 0.85 (0.4, 1.82) | 0.53 (0.16, 1.76) |
| **Major bleeding** | 1.04 (0.9, 1.2) | 1.12 (0.92, 1.37) | 1.04 (0.64, 1.68) | 1.12 (0.57, 2.21) |
| **Intracranial bleeding** | 0.67 (0.48, 0.93) | 1.67 (0.99, 2.82) | 0.67 (0.2, 2.2) | 1.67 (0.31, 9.09) |
| **Major GI bleeding** | 1.46 (1.2, 1.78) | 0.97 (0.72, 1.32) | 1.46 (0.85, 2.49) | 0.97 (0.45, 2.09) |
| **All-cause mortality** | 0.85 (0.71, 1.02) | 0.97 (0.77, 1.21) | 0.85 (0.65, 1.11) | 0.96 (0.68, 1.37) |
| **Cardiovascular death** | 0.89 (0.72, 1.1) | 1.05 (0.81, 1.36) | 0.89 (0.67, 1.18) | 1.05 (0.72, 1.52) |
| **Discontinuation (all)** | 1.07 (1.01, 1.13) | 0.74 (0.67, 0.82) | 1.07 (0.68, 1.69) | 0.74 (0.39, 1.43) |
| **Discontinuation due to AEs** | 1.19 (1.06, 1.34) | 0.63 (0.51, 0.77) | 1.19 (0.53, 2.67) | 0.63 (0.2, 1.98) |

AEs: adverse events, DVT: Deep-vein thrombosis, GI: Gastrointestinal, MI: Myocardial infarction, PE: Pulmonary embolism

**Table D2.14. Comparison of Fixed-Effects and Random-Effects Models for NMA.**

| | HR (95% credible intervals) | |
|---|---|---|
| | Fixed-effects model | Random-effects model |
| | Dabigatran vs. warfarin | Dabigatran vs. warfarin |
| **Stroke/SE** | 0.66 (0.53, 0.82) | 0.66 (0.38, 1.15) |
| **All stroke** | 0.64 (0.51, 0.81) | 0.64 (0.35, 1.16) |
| **Hemorrhagic stroke** | 0.26 (0.14, 0.49) | 0.26 (0.04, 1.55) |
| **Ischemic stroke** | 0.76 (0.59, 0.98) | 0.76 (0.5, 1.15) |
| **MI** | 1.38 (1, 1.91) | 1.38 (0.84, 2.28) |
| **PE/DVT** | 1.61 (0.76, 3.42) | 1.6 (0.63, 4.09) |
| **Major bleeding** | 0.93 (0.81, 1.07) | 0.93 (0.58, 1.5) |
| **Intracranial bleeding** | 0.4 (0.27, 0.6) | 0.4 (0.12, 1.34) |
| **Major GI bleeding** | 1.5 (1.19, 1.89) | 1.5 (0.86, 2.58) |
| **All-cause mortality** | 0.88 (0.77, 1) | 0.88 (0.7, 1.11) |
| **Cardiovascular death** | 0.85 (0.73, 0.99) | 0.85 (0.66, 1.09) |
| **Discontinuation (all)** | 1.44 (1.32, 1.57) | 1.44 (0.9, 2.29) |
| **Discontinuation due to AEs** | 1.89 (1.6, 2.24) | 1.89 (0.84, 4.26) |

DVT: Deep-vein thrombosis, GI: Gastrointestinal, MI: Myocardial infarction, PE: Pulmonary embolism

## Qualitative Synthesis

***Apixaban versus warfarin***

In the ARISTOTLE trial, patients who received apixaban experienced fewer fatal strokes (42 events) compared to those in the warfarin group (67 events). Compared to those who received warfarin, patients who received apixaban had a significantly lower rate of fatal bleeding (HR: 0.50; 95% CI: 0.33 to 0.74; P<0.001), minor bleeding (HR: 0.69; 95% CI: 0.60 to 0.80; P<0.001), hematoma bleeding (HR: 0.46; 95% CI: 0.29 to 0.74; p=0.002)[32], and "other location" bleeding (HR: 0.79; 95% CI: 0.68 to 0.93; p=0.004).[9] See Table D3.3 for the outcomes of all three RCTs.

***Rivaroxaban versus warfarin***

In the ROCKET AF trial, patients who received rivaroxaban had a numerically lower rate of fatal stroke compared to those who received warfarin (HR: 0.71; 95% CI: 0.49 to 1.03; p=0.08). The rates of minor stroke were similar (HR: 1.03; 95% CI: 0.76 to 1.38; p=0.86). In terms of safety, patients who received rivaroxaban had a significantly lower rate of fatal bleeding (HR: 0.50; 95% CI: 0.31 to 0.79; p=0.003), but numerically greater rate of minor bleeding (2.35% per year) compared to those who received warfarin (2.03%) (HR: 1.16; 95% CI: 0.97 to 1.39; p=0.10), although the wide confidence intervals signal uncertainty in this estimate. There was no difference in rates of non-major clinically relevant bleeding (HR: 1.04; 95% CI: 0.96 to 1.13; p=0.35).

***Dabigatran versus warfarin***

In the RE-LY trial, patients who received dabigatran had a significantly lower rate of stroke/SE (RR: 0.66; 95% CI: 0.53 to 0.82; P<0.001), all stroke (RR: 0.64; 95% CI: 0.51 to 0.81; p<0.001), ischemic stroke (RR: 0.76; 95% CI: 0.60 to 0.98; p=0.03), fatal stroke (RR: 0.66; 95% CI: 0.50 to 0.88; p=0.01) and minor stroke compared to those who received warfarin (RR: 0.62; 95% CI: 0.43 to 0.91; p=0.01). Rates of hemorrhagic stroke were significantly lower in those receiving dabigatran versus warfarin (RR: 0.26; 95% CI: 0.14 to 0.49; P<0.001) but rates were low across the two groups compared to the two other RCTs. In terms of safety, patients who received dabigatran had significantly lower rates of minor bleeding in the dabigatran group compared to the warfarin group (RR: 0.91; 95% CI: 0.85 to 0.97; p=0.01) but higher rates of major GI bleeding (RR: 1.50; 95% CI: 1.19 to 1.89; P<0.001). There was no difference in major bleeding (RR: 0.93; 95% CI: 0.53 to 0.82; p=0.31), fatal bleeding (RR: 0.70; 95% CI: 0.43 to 1.14; p=0.15), extracranial bleeding (RR: 1.07; 95% CI: 0.92 to 1.25; p=0.38), nor hematoma bleeding (RR: 0.65; 95% CI: 0.39 to 1.1; p=0.1); though rates of hematoma bleeding were low overall.

There was no data reported on TIA or quality of life from any of the included trials.

***Harms***

The rate of serious adverse events appeared to be similar across the arms and the trials, except RE-LY reported lower rates in both arms than seen in the other studies (Table D3.4).

## Observational Data Results

Graham et al. (2015)[31] reported significantly lower rate of ischemic stroke in Medicare patients who received dabigatran (150 mg) compared to those who received warfarin (HR: 0.70; 95% CI: 0.57 to 0.85). The study also reported significantly lower rates in dabigatran intracranial bleeding (HR: 0.30; 95% CI: 0.21 to 0.42) and all-cause mortality (0.76; 95% CI: 0.67 to 0.86). However, as reported in our NMA analysis, this study also reported significantly higher rates of major GI bleed in dabigatran (HR: 1.51; 95% CI: 1.32 to 1.73). Overall, the results from this study in Medicare patients were aligned with our NMA analyses. The comparisons between the combined dabigatran doses (75 mg and 150 mg) and warfarin are reported in Table D3.36.

# D3. Evidence Tables

**Table D3.1. Study Design**

| Trial/ NCT | Study Design | Treatment Arms | Prohibited Therapy | Excluded Patients | Key Primary Outcomes [Timepoints] | Discontinuation protocol |
|---|---|---|---|---|---|---|
| ELIQUIS (apixaban) | | | | | | |
| **ARISTOTLE** NCT00412984 | Phase 3, Active (Warfarin) Controlled, Randomized, Double-Blind, Parallel Arm Study | • Warfarin: 2 mg tablets to achieve INR: 2-3<br>• Apixaban: 5 mg twice daily (2.5-mg doses were used in a subset of patients with two or more of the following criteria: an age of at least 80 years, a body weight of no more than 60 kg, or a serum creatinine level of 1.5 mg per deciliter or more) | • Patients who were receiving a vitamin K antagonist were instructed to discontinue the drug 3 days before randomization | • AF due to a reversible cause<br>• Moderate or severe mitral stenosis<br>• Conditions other than AF that required anticoagulation (e.g., a prosthetic heart valve)<br>• Stroke within the previous 7 days<br>• Uncontrolled hypertension<br>• Active infective endocarditis<br>• Planned major surgery or AF procedure | • Number of Participants With First Event of Ischemic/Unspecified Stroke, Hemorrhagic Stroke, or SE [Time Frame: Time to first event in "Intended Treatment Period"]<br>• Rate of Adjudicated Stroke or SE [Time Frame: "Intended Treatment Period"] | Participants must discontinue treatment if:<br>• Withdrawal of/inability to provide consent<br>• Any clinical AE, laboratory abnormality or intercurrent illness which impacts participation<br>• Clinical jaundice<br>• If ALT ≥ 5 x ULN on any two consecutive occasions<br>• Total bilirubin ≥ 2.0 x ULN on any two consecutive occasions<br>• Pregnancy<br>• Termination of the study |

| Trial/ NCT | Study Design | Treatment Arms | Prohibited Therapy | Excluded Patients | Key Primary Outcomes [Timepoints] | Discontinuation protocol |
|---|---|---|---|---|---|---|
| XARELTO (rivaroxaban) | | | | | | |
| **ROCKET AF** NCT00403767 | Phase 3, Active (Warfarin) Controlled, Randomized, Double-Blind, Parallel-Group Study | • Rivaroxaban: 20 mg tablet once daily (Patients with moderate renal impairment at screening will have a dose adaptation to rivaroxaban 15 mg, orally) and one warfarin placebo tablet taken orally once daily<br>• Warfarin: INR values 2-3 | Treatment with:<br>• Aspirin >100 mg daily<br>• Aspirin in combination with thienopyridines within 5 days before randomization<br>• Intravenous antiplatelets within 5 days before randomization<br>• Fibrinolytics within 10 days before randomization<br>• Systemic treatment with a strong inhibitor of cytochrome P450 3A4 within 4 days before randomization | • Significant mitral stenosis<br>• Transient atrial fibrillation caused by a reversible disorder<br>• Active internal bleeding<br>• Severe disabling stroke<br>• History of intracranial bleeding<br>• Hemorrhagic disorders | • Stroke/SE: Primary Efficacy (Non-Inferiority) [Time Frame: Up to 4 years]<br>• Stroke/SE: Primary Efficacy (Superiority) [Time Frame: Up to 4 years]<br>• Major/Non-major Clinically Relevant Bleeding Events: Primary Safety [Time Frame: Up to 4 years] | Participant should discontinue treatment if:<br>• Safety reasons it is in best interest to stop treatment<br>• Pregnancy<br>• No longer requires anti-coagulation treatment, non-compliance, or need for excluded medication<br>• Stroke or non-CNS systemic embolism<br>• Diagnosis of HIV<br>• Abnormal liver function tests<br>• Creatinine clearance <25 mL/min on 2 consecutive occasions |

| Trial/ NCT | Study Design | Treatment Arms | Prohibited Therapy | Excluded Patients | Key Primary Outcomes [Timepoints] | Discontinuation protocol |
|---|---|---|---|---|---|---|
| PRADAXA (dabigatran etexilate) | | | | | | |
| **RE-LY**<br>NCT00262600 | Phase 3 Randomized, Double-Blind (dabigatran), Parallel-Group Study with open-label warfarin | • Warfarin unblinded 2.0-3.0 INR<br>• Dabigatran 110 mg twice daily (not FDA approved dose)<br>• Dabigatran 150 mg twice daily | NR | • Prosthetic heart valves requiring anticoagulation or valve disease that requires surgical intervention<br>• Severe, disabling stroke within the previous 6 months, or any stroke within the previous 14 days<br>• Active infective endocarditis<br>• Active liver disease<br>• Anemia<br>• Hypersensitivity to galactose. | • Stroke or systemic embolism [36 months]<br>• Major hemorrhage. | Participant must discontinue if:<br>• sGPT/ALT or sGOT/AST N5× ULN or SGPT/ALT or GOT/AST N3 × ULN associated with total bilirubin N2 × ULN or development of signs and symptoms of hepatic disease. |

| Trial/ NCT | Study Design | Treatment Arms | Prohibited Therapy | Excluded Patients | Key Primary Outcomes [Timepoints] | Discontinuation protocol |
|---|---|---|---|---|---|---|
| ESRD Trials | | | | | | |
| **RENAL- AF** NCT02942407 | Phase 4, Prospective, randomized, open-label, blinded-outcome evaluation trial | • Apixaban 5 mg twice daily (2.5 mg twice daily for selected patients)<br>• Warfarin INR 2-3 | Need for aspirin at a dose > 81 mg a day or need for P2Y12 antagonist therapy (for example clopidogrel, prasugrel, or ticagrelor) | • Not a candidate for oral anticoagulation (hemoglobin < 8.5g/dL, history of intracranial hemorrhage, active bleeding, recent GI or retroperitoneal bleed, severe hepatic impairment, or anaphylactic reaction)<br>• Moderate or severe mitral stenosis<br>• Life expectancy < 3 months<br>• Anticipated kidney transplant within the next 3 months | • Number of Participants Experiencing Major or Clinically Relevant Non-major Bleeding [ Time Frame: Up to Month 15/Final Visit ] | NR |

| Trial/ NCT | Study Design | Treatment Arms | Prohibited Therapy | Excluded Patients | Key Primary Outcomes [Timepoints] | Discontinuation protocol |
|---|---|---|---|---|---|---|
| **Valkyrie** NCT03799822 | Phase 4, randomized, prospective, open-label, three-arm, parallel-group, interventional clinical trial | • VKA (identified as warfarin) INR 2-3<br>• Rivaroxaban 10 mg once daily.<br>• Rivaroxaban and 2000 µg menaquinone-7 thrice weekly after dialysis. | Concurrent use of antiplatelet agents was at the discretion of the treating physicians. | • Known intestinal malabsorption<br>• Inability to stop co-medication that causes interactions with rivaroxaban<br>• Life expectancy is less than 1 year<br>• Prosthetic mechanical heart valve<br>• Contraindication for anticoagulation<br>• Liver dysfunction Child-Pugh grade B-C | Composite of fatal and non-fatal stroke and other cardiovascular events [ Time Frame: through study completion, on average 3 years ] | NR |
| Observational Studies | | | | | | |
| **Lau et al. 2022** | Multinational, active-comparator cohort study design. | Apixaban (2.5 mg or 5 mg twice daily), dabigatran (110 mg or 150 mg twice daily), edoxaban (30 mg or 60 mg once daily), rivaroxaban (15 mg or 20 mg once daily) | • Prescription of warfarin or other DOACs on or within 180 days before the index date<br>• Prescription of another oral anticoagulant on the index date | • History of mitral stenosis, hyperthyroidism, or mechanical heart valve replacement or transient AF<br>• History of an outcome of interest | • Composite of ischemic stroke and systemic embolism<br>• Intracranial hemorrhage<br>• Gastrointestinal bleeding<br>• All-cause mortality | NR |

| Trial/ NCT | Study Design | Treatment Arms | Prohibited Therapy | Excluded Patients | Key Primary Outcomes [Timepoints] | Discontinuation protocol |
|---|---|---|---|---|---|---|
| **Chan et al. 2022** | Nationwide, retrospective, cohort study using the Taiwan National Health Insurance Research Database (NHIRD). | Apixaban, rivaroxaban, edoxaban, dabigatran 110 mg/150 mg, and warfarin. | Excluded patients who have undergone valvular surgery. | • Excluded all patients with AF before June 1, 2012<br>• Excluded for not receiving OACs after June 1, 2012<br>• Diagnosis of venous thrombosis<br>• Valvular surgery<br>• Mitral stenosis<br>• ESKD<br>• Diagnosis of lung disease at baseline | • New-onset idiopathic ILD. | NR |
| **Graham et al. 2015** | New-user retrospective cohort design using Medicare claims data. | Dabigatran 75 mg, Dabigatran 150 mg, Warfarin. | • Prior treatment with a study medication or rivaroxaban or apixaban<br>• Undergoing dialysis ere also excluded | • <6 months of enrollment in Medicare before their index dispensing.<br>• Were aged <65 years. | • Ischemic stroke<br>• Major hemorrhage<br>• Gastrointestinal hemorrhage<br>• Intracranial hemorrhage<br>• Intracerebral hemorrhage<br>• Acute myocardial infarction | NR |

AE: adverse events, AF: Atrial fibrillation, ALT: alanine transaminase, dL: decilitre, ESKD: End-stage kidney disease, GOT/AST: glutamic oxaloacetic transaminase/ Aspartate aminotransferase, GI: gastrointestinal, Mg: milligram, mL/min: milliliter per minute, NR: not reported, OACS: oral anticoagulants, SE: systemic embolism, sGOT/AST: serum glutamic-oxaloacetic transaminase/ Aspartate aminotransferase, sGPT/ALT: serum glutamic-pyruvic transaminase/alanine transaminase, µg: microgram, ULN: upper limit of normal, VKA: vitamin K antagonist

*Patients with 1 dose reduction criterion were older, weighed less, were more frequently female, were more likely to be from the Asia Pacific region, had worse renal function, and had higher CHADS2 (Congestive Heart Failure, Hypertension, Age ≥75 Years, Diabetes Mellitus [1 point for presence of each], and Stroke/TIA [2 points])12 and HAS-BLED scores (represents bleeding risk and assigns 1 point for the presence of each of the following: hypertension

[uncontrolled systolic blood pressure >160mmHg], abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile international normalized ratios, being elderly, and concomitant use of drugs and/or excessive alcohol)13 than patients with no dose-reduction criteria.

**Table D3.2. Baseline Characteristics of ARISTOTLE, ROCKET AF, and RE-LY**

| Trial | | ARISTOTLE | | ROCKET AF | | RE-LY | |
|---|---|---|---|---|---|---|---|
| **Source** | | Granger et al. 2011; clinicaltrials.gov; Melloni et al. 2017; Ezekowitz et al. 2015 [9,33,34] | | Patel et al. 2011; clinicaltrials.gov; Halperin et al. 2014; Van Diepen et al. 2013; Sherwood et al. 2015; Piccini et al. 2014 [10,35-38] | | Connolly et al. 2009; clinicaltrials.gov [26] | |
| **Study Arms** | | Apixaban (5 mg or 2.5 mg BID)* | Warfarin (INR: 2-3) | Rivaroxaban (20mg) | Warfarin (INR: 2-3) | Dabigatran (150 mg) | Warfarin (INR: 2-3) |
| **N** | | 9120 | 9081 | 7131 | 7133 | 6076 | 6022 |
| **Age** | Median (IQR) | 70 (63-76) | 70 (63-76) | 73 (65-78) | 73 (65-78) | NR | NR |
| | <65 years | 2731 (29.9) | 2740 (30.2) | NR | NR | 1030 (17.0) | 953 (15.8) |
| | 65-75 years | 3539 (38.8) | 3513 (38.7) | 3999 (56.1)† | 4008 (56.2)† | 2580 (45.5) | 2646 (43.9) |
| | >= 75 years | 2850 (31.3) | 2828 (31.1) | 3082 (43.2) | 3082 (43.2) | 2466 (40.5) | 2423 (40.2) |
| | Mean (SD) | 69.1 (9.61) | 69.0 (9.74) | NR | NR | 71.5 (8.8) | 71.6 (8.6) |
| **Sex** | Female, n (%) | 3234 (35.5) | 3182 (35.0) | 2831 (39.7) | 2832 (39.7) | 2236 (36.8) | 2213 (36.7) |
| | Male, n (%) | NR | NR | 4300 (60.3) | 4301 (60.3) | 3840 (63.2) | 3809 (63.3) |
| **Race** | White | 7536 (82.6)‡ | 7493 (82.5)‡ | 5872 (82.3) | 5915 (82.9) | 4268 (70.2) | 4203 (69.8) |
| | Black/AA | 125 (1.4)‡ | 102 (1.1)‡ | 94 (1.3) | 86 (1.2) | 57 (0.9) | 67 (1.1) |
| | Asian | 1310 (14.4)‡ | 1332 (14.7)‡ | 897 (12.6) | 889 (12.5) | 965 (15.9) | 955 (15.9) |
| | American Indian/Alaska Native | 26 (0.3)‡ | 24 (0.3)‡ | NR | NR | NR | NR |
| | Native Hawaiian/Other Pacific Islander | 2 (0)‡ | 2 (0)‡ | NR | NR | NR | NR |
| | Other | 121 (1.3)‡ | 127 (1.4)‡ | 218 (3.1) | 201 (2.8) | 786 (12.9) | 797 (13.2) |
| | NR | 0‡ | 1 (0)‡ | 0 | 0 | 0 | 0 |
| **Ethnicity** | Hispanic/Latino | 1808 (19.8) | 1803 (19.9) | NR | NR | 416 (6.8) | 407 (6.8) |
| | Non-Hispanic/Latino | 7312 (80.2) | 7276 (80.1) | NR | NR | 5660 (93.2) | 5615 (93.2) |

| Trial | | ARISTOTLE | | ROCKET AF | | RE-LY | |
|---|---|---|---|---|---|---|---|
| | NR | 0 | 2 (0) | NR | NR | 0 | 0 |
| **Region** | North America | 2249 (24.7) | 2225 (24.5) | 1334 (18.7) | 1339 (18.8) | 2200 (36.2) | 2167 (36.0) |
| | Latin America | 1743 (19.1) | 1725 (19.0) | 940 (13.2) | 938 (13.2) | 320 (5.3) | 316 (5.2) |
| | Europe | 3672 (40.3) | 3671 (40.4) | 3752 (52.6) | 3756 (52.7) | 2261 (37.2) | 2258 (37.5) |
| | Asian Pacific | 1456 (16.0) | 1460 (16.1) | 1055 (14.8) | 1054 (14.8) | 933 (15.4) | 926 (15.4) |
| | Other | NR | NR | NR | NR | 362 (6.0) | 355 (5.9) |
| **Systolic blood pressure, mm Hg** | Median (IQR) | 130 (120-140) | 130 (120-140) | 130 (120-140) | 130 (120-140) | NR | NR |
| | Mean (SD) | NR | NR | NR | NR | 131.0 (17.6) | 131.2 (17.4) |
| **Diastolic blood pressure, mm Hg** | Median (IQR) | NR | NR | 80 (70-85) | 80 (70-85) | NR | NR |
| | Mean (SD) | NR | NR | NR | NR | 77.0 (10.6) | 77.1 (10.4) |
| **Weight, kg** | Median (IQR) | 82 (70-96) | 82 (70-95) | NR | NR | NR | NR |
| | Mean (SD) | NR | NR | NR | NR | 82.5 (19.4) | 82.7 (19.7) |
| **Body-mass index** | Median (IQR) | NR | NR | 28.3 (25.2-32.1) | 28.1 (25.1-31.8) | NR | NR |
| **Type of afib, n(%)** | Paroxysmal | 1374 (15.1) | 1412 (15.5) | 1245 (17.5) | 1269 (17.8) | 1978 (32.6) | 2036 (33.8) |
| | Persistent/permanent | 7744 (84.9) | 7668 (84.4) | 5786 (81.1) | 5762 (80.8) | 4097 (67.4) | 3985 (66.2) |
| | Newly diagnosed or new onset | NR | NR | 100 (1.4) | 102 (1.4) | NR | NR |
| **Prior medication use, n(%)** | Vitamin K antagonist | 5208 (57.1) | 5193 (57.2) | 4443 (62.3) | 4461 (62.5) | 3049 (50.2)§ | 2929 (48.6)§ |
| | Aspirin | NR | NR | 2586 (36.3) | 2619 (36.7) | NR | NR |
| **Risk factors** | Age >= 75 | 2850 (31.3) | 2828 (31.1) | 3082 (43.2) | 3082 (43.2) | 2466 (40.5) | 2423 (40.2) |
| | Prior stroke, TIA, or SE | 1748 (19.2) | 1790 (19.7) | 3892 (54.6) | 3875 (54.3) | 1233 (20.3)# | 1195 (19.8)# |
| | Prior stroke | 1045 (11.5) | 1082 (11.9) | NR | NR | NR | NR |
| | Prior TIA | 603 (6.6) | 654 (7.2) | NR | NR | NR | NR |

| Trial | | ARISTOTLE | | ROCKET AF | | RE-LY | |
|---|---|---|---|---|---|---|---|
| | Heart failure or reduced LVEF | 3235 (35.5) | 3216 (35.4) | NR | NR | 1934 (31.8) | 1922 (31.9) |
| | Diabetes | 2284 (25.0) | 2263 (24.9) | 2851 (40.0) | 2796 (39.2) | 1402 (23.1) | 1410 (23.4) |
| | Prior MI | 1319 (14.5) | 1266 (13.9) | 1182 (16.6) | 1286 (18.0) | 1029 (16.9) | 968 (16.1) |
| | Prior clinically relevant/spontaneous bleeding | 1525 (16.7) | 1515 (16.7) | NR | NR | NR | NR |
| | Hypertension | 7962 (87.3) | 7954 (87.6) | 6389 (89.6) | 6435 (90.2) | 4795 (78.9) | 4750 (78.9) |
| | Active cancer | 76 (0.83) | 81 (0.89) | NR | NR | NR | NR |
| **CHADS2 score** | Mean (SD) | 2.1 (1.1) | 2.1 (1.1) | 3.48 (0.94) | 3.46 (0.95) | 2.2 (1.2) | 2.1 (1.1) |
| | 1 | 3100 (34.0) | 3083 (34.0) | 0 | 0 | 1958 (32.2)¤ | 1859 (30.9)¤ |
| | 2 | 3262 (35.8) | 3254 (35.8) | 925 (13.0) | 934 (13.1) | 2137 (35.2) | 2230 (37.0) |
| | >=3 | 2758 (30.2) | 2744 (30.2) | NR | NR | 1981 (32.6) | 1933 (32.1) |
| **CHA2DS2-VAS score** | Median (IQR) | NR | NR | NR | NR | NR | NR |
| | Mean (SD) | 3.7 (1.5) | 3.7 (1.5) | 4.8 (1.3)** | 4.8 (1.3)** | NR | NR |
| **Current medications** | ACE inhibitor or ARB | 6464 (70.9) | 6368 (70.1) | 3915 (55.06) | 3845 (53.96) | 4053/6075 (66.7) | 3939/6017 (65.5) |
| | Amiodarone | 1009 (11.1) | 1042 (11.5) | NR | NR | 665/6075 (10.9) | 644/6017 (10.7) |
| | Beta-blocker | 5797 (63.6) | 5685 (62.6) | 4631 (65.12) | 4686 (65.77) | 3872/6075 (63.7) | 3719/6017 (61.8) |
| | Aspirin | 2859 (31.3) | 2773 (30.5) | 2726 (38.33) | 2759 (38.72) | 2352/6075 (38.7) | 2442/6017 (40.6) |
| | Clopidogrel | 170 (1.9) | 168 (1.9) | NR | NR | NR | NR |
| | Digoxin | 2916 (32.0) | 2912 (32.1) | 2758 (38.78) | 2768 (38.85) | NR | NR |
| | Calcium blocker | 2744 (30.1) | 2823 (31.1) | NR | NR | NR | NR |
| | Statin | 4104 (45.0) | 4095 (45.1) | 3055 (42.96) | 3077 (43.19) | 2667/6075 (43.9) | 2673/6017 (44.4) |
| | Nonsteroidal anti-inflammatory agent | 752 (8.2) | 768 (8.5) | NR | NR | NR | NR |

| Trial | | ARISTOTLE | | ROCKET AF | | RE-LY | |
|---|---|---|---|---|---|---|---|
| | Proton-pump inhibitor | NR | NR | NR | NR | 847/6075 (13.9) | 832/6017 (13.8) |
| | H2-receptor antagonist | NR | NR | NR | NR | 241/6075 (4.0) | 256/6017 (4.3) |
| | Gastric antacid drugs | 1683 (18.5) | 1667 (18.4) | NR | NR | NR | NR |
| **HAS-BLED score** | Median (IQR) | NR | NR | NR | NR | 2 (1-2)†† | |
| | Mean (SD) | 1.08 (1.05) | 1.8 (1.06) | 2.8 (0.9) | | NR | NR |
| | 0-1 | 3741 (41.0) | 3720 (41.0) | 530 (7.4)‡‡ | 533 (7.5)‡‡ | NR | NR |
| | 2 | 3282 (36.0) | 3286 (36.0) | 2150 (30.2)‡‡ | 2079 (29.1)‡‡ | NR | NR |
| | >=3 | 2097 (23.8) | 2075 (24.0) | 4373 (61.3)‡‡ | 4464 (62.2)‡‡ | NR | NR |
| **Renal function** | Normal, >80 ml/min | 3761 (41.2) | 3757 (41.4) | 2285 (32.0) | 2222 (31.2) | NR | NR |
| | Mild impairment, >50 to 80 ml/min | 3817 (41.9) | 3770 (41.5) | 3298 (46.2) | 3400 (47.7) | NR | NR |
| | Moderate impairment (>30 to 50 ml/min) | 1365 (15.0) | 1382 (15.2) | 1490 (20.9)§§ | 1459 (20.5)§§ | NR | NR |
| | Severe impairment (≤30 ml/min) | 137(1.5) | 133 (1.5) | NR | NR | NR | NR |
| | Not reported | 40 (0.4) | 39 (0.4) | NR | NR | NR | NR |
| **Creatinine clearance, ml/min** | Median (IQR) | NR | NR | 67 (52-88) | 67 (52-86) | NR | NR |

AA: African American, ACE: angiotensin-converting enzyme, Afib: Atrial fibrillation, ARB: angiotensin receptor blocker, BID: twice a day, INR: international normalized ratio, IQR: interquartile range, kg: kilogram, LVEF: left ventricular ejection fraction, mg: milligram, MI: myocardial infarction, ml/min: milliliter per minute, mm Hg: millimeters of mercury, N: number, NR: not reported, SD: standard deviation, SE: systemic embolism, TIA: transient ischemic attack, %: percent

*428 (4.7%) participants taking 2.5 mg dosage

†<75 years old

‡Calculated from clinicaltrials.gov

§Long-term use of vitamin K antagonists

#Prior stroke or TIA

¤0 or 1

**Based on subsample of 14171 participants (van Diepen et al. 2013)[38]

††Overall sample (including dabigatran 110mg)
‡‡N calculated from Piccini et al. 2014[37]
§§<50 ml/min

**Table D3.3. Outcomes of ARISTOTLE, ROCKET AF, and RE-LY**

| Trial | | ARISTOTLE | | ROCKET AF | | RE-LY | |
|---|---|---|---|---|---|---|---|
| Source | | Granger et al. 2011; clinicaltrials.gov; Goto et al. 2018; Bahit et al 2017; Hylek et al. 2014; Carnicelli et al. 2020 [9,32,39-41] | | Patel et al. 2011 (during treatment); Goodman et al. 2014; Sherwood et al. 2015* [10,36,42] | | Connolly et al. 2009; Eikelboom et al. 2011; Hart et al. 2012 [26,43,44] | |
| Study Arms | | Apixaban (5 mg or 2.5 mg BID)† | Warfarin (INR: 2-3) | Rivaroxaban (20mg) | Warfarin (INR: 2-3) | Dabigatran (150 mg) | Warfarin (INR: 2-3) |
| Timepoint | | Median of 1.8 years | | 590 days | | Median of 2 years | |
| Efficacy Outcomes | | | | | | | |
| N | | 9120 | 9081 | 7061 | 7082 | 6076 | 6022 |
| Stroke | Number of events | 199 | 250 | 184 | 221 | 122 | 185 |
| | % per year | 1.19 | 1.51 | 1.65 | 1.96 | 1.01 | 1.57 |
| | HR (95% CI) | 0.79 (0.65, 0.95) | REF | 0.85 (0.70, 1.03) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.64 (0.51, 0.81) | REF |
| | P value | 0.01 | REF | 0.092 | REF | <0.001 | REF |
| Major stroke | Number of events | 84‡ | 117‡ | 43 | 57 | NR | NR |
| | % per year | 0.5 | 0.71 | 0.39 | 0.5 | NR | NR |
| | HR (95% CI) | 0.71 (0.54, 0.94) | NR | 0.77 (0.52, 1.14) | NR | NR | NR |
| | P value | NR | NR | 0.188 | NR | NR | NR |
| Minor/nondisabling stroke | Number of events | 77 | | 88 | 87 | 44 | 69 |
| | % per year | NR | NR | 0.79 | 0.77 | 0.37 | 0.58 |
| | HR (95% CI) | NR | NR | 1.03 (0.76, 1.38) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.62 (0.43, 0.91) | REF |
| | P value | NR | NR | 0.863 | REF | 0.01 | REF |
| Ischemic stroke | Number of events | 162 | 175 | 149 | 161 | 111§ | 142§ |
| | % per year | 0.97 | 1.05 | 1.34 | 1.42 | 0.92 | 1.2 |

| Trial | | ARISTOTLE | | ROCKET AF | | RE-LY | |
|---|---|---|---|---|---|---|---|
| | HR (95% CI) | 0.92 (0.74, 1.13) | REF | 0.94 (0.75, 1.17) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.76 (0.60, 0.98) | REF |
| | P value | 0.42 | REF | 0.581 | REF | 0.03 | REF |
| **Hemorrhagic stroke** | Number of events | 40 | 78 | 29 | 50 | 12 | 45 |
| | % per year | 0.24 | 0.47 | 0.26 | 0.44 | 0.1 | 0.38 |
| | HR (95% CI) | 0.51 (0.35, 0.75) | REF | 0.59 (0.37, 0.93) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.26 (0.14, 0.49) | REF |
| | P value | <0.001 | REF | 0.024 | REF | <0.001 | REF |
| **Fatal stroke** | Number of events | 42 | 67 | 47 | 67 | 80# | 118# |
| | % per year | NR | NR | 0.42 | 0.59 | 0.66 | 1 |
| | HR (95% CI) | NR | NR | 0.71 (0.49, 1.03) | REF | NR | NR |
| | RR (95% CI) | 0.62 (0.42, 0.92)¤ | REF | NR | NR | 0.66 (0.50, 0.88) | REF |
| | P value | NR | NR | 0.075 | REF | 0.005 | REF |
| **Systemic embolism** | Number of events | 15 | 17 | 5 | 22 | 12** | 14** |
| | % per year | 0.09 | 0.1 | 0.04 | 0.19 | NR | NR |
| | HR (95% CI) | 0.87 (0.44, 1.75) | REF | 0.23 (0.09, 0.61) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.85 (0.39, 1.83)¤ | REF |
| | P value | 0.7 | REF | 0.003 | REF | NR | NR |
| **Stroke/SE** | Number of events | 212 | 265 | 188†† | 240‡‡ | 134 | 199 |
| | % per year | 1.27 | 1.6 | 1.7 | 2.2 | 1.11 | 1.69 |
| | HR (95% CI) | 0.79 (0.66, 0.95) | REF | 0.79 (0.66, 0.96) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.66 (0.53, 0.82) | REF |
| | P value | 0.01 | REF | 0.02 | REF | <0.001 | REF |
| **Stroke/SE/Death** | Number of events | 752 | 837 | 346§§ | 410§§ | NR | NR |
| | % per year | 4.49 | 5.04 | 3.11 | 3.63 | 4.32 | 5.2 |
| | HR (95% CI) | 0.89 (0.81, 0.98) | REF | 0.86 (0.74, 0.99) | REF | 0.83 (0.74, 0.93) | REF |
| | P value | 0.02 | REF | 0.034 | REF | 0.002 | NR |
| **Stroke/SE/Death/MI** | Number of events | 810 | 906 | 433## | 519## | 832¤¤ | 901¤¤ |
| | % per year | 4.85 | 5.49 | 3.91 | 4.62 | 6.91 | 7.64 |

| Trial | | ARISTOTLE | | ROCKET AF | | RE-LY | |
|---|---|---|---|---|---|---|---|
| | HR (95% CI) | 0.88 (0.80, 0.97) | REF | 0.85 (0.74, 0.96) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.91 (0.82, 1.00) | REF |
| | P value | 0.01 | REF | 0.01 | REF | 0.04 | REF |
| **Bleeding Outcomes** | | | | | | | |
| **N** | | 9088 | 9052 | 7111 | 7125 | 6076 | 6022 |
| **All bleeding** | Number of events | 2356 | 3060 | 1475*** | 1449*** | 1977††† | 2142††† |
| | % per year | 18.1 | 25.8 | 14.9 | 14.5 | 16.42 | 18.15 |
| | HR (95% CI) | 0.71 (0.68, 0.75) | REF | 1.03 (0.96, 1.11) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.91 (0.86, 0.97) | REF |
| | P value | <0.001 | REF | 0.44 | REF | 0.002 | REF |
| **Minor bleeding** | Number of events | 918‡‡‡ | 1286‡‡‡ | 258 | 226 | 1787 | 1931 |
| | % per year | 6.4 | 9.4 | 2.35§§§ | 2.03§§§ | 14.84 | 16.37 |
| | HR (95% CI) | 0.69 (0.63, 0.75) | REF | 1.16 (0.97, 1.39) | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.91 (0.85, 0.97) | REF |
| | P value | NR | NR | 0.102 | NR | 0.005 | REF |
| **Major bleeding** | Number of events | 327 | 462 | 395 | 386 | 375 | 397 |
| | % per year | 2.13 | 3.09 | 3.6 | 3.4 | 3.11 | 3.36 |
| | HR (95% CI) | 0.69 (0.60, 0.80) | REF | 1.04 (0.9, 1.2) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.93 (0.81, 1.07) | REF |
| | P value | <0.001 | REF | 0.58 | REF | 0.31 | REF |
| **Fatal bleeding** | Number of events | 36 | 71 | 27 | 55 | 28 | 39 |
| | % per year | NR | NR | 0.2 | 0.5 | 0.23 | 0.33 |
| | HR (95% CI) | 0.50 (0.33, 0.74) | NR | 0.5 (0.31, 0.79) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.70 (0.43, 1.14) | REF |
| | P value | <0.001 | NR | 0.003 | REF | 0.15 | REF |
| **Critical bleeding** | Number of events | NR | NR | 91 | 133 | NR | NR |
| | % per year | NR | NR | 0.8 | 1.2 | NR | NR |
| | HR (95% CI) | NR | NR | 0.69 (0.53, 0.91) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | NR | NR |

| Trial | | ARISTOTLE | | ROCKET AF | | RE-LY | |
|---|---|---|---|---|---|---|---|
| | P value | NR | NR | 0.007 | REF | NR | NR |
| **Intracranial bleeding** | Number of events | 52 | 122 | 55 | 84 | 37 | 90 |
| | % per year | 0.33 | 0.8 | 0.5 | 0.7 | 0.31 | 0.76 |
| | HR (95% CI) | 0.42 (0.30, 0.58) | REF | 0.67 (0.47, 0.93) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.40 (0.27, 0.60) | REF |
| | P value | <0.001 | REF | 0.02 | REF | <0.001 | REF |
| **Extracranial bleeding** | Number of events | NR | NR | NR | NR | 342 | 315 |
| | % per year | NR | NR | NR | NR | 2.84 | 2.67 |
| | HR (95% CI) | NR | NR | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 1.07 (0.92-1.25) | REF |
| | P value | NR | NR | NR | NR | 0.38 | REF |
| **Hematoma bleeding** | Number of events | 25 | 53 | NR | NR | 24 | 36 |
| | % per year | 0.16 | 0.35 | NR | NR | 0.2 | 0.31 |
| | HR (95% CI) | 0.46 (0.29, 0.74) | REF | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.65 (0.39, 1.1) | REF |
| | P value | 0.0015 | REF | NR | NR | 0.1 | REF |
| **Major gastrointestinal** | Number of events | 105 | 119 | 224 | 154 | 182 | 120 |
| | % per year | 0.76 | 0.86 | 3.15 | 2.16 | 1.51 | 1.02 |
| | HR (95% CI) | 0.89 (0.70, 1.15) | REF | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | 1.46 (1.19, 1.78)¤ | NR | 1.50 (1.19, 1.89) | REF |
| | P value | 0.37 | REF | 0.02 | REF | <0.001 | REF |
| **Gastrointestinal** | Number of events | NR | NR | 394 | 290 | 223 | 148 |
| | % per year | NR | NR | 3.61 | 2.6 | 1.85 | 1.25 |
| | HR (95% CI) | NR | NR | 1.42 (1.22, 1.66) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 1.49 (1.21, 1.84) | REF |
| | P value | NR | NR | <0.0001 | REF | <0.001 | REF |
| | Number of events | 275### | 340### | 1185¤¤¤ | 1151¤¤¤ | NR | NR |

| Trial | | ARISTOTLE | | ROCKET AF | | RE-LY | |
|---|---|---|---|---|---|---|---|
| **Clinically relevant bleeding** | % per year | 1.79 | 2.27 | 11.8 | 11.4 | NR | NR |
| | HR (95% CI) | 0.79 (0.68, 0.93) | REF | 1.04 (0.96, 1.13) | REF | NR | NR |
| | P value | 0.004 | REF | 0.35 | REF | NR | NR |
| **Other Outcomes** | | | | | | | |
| **N** | | 9120 | 9081 | 7061 | 7082 | 6076 | 6022 |
| **All-cause death** | Number of events | 603 | 669 | 208 | 250 | 438 | 487 |
| | % per year | 3.52 | 3.94 | 1.87 | 2.21 | 3.64 | 4.13 |
| | HR (95% CI) | 0.89 (0.80, 0.998) | REF | 0.85 (0.70, 1.02) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.88 (0.77, 1.00) | REF |
| | P value | 0.047 | REF | 0.073 | REF | 0.051 | REF |
| **Cardiovascular death** | Number of events | NR | NR | 170 | 193 | 274 | 317 |
| | % per year | 1.8 | 2.02 | 1.53 | 1.71 | 2.28 | 2.69 |
| | HR (95% CI) | 0.89 (0.76, 1.04) | REF | 0.89 (0.73, 1.10) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 0.85 (0.72, 0.99) | REF |
| | P value | NR | NR | 0.289 | REF | 0.04 | REF |
| **Myocardial infarction** | Number of events | 90 | 102 | 101 | 126 | 89 | 63 |
| | % per year | 0.53 | 0.61 | 0.91 | 1.12 | 0.74 | 0.53 |
| | HR (95% CI) | 0.88 (0.66, 1.17) | REF | 0.81 (0.63, 1.06) | REF | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | 1.38 (1.00, 1.91) | REF |
| | P value | 0.37 | REF | 0.121 | REF | 0.048 | REF |
| **Pulmonary embolism or deep-vein thrombosis** | N | 9120 | 9081 | 7111 | 7125 | 6076 | 6022 |
| | Number of events | 7 | 9 | 27 | 32 | 18**** | 11**** |
| | % per year | 0.04 | 0.05 | NR | NR | 0.15 | 0.09 |
| | HR (95% CI) | 0.78 (0.29, 2.10) | REF | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | 0.85 (0.51, 1.41)¤ | NR | 1.61 (0.76, 3.42) | REF |
| | P value | 0.63 | REF | NR | NR | 0.21 | REF |
| **Permanent Discontinuation Rates** | Number of events | 1948†††† | 2115†††† | 1691‡‡‡‡ | 1584‡‡‡‡ | 1047§§§§ | 722§§§§ |
| | % | 21.4 | 23.4 | 23.7 | 22.2 | 17 | 12 |
| | HR (95% CI) | 0.90 (0.85, 0.96) | REF | NR | NR | NR | NR |

| Trial | | ARISTOTLE | | ROCKET AF | | RE-LY | |
|---|---|---|---|---|---|---|---|
| | RR (95% CI) | NR | NR | 1.07 (1.01, 1.13)¤ | NR | 1.44 (1.32, 1.57)¤ | NR |
| | P value | 0.002 | REF | NR | NR | <0.001 | NR |
| **Temporary Discontinuation Rates** | Number of events | NR | NR | 3734 | 4511 | NR | NR |
| | % | NR | NR | 52.9 | 63.7 | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | NR | NR |
| | P value | NR | NR | p<0.0001 | REF | NR | NR |
| **Not Completed** | | 2310 (25.3) | 2493 (27.5) | NR | NR | 252 | 266 |

BID: twice a day, CI: confidence interval, non-CNS: Non-central nervous system, HR: Hazard ratio, INR: international normalized ratio, ITT: intention to treat, mg: milligram, MI: myocardial infarction, N: number, NR: not reported, PE: pulmonary embolism, RR: relative risk, SE: systemic embolism, %: percent

*Safety, as-treated or intention-to-treat population as noted

†428 (4.7%) participants were prescribed 2.5 mg dosage

‡Fatal or disabling stroke

§Ischemic or unspecified

#Disabling or fatal

¤Risk ratio was calculated based on the event number

**Calculated based upon number of those with stroke/SE - number of those with stroke (Connolly et al. 2009)

††ITT population during treatment. N=7081

‡‡ITT population during treatment. N=7090

§§Stroke, non-CNS embolism, and vascular death

##Stroke, non-CNS embolism, vascular death, and myocardial infarction

¤¤Stroke, SE, PE, MI, death, or major bleeding

***Major and nonmajor clinically relevant bleeding

†††Major and minor bleeding

‡‡‡ Non-major bleeding

§§§ Rate per 100 patient years

### ”Other location" major bleeding

¤¤¤ Non-major clinically relevant bleeding

**** Only pulmonary embolism

††††Excluded those who discontinued due to death

‡‡‡‡ Based upon 7131 vs 7133[10]

§§§§ Discontinuation with outcome event removed

**Table D3.4. Harms in ARISTOTLE, ROCKET-AF, and RE-LY**

| Trial | ARISTOTLE | | ROCKET AF | | RE-LY | |
|---|---|---|---|---|---|---|
| **Source** | Granger et al. 2011; clinicaltrials.gov; Carnicelli et al. 2020[9,41] | | Patel et al. 2011; Goodman et al. 2014[42,45] | | Connolly et al. 2009; clinicaltrials.gov[26] | |
| **Study Arms** | Apixaban (5 mg or 2.5 mg BID) | Warfarin (INR: 2-3) | Rivaroxaban (20 mg) | Warfarin (INR: 2-3) | Dabigatran (150 mg) | Warfarin (INR: 2-3) |
| **N** | 9088* | 9052 | 7111 | 7125 | 6076 | 6022 |
| **Discontinued due to AE** | 688 (7.6)† | 758 (8.4)‡ | 594 (8.3)§ | 498 (7) | 376 (6.2)# | 197 (3.3) |
| **Discontinued due to stroke** | 75 (3.9) | 108 (5.1) | NR | NR | NR | NR |
| **Discontinued due to SE** | 14 (0.7) | 8 (0.4) | NR | NR | NR | NR |
| **Discontinued due to bleeding** | 154 (7.9) | 190 (9.0) | 322 (4.5) | 286 (4.0) | NR | NR |
| **Not completed due to AE** | 679 (7.5%) | 738 (8.2%) | 993 (14.0) | 919 (12.9) | NR | NR |
| **All adverse events, n (%)** | 7406 (81.5) | 7521 (83.1) | 5791 (81.44) | 5810 (81.54) | 2273/6059 (37.5)¤ | 2118/5998 (35.3) |
| **Serious adverse events, n (%)** | 3182 (35.0) | 3302 (36.5) | 2649 (37.25) | 2720 (38.18) | 1289/6059 (21.3) | 1357/5998 (22.6) |

AE: adverse event, INR: international normalized ratio, mg: milligram, N: number, NR: not reported. %: percent

* Safety population of patients receiving at least one dose of study drug

†679 if excluding those who discontinued due to death. No sig. difference for reasons for discontinuation between arms.

‡737 if excluding those who discontinued due to death

§Patel et al. 2011[10] total N=7131 vs 7133

#The sum of SEA, GI symptoms, GI bleeding

¤Other AEs not including SAEs

**Table D3.5. ARISTOTLE Subgroups – Stroke/SE**

| Stroke and systemic embolism, n (% per year) | | ARISTOTLE | | |
|---|---|---|---|---|
| | | Granger et al. 2011[9] | | |
| | | Apixaban (5 mg or 2.5 mg BID)* | Warfarin (INR: 2-3) | P Value for Interaction |
| Prior use of warfarin or other vitamin k antagonist | Yes | 102 (1.1) | 138 (1.5) | 0.39 |
| | No | 110 (1.5) | 127 (1.8) | |
| Age | <65 | 51 (1.0) | 44 (0.9) | 0.12 |
| | 65-75 | 82 (1.3) | 112 (1.7) | |
| | ≥75 | 79 (1.6) | 109 (2.2) | |
| Renal impairment | Severe/moderate | 54 (2.1) | 69 (2.7) | 0.72 |
| | Mild | 87 (1.2) | 116 (1.7) | |
| | No impairment | 70 (1.0) | 79 (1.1) | |
| Apixaban dose | 2.5 mg | 12 (1.7) | 22 (3.3) | 0.22 |
| | 5 mg | 200 (1.3) | 243 (1.5) | |

BID: twice a day, INR: international normalized ratio, Mg: milligram, N: number, SE: systemic embolism, %: percent

*2.5 mg BID: 428 (4.7%)

**Table D3.6. ARISTOTLE Subgroups – Major Bleeding**

| Major Bleeding | | ARISTOTLE | | |
|---|---|---|---|---|
| | | Granger et al. 2011[9] | | |
| | | Apixaban (5 mg or 2.5 mg BID) | Warfarin (INR: 2-3) | P Value for Interaction |
| Prior use of warfarin or other vitamin k antagonist, n (% per year) | Yes | 185 (2.1) | 274 (3.2) | 0.5 |
| | No | 142 (2.2) | 188 (3.0) | |
| Age | <65 | 56 (1.2) | 72 (1.5) | 0.64 |
| | 65-75 | 120 (2.0) | 166 (2.8) | |
| | >=75 | 151 (3.3) | 224 (5.2) | |
| Renal impairment | Severe/moderate | 73 (3.2) | 142 (6.4) | 0.03 |
| | Mild | 157 (2.5) | 199 (3.2) | |
| | No impairment | 96 (1.5) | 119 (1.8) | |
| Apixaban dose | 2.5 mg | 20 (3.3) | 37 (6.7) | 0.21 |
| | 5 mg | 307 (2.1) | 425 (3.0) | |

BID: twice a day, INR: international normalized ratio, Mg: milligram, N: number, SE: systemic embolism, %: percent

*2.5 mg BID: 428 (4.7%)

**Table D3.7. ARISTOTLE Subgroups – Association Between Cancer Status and Outcomes**

| Association between cancer status and outcomes | | ARISTOTLE | | |
|---|---|---|---|---|
| | | Melloni et al 2017[33] | | |
| | | Cancer (n=1236) | | |
| | | Apixaban (n= 615) | Warfarin (n=621) | HR (95% CI) |
| Ischemic Outcomes | Stroke or SE | 15 (1.4) | 14 (1.2) | 1.09 (0.53, 2.26) |
| | Death from any cause | 54 (4.7) | 42 (3.6) | 1.32 (0.88, 1.97) |
| | Ischemic Stroke | 14 (1.3) | 9 (0.8) | 1.59 (0.69, 3.66) |
| | MI | 12 (1.1) | 12 (1.1) | 102 (0.46, 2.27) |
| | PE/DVT | 3 (0.3) | 4 (0.4) | 0.76 (0.17, 3.41) |
| Bleeding Outcomes | ISTH Major Bleeding | 24 (2.4) | 32 (3.2) | 0.76 (0.45, 1.29) |
| | Major or minor bleeding | 53 (5.5) | 67 (6.9) | 0.80 (0.56, 1.14) |
| | Any bleeding | 204 (26.5) | 245 (32.2) | 0.83 (0.69, 0.99) |
| | Intracranial Bleeding | 0 (0) | 9 (0.9) | NE |
| Net composite endpoint | Efficacy endpoint | 74 (6.6) | 65 (5.7) | 1.17 (0.84, 1.63) |
| | End point | 93 (8.5) | 89 (8.0) | 1.07 (0.80, 1.43) |

DVT: deep vein thrombosis, ISTH: international society on thrombosis and hemostasis, MI: myocardial infarction, NE: not estimable, PE: pulmonary embolism

**Table D3.8. ARISTOTLE Subgroups – Outcomes in Patients with Active Cancer**

| Effects of Apixaban Vs. Warfarin in Patients with Atrial Fibrillation and Active Cancer | | ARISTOTLE | | | |
|---|---|---|---|---|---|
| | | Melloni et al 2017[33] | | | |
| | | Apixaban (n=76) | Warfarin (n=81) | Apixaban vs. Warfarin | |
| | | Event (Rate) | Event (Rate) | HR (95% CI) | P Value for Interaction |
| Ischemic outcomes | Stroke or SE | 0 (0) | 5 (3.8) | NA | NA |
| | Death from any cause | 5 (3.7) | 11 (8.1) | 0.45 (0.16, 1.29) | 0.0127 |
| | Ischemic Stroke | 0 (0) | 3 (2.3) | NA | NA |
| | MI | 0 (0) | 1 (0.8) | NA | NA |
| | PE/DVT | 0 (0) | 1 (0.8) | NA | NA |
| Bleeding Outcomes | ISTH Major Bleeding | 1 (0.8) | 5. (4.5) | 0.19 (0.02, 1.59) | 0.3485 |
| | Major or minor bleeding | 6 (5.2) | 10 (9.5) | 0.56 (0.20, 1.54) | 0.507 |
| | Any bleeding | 27 (31.4) | 30 (34.9) | 0.93 (0.55, 1.56) | 0.2412 |
| | Intracranial Bleeding | 0 (0) | 2 (1.8) | NA | NA |
| Net composite endpoint | Composite efficacy end point* | 5 (3.7) | 16 (12.1) | 0.30 (0.11, 0.83) | 0.0028 |
| | Composite end point† | 6 (4.4) | 18 (13.9) | 0.32 (0.13, 0.81) | 0.0048 |

DVT: deep vein thrombosis, ISTH: international society on thrombosis and hemostasis, MI: myocardial infarction, NA: not applicable, PE: pulmonary embolism

*stroke/systemic embolism, myocardial infarction and death

†Stroke/systemic embolism, myocardial infarction, death, and ISTH major bleeding

**Table D3.9. ARISTOTLE Subgroups – Association Between Cancer Status and Outcomes**

| Association between cancer status and outcomes | | ARISTOTLE | | | |
|---|---|---|---|---|---|
| | | Melloni et al 2017[33] | | | |
| | | Active Cancer (n= 157) | No Cancer (N= 16,947) | Active vs. No cancer | |
| | | Event (Rate) | Event (Rate) | HR (95% CI) | P Value for Interaction |
| Ischemic Outcomes | Stroke or SE | 5 (1.9) | 447 (1.4) | 1.37 (0.57, 3.33) | 0.4838 |
| | Death from any cause | 16 (5.9) | 1174 (3.7) | 1.62 (0.99, 2.67) | 0.0567 |
| | Ischemic Stroke | 3 (1.1) | 313 (1.0) | 1.14 (0.37, 3.58) | 0.8177 |
| | MI | 1 (0.4) | 168 (0.5) | 0.48 (0.07, 3.44) | 0.4649 |
| | PE/DVT | 1 (0.4) | 6 (0.2) | 1.80 (0.25, 13.2) | 0.5632 |
| Bleeding Outcomes | ISTH Major Bleeding | 6 (2.6) | 733 (2.6) | 0.59 (0.24, 1.43) | 0.242 |
| | Major or minor bleeding | 16 (7.2) | 1370 (4.9) | 1.00 (0.60, 1.66) | 0.9845 |
| | Any bleeding | 57 (33.1) | 4964 (21.3) | 1.18 (0.90, 1.54) | 0.2242 |
| | Intracranial Bleeding | 2 (0.9) | 165 (0.6) | 1.34 (0.33, 5.45) | 0.6876 |

DVT: deep vein thrombosis, ISTH: international society on thrombosis and hemostasis, MI: myocardial infarction, PE: pulmonary embolism

**Table D3.10. ARISTOTLE Subgroups – Patients with or without Stage 4 CKD**

| Safety and Efficacy Outcomes and Hazard Ratios for Apixaban Vs. Warfarin in Patients With or Without Stage 4 Chronic Kidney Disease, Event rates (n) | | ARISTOTLE | | | |
|---|---|---|---|---|---|
| | | Stanifer et al. 2020[46] | | | |
| | | Apixaban | Warfarin | HR (95% CI) | P value |
| Major bleeding | CrCl 25-30 mL/min | 3.78 (7) | 11.94 (19) | 0.34 (0.14, 0.80) | 0.08 |
| | CrCl > 30 mL/min | 2.12 (319) | 2.99 (441) | 0.71 (0.61, 0.82) | |
| Major or CRNM bleeding | CrCl 25-30 mL/min | 5.43 (10) | 16.75 (26) | 0.35 (0.17, 0.72) | 0.05 |
| | CrCl > 30 mL/min | 4.05 (600) | 5.90 (848) | 0.69 (0.62, 0.76) | |
| Intracranial bleeding | CrCl 25-30 mL/min | 0.00 (0) | 2.40 (4) | NA | 0.96 |
| | CrCl > 30 mL/min | 0.33 (51) | 0.79 (118) | 0.42 (0.31, 0.59) | |
| Stroke or SE | CrCl 25-30 mL/min | 2.81 (6) | 5.06 (10) | 0.55 (0.20, 1.51) | 0.5 |
| | CrCl > 30 mL/min | 1.25 (205) | 1.56 (254) | 0.80 (0.67, 0.96) | |
| Death from any cause | CrCl 25-30 mL/min | 15.2 (33) | 15.3 (32) | 1.02 (0.64, 1.67) | 0.67 |
| | CrCl > 30 mL/min | 3.38 (568) | 3.80 (635) | 0.89 (0.79, 0.97) | |
| Cardiovascular death | CrCl 25-30 mL/min | 6.89 (15) | 6.68 (14) | 1.05 (0.51, 2.18) | 0.67 |
| | CrCl > 30 mL/min | 1.73 (291) | 1.97 (329) | 0.88 (0.75, 1.03) | |
| Myocardial infarction | CrCl 25-30 mL/min | 2.34 (5) | 1.49 (3) | 1.60 (0.38, 6.69) | 0.42 |
| | CrCl > 30 mL/min | 0.51 (85) | 0.60 (99) | 0.85 (0.64, 1.14) | |

CKD: chronic kidney disease, CI: confidence interval, CRNM: clinically relevant non-major, mL/min: milliliters per minute, N: number, NA: Not applicable, SE: systemic embolism,

**Table D3.11. ARISTOTLE Subgroups – Renal Function Over Time**

| Apixaban vs Warfarin according to category of Renal function over time | | ARISTOTLE | | | | | |
|---|---|---|---|---|---|---|---|
| | | Hijazi et al 2016[47] | | | | | |
| | | Apixaban | | Warfarin | | HR (95% CI) | Equation |
| | | Person-years | No. of Events | Person-years | No. of Events | | |
| Stroke/SE | < 50 mL/min | 2772.8 | 45 (1.62) | 2656.1 | 61 (2.30) | 0.70 (0.48, 1.03) | Cockcroft-Gault |
| | 50-80 mL/min | 6640.5 | 77 (1.16) | 6552.4 | 98 (1.50) | 0.78 (0.58, 1.04) | |
| | >80 mL/min | 6457.4 | 53 (0.82) | 6478 | 61 (0.94) | 0.87 (0.60, 1.26) | |
| | < 50 mL/min | 2702.2 | 30 (1.11) | 2600.2 | 45 (1.73) | 0.64 (0.41, 1.02) | Chronic Kidney Disease Epi |
| | 50-80 mL/min | 8918.3 | 111 (1.24) | 8766.8 | 125 (1.43) | 0.87 (0.68, 1.13) | |
| | >80 mL/min | 4310.2 | 35 (0.81) | 4367.2 | 51 (1.17) | 0.70 (0.45, 1.07) | |
| Major Bleeding | < 50 mL/min | 2603 | 82 (3.15) | 2428.7 | 130 (5.35) | 0.59 (0.45, 0.77) | Cockcroft-Gault |
| | 50-80 mL/min | 6347 | 136 (2.14) | 6203 | 176 (2.84) | 0.76 (0.60, 0.94) | |
| | >80 mL/min | 6235.5 | 83 (1.33) | 6187.9 | 103 (1.66) | 0.80 (0.60, 1.07) | |
| | < 50 mL/min | 2504.9 | 82 (3.27) | 2348.7 | 124 (5.28) | 0.62 (0.47, 0.82) | Chronic Kidney Disease Epi |
| | 50-80 mL/min | 8544.3 | 172 (2.01) | 8348.2 | 209 (2.50) | 0.80 (0.66, 0.98) | |
| | >80 mL/min | 4195.1 | 48 (1.14) | 4170.5 | 78 (1.87) | 0.61 (0.43, 0.88) | |

CI: confidence interval, HR: hazard ratio, mL/min: milliliters per minute, No: number, SE: systemic embolism,

**Table D3.12. ARISTOTLE Subgroups – Renal Function**

| Apixaban vs. warfarin according to renal function | | ARISTOTLE | | | | |
|---|---|---|---|---|---|---|
| | | Hohnloser et al 2012[48] | | | | |
| | | Apixaban | Warfarin (INR: 2-3) | HR (95% CI) | P-value | Equation |
| | | %/year (n) | %/year (n) | | | |
| All-cause Mortality | >80 mL/min | 2.33 (169) | 2.71 (195) | 0.86 (0.70, 1.06) | 0.627 | Cockcroft-Gault |
| | | 2.82 (139) | 3.11 (151) | 0.91 (0.72, 1.14) | 0.319 | CKD-EPI |
| | | 2.20 (165) | 2.53 (188) | 0.87 (0.71, 1.07) | 0.706 | Cystatin C |
| | >50-80 mL/min | 3.41 (244) | 3.56 (251) | 0.96 (0.81, 1.14) | 0.627 | Cockcroft-Gault |
| | | 3.26 (312) | 3.42 (327) | 0.95 (0.82, 1.11) | 0.319 | CKD-EPI |
| | | 4.14 (208) | 4.50 (230) | 0.92 (0.76, 1.11) | 0.706 | Cystatin C |
| | ≤50 mL/min | 7.12 (188) | 8.30 (221) | 0.86 (0.70, 1.05) | 0.627 | Cockcroft-Gault |
| | | 5.83 (152) | 7.48 (191) | 0.78 (0.63, 0.96) | 0.319 | CKD-EPI |
| | | 7.19 (142) | 7.21 (135) | 1.00 (0.79, 1.26) | 0.706 | Cystatin C |

%: percent, CI: confidence interval, HR: hazard ratio, mL/min: milliliters per minute, INR: international normalized ratio, N: number

**Table D3.13. ARISTOTLE Subgroups – Elderly Patients**

| Efficacy and safety of apixaban in the elderly | | ARISTOTLE | | | |
|---|---|---|---|---|---|
| | | Halvorsen et al. 2014[49] | | | |
| Outcome, n (%/year) | Age, years | Apixaban (5 mg or 2.5 mg BID) | Warfarin (INR: 2-3) | HR (95% CI) | Interaction P value |
| Stroke or systemic embolism | <65 | 51 (1.00) | 44 (0.86) | 1.16 (0.77, 1.73) | 0.11 |
| | 65-75 | 82 (1.25) | 112 (1.73) | 0.72 (0.54, 0.96) | |
| | >=75 | 79 (1.56) | 109 (2.19) | 0.71 (0.53, 0.95) | |
| All-cause mortality | <65 | 143 (2.74) | 134 (2.56) | 1.07 (0.84, 1.35) | 0.43 |
| | 65-75 | 179 (2.67) | 229 (3.46) | 0.77 (0.64, 0.94) | |
| | >=75 | 281 (5.42) | 306 (5.97) | 0.91 (0.77, 1.07) | |
| Major bleeding | <65 | 56 (1.17) | 72 (1.51) | 0.78 (0.55, 1.11) | 0.63 |
| | 65-75 | 120 (1.99) | 166 (2.82) | 0.71 (0.56, 0.89) | |
| | >=75 | 151 (3.33) | 224 (5.19) | 0.64 (0.54, 0.79) | |
| All bleeding | <65 | 570 (13.6) | 746 (19.1) | 0.73 (0.65, 0.81) | 0.94 |
| | 65-75 | 926 (17.9) | 1196 (25.9) | 0.70 (0.65, 0.77) | |
| | >=75 | 860 (23.5) | 1118 (33.7) | 0.71 (0.65, 0.78) | |
| Intracranial bleeding | <65 | 15 (0.31) | 17 (0.35) | 0.87 (0.43, 1.74) | 0.2 |
| | 65-75 | 17 (0.28) | 48 (0.81) | 0.35 (0.20, 0.60) | |
| | >=75 | 20 (0.43) | 57 (1.29) | 0.34 (0.20, 0.57) | |
| Net clinical events | <65 | 228 (4.51) | 218 (4.29) | 1.05 (0.87, 1.26) | 0.18 |
| | 65-75 | 340 (5.27) | 426 (6.71) | 0.79 (0.68, 0.91) | |
| | >=75 | 441 (8.91) | 524 (10.9) | 0.82 (0.72, 0.93) | |

BID: twice a day, CI: confidence interval, HR: hazard ratio, INR: International Normalized Ratio, N: number

**Table D3.14. ARISTOTLE Subgroups – Discontinuation After Bleeding Events**

| Study discontinuation after bleeding events | | ARISTOTLE | | | | | |
|---|---|---|---|---|---|---|---|
| | | Held et al 2015[50] | | | | | |
| | | Events | Not on Study Drug | On study drug | No interruption | Interruption | Not resumed |
| | | N | percentages/ no. events | percentages/ no. events | percentage/no. of events on drug | percentage/no. of events on drug | Percentage/ no. interruptions |
| ISTH major Bleeding | Overall | 848 | 208 (24.5) | 640 (75.5) | 187 (29.2) | 453 (70.8) | 225 (56.3) |
| | Apixaban | 361 | 102 (28.3) | 259 (71.7) | 86 (33.2) | 173 (66.8) | 91 (52.6) |
| | Warfarin | 487 | 106 (21.8) | 381 (78.2) | 101 (26.5) | 280 (73.5) | 164 (58.6) |
| ISTH major/CRNM bleeding | Overall | 1569 | 298 (19.0) | 1271 (81) | 505 (39.7) | 766 (60.3) | 332 (43.3) |
| | Apixaban | 664 | 149 (22.4) | 515 (77.6) | 222 (43.1) | 293 (56.9) | 110 (37.5) |
| | Warfarin | 905 | 149 (16.5) | 756 (83.5) | 283 (37.4) | 473 (62.6) | 222 (46.9) |
| Intracranial Bleeding | Overall | 176 | 25 (14.2) | 151 (85.8) | 14 (9.3) | 137 (90.7) | 121 (88.3) |
| | Apixaban | 53 | 7 (13.2) | 46 (86.8) | 3 (6.5) | 43 (93.5) | 40 (93) |
| | Warfarin | 123 | 18 (14.6) | 105 (85.4) | 11 (10.5) | 94 (89.5) | 81 (86.2) |
| Gastro-intestinal Bleeding | Overall | 264 | 52 (19.7) | 212 (80.3) | 53 (25) | 159 (75) | 78 (49.1) |
| | Apixaban | 131 | 26 (19.9) | 1055 (80.1) | 27 (25.7) | 78 (74.3) | 36 (46.2) |
| | Warfarin | 133 | 26 (19.6) | 107 (80.4) | 26 (24.3) | 81 (75.7) | 42 (51.9) |

CRNM: clinically relevant non-major bleeding, ISTH: international society on Thrombosis and hemostasis, N: number, No.: number,

**Table D3.15. ROCKET AF Subgroups – Baseline Characteristics of ROCKET AF Patients According to Major Bleeding Events**

| Baseline characteristics of ROCKET AF patients according to Major Bleeding events, n (%)* | | ROCKET AF† | | |
|---|---|---|---|---|
| | | Piccini et al. 2014[37] | | |
| | | Rivaroxaban | Warfarin | P Value for Interaction |
| Age, median (SD), years | | 76 (69-70) | 75 (68-79) | 0.2124 |
| Creatinine clearance, median (SD) | | 64 (49-85) | 62 (49-77) | 0.0382 |
| Creatinine clearance <50 mL/min, no. (%) | | 99 (25.1) | 99 (25.8) | 0.7869 |
| Race | White | 332 (84.3) | 299 (78.1) | 0.0231 |
| | Asian | 44 (11.2) | 70 (18.3) | |
| | Black | 6 (1.5) | 3 (0.8) | |
| | Other | 12 (3) | 11 (2.9) | |
| Previous medication use, no (%) | VKA | 270 (68.4) | 248 (64.6) | 0.1505 |

N: number, No.: number, mL/min: milliliters per minute, SD: standard deviation, VKA: vitamin K antagonist

*Percent of all major bleeds for that treatment arm

†ITT population

**Table D3.16. ROCKET AF Subgroups – Clinically Relevant Major Bleeding and Non-Major Bleeding**

| Major Bleeding and Non-Major Clinically Relevant Bleeding While on Treatment, n (%) | | ROCKET AF | | |
|---|---|---|---|---|
| | | Patel et al. 2011[10] | | |
| | | Rivaroxaban 20mg | Warfarin (INR: 2-3) | P Value for Interaction |
| Prior VKA Use | Yes | 1013 (22.86) | 965 (21.65) | 0.044 |
| | No | NR | NR | |
| Age | <65 years | 241 (14.64) | 260 (15.83) | 0.118 |
| | 65-75 years | 541 (19.48) | 556 (19.99) | |
| | ≥75 years | 693 (25.78) | 633 (23.43) | |
| CrCL (mL/min) | <50 mL/min | 336 (22.37) | 342 (23.17) | 0.735 |
| | 50 to 80 mL/min | 725 (21.88) | 719 (21.09) | |
| | >80 mL/min | 412 (18.01) | 388 (17.40) | |

CrCL: creatinine clearance, INR: international normalized ratio, N; number, NR: not reported, mL/min: milliliters per minute, mg: milligrams, VKA: vitamin K antagonist

**Table D3.17. ROCKET AF Subgroups – Major Bleeding on Treatment**

| Major Bleeding On Treatment, n (% per year) | | ROCKET AF | | | |
|---|---|---|---|---|---|
| | | Goodman et al. 2014[42] | | | |
| | | Rivaroxaban 20mg | Warfarin (INR: 2-3) | HR (95% CI) | P value for interaction |
| Prior VKA Use | Yes | 270 (3.8) | 249 (3.38) | 1.12 (0.94, 1.13) | 0.15 |
| | No | 125 (3.23) | 137 (3.59) | 0.90 (0.71, 1.15) | |
| Age | <65 | 59 (2.21) | 59 (2.16) | 1.02 (0.71, 1.46) | 0.59 |
| | 65-75 | 113 (3.03) | 123 (3.24) | 0.94 (0.73, 1.21) | |
| | >=75 | 223 (4.86) | 204 (4.40) | 1.11 (0.92, 1.34) | |
| CrCL (mL/min) | <50 | 99 (4.72) | 101 (4.73) | 1.00 (0.75, 1.31) | 0.28 |
| | 50 to 80 | 183 (3.54) | 196 (3.70) | 0.96 (0.79, 1.18) | |
| | >80 | 112 (3.02) | 89 (2.38) | 1.26 (0.95, 1.66) | |

CI: confidence interval, CrCL: creatinine clearance, HR: hazard ratio, INR: international normalized ratio, N; number, mL/min: milliliters per minute, mg: milligrams, VKA: vitamin K antagonist

**Table D3.18. ROCKET AF Subgroups – Efficacy Endpoints by Age and Treatment Allocation (ITT)**

| Efficacy End Points According to Age Category and Treatment Allocation: Intention-to-Treat Population | | | ROCKET AF | | | |
|---|---|---|---|---|---|---|
| | | | Halperin et al. 2014[35] | | | |
| | | | Rivaroxaban 20mg* | Warfarin (INR: 2-3)* | HR (95% CI) | P value for interaction |
| Stroke and systemic embolism | | Age ≥75 years | 2.29 | 2.85 | 0.80 (0.63, 1.02) | 0.3131 |
| | | Age <75 years | 2 | 2.1 | 0.95 (0.76, 1.19) | |
| Stroke, systemic embolism, vascular death | | Age ≥75 years | 5.27 | 5.74 | 0.92 (0.78, 1.087) | 0.7441 |
| | | Age <75 years | 3.94 | 4.12 | 0.95 (0.81, 1.12) | |
| Stroke, systemic embolism, MI, vascular death | | Age ≥75 years | 6.07 | 6.68 | 0.91 (0.78, 1.06) | 0.7493 |
| | | Age <75 years | 4.61 | 4.89 | 0.94 (0.81, 1.09) | |
| Stroke | Ischemic | Age ≥75 years | 1.71 | 1.95 | 0.88 (0.67, 1.16) | 0.2448 |
| | | Age <75 years | 1.55 | 1.4 | 1.10 (0.84, 1.44) | |
| | Hemorrhagic | Age ≥75 years | 0.34 | 0.49 | 0.70 (0.39, 1.25) | 0.3651 |
| | | Age <75 years | 0.19 | 0.41 | 0.47 (0.25, 0.89) | |
| | Undetermined | Age ≥75 years | 0.09 | 0.16 | 0.55 (0.19, 1.65) | 0.1388 |
| | | Age <75 years | 0.19 | 0.12 | 1.56 (0.68, 3.61) | |

CI: confidence interval, HR: hazard ratio, INR: international normalized ratio, ITT: intention-to-treat, N; number

*Event rates per 100 patient-years of follow-up

**Table D3.19. ROCKET AF Subgroups – Bleeding Events According to Age and Treatment Allocation (ITT)**

| Bleeding Events According to Age Category and Treatment Allocation | | ROCKET AF | | | |
|---|---|---|---|---|---|
| | | Halperin et al. 2014[35] | | | |
| | | Rivaroxaban 20mg* | Warfarin (INR: 2-3)* | HR (95% CI) | P value for interaction |
| Primary safety endpoint† | Age ≥75 years | 19.83 | 17.55 | 1.13 (1.02, 1.25) | 0.009 |
| | Age <75 years | 11.85 | 12.43 | 0.93 (0.84, 1.04) | |
| Major Bleeding | Age ≥75 years | 4.86 | 4.4 | 1.11 (0.92, 1.34) | 0.3357 |
| | Age <75 years | 2.69 | 2.79 | 0.96 (0.78, 1.19) | |
| Fatal bleeding | Age ≥75 years | 0.28 | 0.61 | 0.45 (0.23, 0.87) | 0.6839 |
| | Age <75 years | 0.22 | 0.39 | 0.55 (0.29, 1.05) | |
| Intracranial hemorrhage | Age ≥75 years | 0.66 | 0.83 | 0.80 (0.50, 1.28) | 0.2654 |
| | Age <75 years | 0.37 | 0.68 | 0.54 (0.33, 0.89) | |

CI: confidence interval, HR: hazard ratio, INR: international normalized ratio, ITT: intention-to-treat

*Event rates per 100 patient-years of follow-up

†Major and non-major clinically relevant bleeding

**Table D3.20. ROCKET AF Subgroups – Bleeding Site According to Age and Treatment Allocation (ITT)**

| Bleeding Sites According to Age Category and Treatment Allocation | | ROCKET AF | | |
|---|---|---|---|---|
| | | Halperin et al. 2014[35] | | |
| | | Rivaroxaban 20mg* | Warfarin (INR: 2-3)* | P value for interaction |
| Gastrointestinal (upper, lower, and rectal) | Age ≥75 years | 2.81 | 1.66 | 0.0002 |
| | Age <75 years | 1.41 | 0.94 | 0.0136 |

HR: hazard ratio, INR: international normalized ratio, ITT: intention-to-treat, mg: milligram

**Table D3.21. ROCKET AF Subgroups –Bleeding Events According to Renal Function and Treatment Allocation**

| Bleeding Events According to Renal Function and Treatment Allocation | | ROCKET AF | | | |
|---|---|---|---|---|---|
| | | Fox et al. 2011[51] | | | |
| | | Rivaroxaban*† | Warfarin* | HR (95% CI) | P value for interaction |
| Primary safety endpoint | CrCl 30-49 mL/min | 17.82 | 18.28 | 0.98 (0.84, 1.14) | 0.4496 |
| | CrCl >= 50 mL/min | 14.24 | 13.67 | 1.04 (0.96, 1.13) | |
| Major Bleeding | CrCl 30-49 mL/min | 4.49 | 4.7 | 0.95 (0.72, 1.26) | 0.48 |
| | CrCl >= 50 mL/min | 3.39 | 3.17 | 1.07 (0.91, 1.26) | |
| Fatal bleeding | CrCl 30-49 mL/min | 0.28 | 0.74 | 0.39 (0.15, 0.99) | 0.5302 |
| | CrCl >= 50 mL/min | 0.23 | 0.43 | 0.55 (0.32, 0.93) | |
| Intracranial hemorrhage | CrCl 30-49 mL/min | 0.71 | 0.88 | 0.81 (0.41, 1.60) | 0.5065 |
| | CrCl >= 50 mL/min | 0.44 | 0.71 | 0.62 (0.42, 0.92) | |

CI: confidence intervals, CrCl: creatine clearance, HR: hazard ratio, mL/min: milliliters per minute

*Event rates per 100 patient years of follow-up

†CrCl 30-49 mL/min group receiving reduced 15mg dosage of rivaroxaban

**Table D3.22. ROCKET AF Subgroups – Bleeding Sites According to Renal Function and Treatment Allocation (ITT)**

| Bleeding Sites According to Renal Function and Treatment Allocation | | ROCKET AF | |
|---|---|---|---|
| | | Fox et al 2011[51] | |
| | | Rivaroxaban*† | Warfarin* |
| Gastrointestinal (upper, lower, and rectal) | CrCl 30-49 mL/min | 2.88 | 1.77 |
| | CrCl >= 50 mL/min | 1.79 | 1.12 |

CrCl: creatine clearance, ITT: intention-to-treat

*Event rates per 100 patient years of follow-up

†CrCl 30-49 mL/min group receiving reduced 15mg dosage of rivaroxaban

**Table D3.23. ROCKET AF Subgroups – Efficacy Endpoints According Renal Function in ITT**

| Efficacy Endpoints According to the intention to Treat | | | ROCKET AF | | | |
|---|---|---|---|---|---|---|
| | | | Fox et al. 2011[51] | | | |
| | | | Rivaroxaban*† | Warfarin* | HR (95% CI) | P value for interaction |
| Stroke and systemic embolism | | CrCl 30-49 mL/min | 2.95 | 3.44 | 0.86 (0.63, 1.17) | 0.85 |
| | | CrCl >= 50 mL/min | 1.92 | 2.16 | 0.89 (0.73, 1.08) | |
| Stroke, systemic embolism, vascular death | | CrCl 30-49 mL/min | 7 | 7.67 | 0.91 (0.74, 1.12) | 0.74 |
| | | CrCl >= 50 mL/min | 3.89 | 4.09 | 0.95 (0.83, 1.09) | |
| Stroke, systemic embolism, MI, vascular death | | CrCl 30-49 mL/min | 7.86 | 8.83 | 0.89 (0.73, 1.08) | 0.61 |
| | | CrCl >= 50 mL/min | 4.59 | 4.86 | 0.94 (0.83, 1.07) | |
| Stroke | Ischemic | CrCl 30-49 mL/min | 2.34 | 2.3 | 1.02 (0.71, 1.46) | 0.89 |
| | | CrCl >= 50 mL/min | 1.44 | 1.46 | 0.99 (0.78, 1.24) | |
| | Hemorrhagic | CrCl 30-49 mL/min | 0.27 | 0.47 | 0.58 (0.23, 1.47) | 0.99 |
| | | CrCl >= 50 mL/min | 0.25 | 0.44 | 0.58 (0.36, 0.94) | |
| | Undetermined | CrCl 30-49 mL/min | 0.2 | 0.2 | 1.00 (0.29, 3.45) | 0.92 |
| | | CrCl >= 50 mL/min | 0.13 | 0.13 | 1.08 (0.51, 2.29) | |

CI: confidence interval, HR: hazard ratio, MI: myocardial infarction

*Event rates per 100 patient-years of follow-up

†CrCl 30-49 mL/min group receiving reduced 15mg dosage of rivaroxaban

**Table D3.24. ROCKET AF Subgroups – Stroke/SE**

| Stroke or Systemic Embolism, n (%) | | ROCKET AF | | |
|---|---|---|---|---|
| | | Patel et al. 2011[10] | | |
| | | Rivaroxaban 20mg | Warfarin (INR: 2-3) | P Value for Interaction |
| Prior VKA Use | Yes | 168 (3.81) | 175 (3.94) | 0.16 |
| | No | 101 (3.79) | 131 (4.94) | |
| Age | <75 years | 144 (3.6) | 152 (3.79) | 0.313 |
| | ≥75 years | 125 (4.06) | 154 (5) | |
| CrCL (mL/min) | <50 | 77 (5.17) | 86 (5.89) | 0.9 |
| | 50 to 80 | 126 (3.82) | 151 (4.44) | |
| | >80 | 65 (2.84) | 68 (3.06) | |

CrCl: creatine clearance, ITT: intention-to-treat, INR: international normalized ratio, mg: milligrams, mL/min: milligrams per minute

*Event rates per 100 patient-years of follow-up

**Table D3.25. ROCKET AF Subgroups – Worsening Renal Function**

| Outcome of patients with worsening renal function with rivaroxaban vs. warfarin | | Rocket AF | |
|---|---|---|---|
| | | Fordyce et al. 2016[52] | |
| | | HR (95% CI) | P Interaction |
| Efficacy Outcomes | Stroke/SE | 0.50 (0.27, 0.93) | 0.05 |
| | Vascular death | 0.98 (0.53, 1.79) | 0.56 |
| | MI | 0.52 (0.22, 1.23) | 0.2 |
| | Stroke/SE/V-death/MI | 0.64 (0.43, 0.94) | 0.085 |
| | Death | 0.83 (0.50, 1.39) | 0.73 |
| Safety Outcome | Major/NMCR bleed | 1.06 (0.80, 1.39) | 0.61 |
| | Major bleed | 1.45 (0.90, 2.35) | 0.13 |
| | Fatal bleed | 0.67 (0.11, 3.99) | 0.98 |
| | Intracranial hemorrhage | 0.62 (0.20, 1.90) | 0.67 |
| | NMCR bleed | 0.89 (0.65, 1.23) | 0.49 |

CI: confidence interval, HR: hazard ratio, NMCR: non-major clinically relevant, MI: myocardial infarction, SE: systemic embolism

**Table D3.26. RE-LY Subgroups – Renal Function**

| Interaction Between Categorical Renal Function According to Treatment, events/n (%/y)† | | RE-LY | | | |
|---|---|---|---|---|---|
| | | Hijazi et al. 2014[53] | | | |
| Outcome | Renal function level (mL/min) | Dabigatran (150 mg) | Warfarin (INR: 2-3) | HR (95% CI) | P value |
| Stroke or systemic embolism | ≥80 | 28/1945 (0.71) | 41/1941 (1.05) | 0.67 (0.42, 1.09) | 0.7522 |
| | 50 to <80 | 70/2852 (1.25) | 103/2898 (1.83) | 0.68 (0.50, 0.92) | |
| | <50 | 36/1232 (1.53) | 57/1126 (2.70) | 0.56 (0.37, 0.85) | |
| All-cause mortality | ≥80 | 81/1945 (2.04) | 97/1941 (2.48) | 0.82 (0.61, 1.11) | 0.361 |
| | 50 to <80 | 198/2852 (3.53) | 244/2898 (4.32) | 0.81 (0.67, 0.98) | |
| | <50 | 159/1232 (6.77) | 143/1126 (6.77) | 1.00 (0.80, 1.25) | |
| Major bleed | ≥80 | 81/1945 (2.04) | 95/1941 (2.43) | 0.84 (0.62, 1.13) | 0.6393 |
| | 50 to <80 | 188/2852 (3.35) | 209/2898 (3.70) | 0.91 (0.75, 1.11) | |
| | <50 | 129/1232 (5.50) | 116/1126 (5.49) | 1.01 (0.79, 1.30) | |
| Life-threatening bleed | ≥80 | 31/1945 (0.78) | 50/1941 (1.28) | 0.61 (0.39, 0.95) | 0.4254 |
| | 50 to <80 | 87/2852 (1.55) | 107/2898 (1.90) | 0.82 (0.62, 1.08) | |
| | <50 | 60/1232 (2.56) | 61/1126 (2.89) | 0.88 (0.62, 1.26) | |
| Intracranial bleeding | ≥80 | 7/1945 (0.18) | 15/1941 (0.38) | 0.46 (0.19, 1.13) | 0.693 |
| | 50 to <80 | 22/2852 (0.39) | 49/2898 (0.87) | 0.45 (0.27, 0.74) | |
| | <50 | 9/1232 (0.38) | 26/1126 (1.23) | 0.31 (0.14, 0.66) | |
| Net clinical benefit* | ≥80 | 182/1945 (4.59) | 207/1941 (5.29) | 0.87 (0.71, 1.06) | 0.8534 |
| | 50 to <80 | 396/2852 (7.05) | 453/2898 (8.03) | 0.88 (0.77, 1.01) | |
| | <50 | 269/1232 (11.46) | 260/1126 (12.31) | 0.93 (0.78, 1.10) | |

CI: confidence interval, HR: hazard ratio, INR: international normalized ratio, N: number, mg: milligram, mL/min, milliliter per minute

* Net clinical benefit: Composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleed

†Cockcroft-Gault Formula and Treatment in a Cox Model for outcome

**Table D3.27. RE-LY Subgroups – Stroke/SE**

| Stroke and systemic embolism (% per year) | | RE-LY | | |
|---|---|---|---|---|
| | | Connolly et al. 2009[26] | | |
| | | Dabigatran (150 mg) | Warfarin (INR: 2-3) | P Value for Interaction |
| Long-term VKA therapy | Yes | 1.15 | 1.7 | 0.81 |
| | No | 1.07 | 1.67 | |
| Creatinine clearance | <50ml/min | 1.52 | 2.78 | 0.54 |
| | 50-79 ml/min | 1.2 | 1.76 | |
| | >=80 ml/min | 0.75 | 0.98 | |

INR: international normalized ratio, mL/min, milliliter per minute

**Table D3.28. RE-LY Subgroups – Risk of Clinical Outcomes by Age**

| Risk of clinical outcome events stratified by age categories | | RE-LY | | | | |
|---|---|---|---|---|---|---|
| | | Lauw et al. 2017[54] | | | | |
| | | Dabigatran 150mg (%/year) | Warfarin (INR: 2-3) (%/year) | HR (95% CI) | P value (age groups) | P value (age continuous) |
| | Age, Years | | | | | |
| Stroke/Non-CNS systemic embolism | <75 | 65 (0.90) | 101 (1.43) | 0.63 (0.46, 0.86) | 0.996 | 0.498 |
| | 75-79 | 32 (1.14) | 49 (1.76) | 0.65 (0.42, 1.01) | | |
| | 80-84 | 27 (1.73) | 38 (2.58) | 0.67 (0.41, 1.10) | | |
| | >=85 | 10 (2.15) | 14 (3.09) | 0.70 (0.31, 1.57) | | |
| Major bleeding | <75 | 153 (2.12) | 215 (3.04) | 0.70 (0.57, 0.86) | 0.001 | <0.001 |
| | 75-79 | 120 (4.28) | 116 (4.16) | 1.04 (0.81, 1.35) | | |
| | 80-84 | 92 (5.91) | 63 (4.28) | 1.41 (1.02, 1.94) | | |
| | >=85 | 34 (7.29) | 27 (5.96) | 1.22 (0.74, 2.02) | | |
| Intracranial bleeding | <75 | 19 (0.26) | 43 (0.61) | 0.43 (0.25, 0.74) | 0.481 | 0.548 |
| | 75-79 | 5 (0.18) | 22 (0.79) | 0.23 (0.09, 0.60) | | |
| | 80-84 | 10 (0.64) | 17 (1.16) | 0.55 (0.25, 1.21) | | |
| | >=85 | 5 (1.07) | 8 (1.77) | 0.61 (0.20, 1.87) | | |
| All-cause mortality | <75 | 192 (2.66) | 245 (3.46) | 0.77 (0.64, 0.93) | 0.068 | 0.014 |
| | 75-79 | 103 (3.68) | 124 (4.45) | 0.82 (0.63, 1.07) | | |
| | 80-84 | 100 (6.42) | 82 (5.57) | 1.16 (0.87, 1.55) | | |
| | >=85 | 43 (9.23) | 36 (7.95) | 1.15 (0.74, 1.79) | | |

CI: confidence interval, CNS: central nervous system, HR: hazard ratio, INR: international normalized ratio, mg: milligram, %: percent

**Table D3.29. RE-LY Subgroups – Risk of Bleeds in Elderly Patients**

| Risks of Major, Intracranial, and Extracranial Bleeding With Patients Aged <75 | | RE-LY | | | |
|---|---|---|---|---|---|
| | | Eikelboom et al. 2011[43] | | | |
| | | Warfarin (INR: 2-3) (%/y) | Dabigatran 150mg (%/y) | HR (95% CI) | P value for interaction |
| Stroke/SE | ≥75 years | 101 (1.43) | 65 (0.90) | 0.63 (0.46, 0.86) | 0.81 |
| | <75 years | 101 (2.14) | 69 (1.43) | 0.67 (0.49, 0.90) | |
| Major Bleeding | ≥75 years | 215 (3.04) | 153 (2.12) | 0.70 (0.57, 0.86) | <0.001 |
| | <75 years | 206 (4.37) | 246 (5.10) | 1.18 (0.98, 1.42) | |
| Intracranial Bleeding | ≥75 years | 43 (0.61) | 19 (0.26) | 0.43 (0.25, 0.74) | 0.91 |
| | <75 years | 47 (1.00) | 20 (0.41) | 0.42 (0.25, 0.70) | |
| Gastrointestinal Bleeding | ≥75 years | 73 (1.03) | 88 (1.22) | 1.19 (0.87, 1.63) | 0.06 |
| | <75 years | 75 (1.59 | 135 (2.80) | 1.79 (1.35, 2.37) | |

CI: confidence interval, HR: hazard ratio, INR: international normalized ratio, mg: milligram, SE: systemic embolism

**Table D3.30. Baseline Characteristics in Valkyrie and RENAL-AF**

| Trial | | Valkyrie | | RENAL-AF | |
|---|---|---|---|---|---|
| **Source** | | De Vriese et al. 2020; De Vriese et al. 2021 [28,55] | | Pokorney et al. 2022; clinicaltrials.gov [27] | |
| **Study Arms** | | Rivaroxaban (10mg) | VKA (INR: 2-3) | Apixaban (5mg or 2.5mg BID) | Warfarin (INR: 2-3) |
| **N** | | 46 | 44 | 82 | 72 |
| **Age** | Median (IQR) | 79.9 (74.4-83.9) | 80.3 (71.5-84.3) | 69.0 (61.0, 76.0) | 68.0 (60.5, 72.5) |
| | <65 years | NR | NR | 32 (39.0) | 25 (34.7) |
| | 65-75 years | NR | NR | 26 (31.7) | 32 (44.4) |
| | >= 75 years | NR | NR | 24 (29.3) | 15 (20.8) |
| | Mean (SD) | NR | NR | NR | NR |
| **Sex** | Female, n (%) | NR | NR | 34 (41.5) | 22 (30.6) |
| | Male, n (%) | 35 (76.1) | 25 (56.8) | 48 (58.5) | 50 (69.4) |
| **Race** | White | NR | NR | 43 (52.4) | 36 (50.0) |
| | Black/AA | NR | NR | 35 (42.7) | 34 (47.2) |
| | Asian | NR | NR | 3 (3.7) | 1 (1.4) |
| | American Indian/Alaska Native | NR | NR | 1 (1.2) | 0 |
| | Native Hawaiian/Other Pacific Islander | NR | NR | 0 | 0 |
| | Other | NR | NR | 0* | 1 (1.4)* |
| | NR | NR | NR | 0 | 1 |
| **Ethnicity** | Hispanic/Latino | NR | NR | 5 (6.1) | 3 (4.2) |
| | Non-Hispanic/Latino | NR | NR | 77 (93.9) | 67 (93.1) |
| | NR | NR | NR | 0 | 2 (2.8) |
| **Region** | North America | NR | NR | 82 (100) | 72 (100) |
| | Latin America | NR | NR | 0 | 0 |
| | Europe | NR | NR | 0 | 0 |
| | Asian Pacific | NR | NR | 0 | 0 |
| | Other | NR | NR | 0 | 0 |
| | Median (IQR) | 122 (112-145) | 133 (116-153) | 131.0 (115.5, 151.5) | 136.0 (120.5, 149.0) |

| Trial | | Valkyrie | | RENAL-AF | |
|---|---|---|---|---|---|
| **Systolic blood pressure, mm Hg** | Mean (SD) | NR | NR | NR | NR |
| **Diastolic blood pressure, mm Hg** | Median (IQR) | 62 (53-68) | 65 (56-71) | NR | NR |
| | Mean (SD) | NR | NR | NR | NR |
| **Weight, kg** | Median (IQR) | NR | NR | 86.3 (69.5, 100.5) | 90.5 (72.8, 112.2) |
| | Mean (SD) | NR | NR | 87.6 (24.1) | 93.7 (24.9) |
| **Body-mass index** | Median (IQR) | 24.7 (22.0-27.5) | 25.6 (22.3-30.4) | NR | NR |
| **Type of afib, n(%)** | Paroxysmal | NR | NR | 45 (54.9) | 40 (55.6) |
| | Persistent/permanent | 26 (56.5)† | 21 (51.2)† | 37 (45.2) | 32 (44.5) |
| | Newly diagnosed or new onset | NR | NR | NR | NR |
| **Prior medication use, n(%)** | Vitamin K antagonist | NR | NR | 19 (23.2) | 21 (29.2) |
| | Aspirin | NR | NR | NR | NR |
| **Risk factors** | Age >= 75 | NR | NR | 24 (29.3) | 15 (20.8) |
| | Prior stroke, TIA, or SE | NR | NR | NR | NR |
| | Prior stroke | 15 (32.6) | 16 (36.4) | 17 (20.7) | 12 (16.7) |
| | Prior TIA | NR | NR | 7 (8.5) | 3 (4.2) |
| | Heart failure or reduced LVEF* | 17 (37.0) | 9 (20.5) | 43 (52.4) | 41 (56.9) |
| | Diabetes | 20 (43.5) | 20 (45.5) | 42 (51.2) | 47 (65.3) |
| | Prior MI | 21 (45.7) | 21 (47.7) | 16 (19.5) | 22 (30.6) |
| | Prior clinical relevant/spontaneous bleeding | 9 (19.6)‡ | 12 (27.3)‡ | 18 (22.0) | 14 (19.4) |
| | Hypertension | 25 (54.3)§ | 28 (63.3)§ | 79 (96.3) | 67 (93.1) |
| | Active cancer | NR | NR | NR | NR |
| **CHADS2 score** | Mean (SD) | NR | NR | NR | NR |
| | 1 | NR | NR | NR | NR |
| | 2 | NR | NR | NR | NR |
| | >=3 | NR | NR | NR | NR |

| Trial | | Valkyrie | | RENAL-AF | |
|---|---|---|---|---|---|
| **CHA2DS2-VAS score** | Median (IQR) | 5 (4-5) | 5 (4-6) | 4.0 (3.0, 5.0) | 4.0 (3.0, 5.0) |
| | Mean (SD) | 4.7 (1.4) | 4.8 (1.5) | NR | NR |
| **Current medications** | ACE inhibitor or ARB | 10 (21.7) | 8 (18.2) | 18 (22.8) | 20 (28.6) |
| | Amiodarone | 5 (10.9) | 9 (20.5) | NR | NR |
| | Beta-blocker | 24 (52.2) | 23 (52.3) | 43 (54.4) | 45 (64.3) |
| | Aspirin | 15 (32.6) | 14 (31.8) | 29 (36.7) | 32 (45.7) |
| | Clopidogrel | NR | NR | 2 (2.5) | 1 (1.4) |
| | Digoxin | NR | NR | 0 (0.0) | 3 (4.3) |
| | Calcium blocker | 18 (39.1) | 12 (27.3) | 28 (35.4) | 26 (37.1) |
| | Statin | 12 (26.1) | 13 (29.5) | 41 (51.9) | 41 (58.6) |
| | Nonsteroidal anti-inflammatory agent | NR | NR | 4 (5.1) | 7 (10.0) |
| | Proton-pump inhibitor | 26 (56.5) | 22 (50) | NR | NR |
| | H2-receptor antagonist | NR | NR | NR | NR |
| | Gastric antacid drugs | NR | NR | NR | NR |
| **HAS-BLED score** | Median (IQR) | 5 (4-5) | 5 (4-6) | NR | NR |
| | Mean (SD) | 4.7 (1.4) | 4.8 (1.5) | NR | NR |
| | 0-1 | NR | NR | NR | NR |
| | 2 | NR | NR | NR | NR |
| | >=3 | NR | NR | NR | NR |
| **Renal function** | Normal, >80 ml/min | NR | NR | NR | NR |
| | Mild impairment, >50 to 80 ml/min | NR | NR | NR | NR |
| | Moderate impairment (>30 to 50 ml/min) | NR | NR | NR | NR |
| | Severe impairment (≤30 ml/min) | NR | NR | NR | NR |
| | Not reported | NR | NR | NR | NR |
| **Creatinine clearance, ml/min** | Median (IQR) | NR | NR | NR | NR |

AA: African American, ACE: angiotensin-converting enzyme, Afib: Atrial fibrillation, ARB: angiotensin receptor blocker, CHADS2: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), CHADS2-VASc: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female), INR: international normalized ratio, IQR: interquartile range, kg: kilogram, LVEF: left ventricular ejection fraction, mg: milligram, HAS-BLED: Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage, ACEI/ARB: Angiotensin converting enzyme inhibitors and angiotensin receptor blockers, MI: myocardial infarction, ml/min: milliliter per minute, mm Hg: millimeters of mercury, N: number, NR: not reported, SD: standard deviation, SE: systemic embolism, TIA: transient ischemic attack, %: percent

*Other or more than 1 race

†All permanent type atrial fibrillation

‡GI bleeding

§Pre-existing vascular disease

**Table D3.31. Outcomes in Valkyrie and RENAL-AF**

| Trial | | Valkyrie | | RENAL-AF | |
|---|---|---|---|---|---|
| **Source** | | De Vriese et al. 2021; De Vriese et al. 2020 [28,55] | | Pokorney et al. 2022 [27] | |
| **Study Arms** | | Rivaroxaban (10mg) | VKA (INR: 2-3) | Apixaban (5mg or 2.5mg BID) | Warfarin (INR: 2-3) |
| **Timepoint** | | Median 1.88 years | | Median 350.5 days | Median 340.5 days |
| **Efficacy Outcomes** | | | | | |
| **N** | | 46 | 44 | 82 | 72 |
| **Stroke** | Number of events | NR | NR | 2 | 2 |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Major stroke** | Number of events | NR | NR | NR | NR |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Minor/nondisabling stroke** | Number of events | NR | NR | NR | NR |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Ischemic stroke** | Number of events | 4* | 7* | 1 | 2 |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | 0.2 | REF | NR | NR |

| Trial | | Valkyrie | | RENAL-AF | |
|---|---|---|---|---|---|
| **Hemorrhagic stroke** | Number of events | 0† | 2† | 1 | 0 |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | 0.21 | REF | NR | NR |
| **Fatal stroke** | Number of events | 0 | 1 | 1 | 1 |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Systemic embolism** | Number of events | 0 | 0 | 0 | 0 |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Stroke/SE** | Number of events | 4‡ | 9§ | 2 | 2 |
| | % per year | NR | NR | 3 | 3.3 |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Stroke/SE/Death** | Number of events | NR | NR | 27# | 29# |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Stroke/SE/Death/MI** | Number of events | 23¤ | 35¤ | NR | NR |
| | % per year | 26.2** | 63.8** | NR | NR |
| | HR (95% CI) | 0.41 (0.25, 0.68) | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | 0.0006 | NR | NR | NR |

| Trial | | Valkyrie | | RENAL-AF | |
|---|---|---|---|---|---|
| **Bleeding Outcomes** | | | | | |
| **N** | | 46 | 44 | 82 | 72 |
| **All bleeding** | Number of events | 21 | 24 | 21†† | 16†† |
| | % per year | NR | NR | 31.5 | 25.5 |
| | HR (95% CI) | 0.77 (0.43, 1.39) | REF | 1.20 (0.63, 2.3) | REF |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | 0.39 | REF | 0.321 | REF |
| **Minor bleeding** | Number of events | 16 | 13 | NR | NR |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | 0.85 | REF | NR | NR |
| **Major bleeding** | Number of events | 6 | 10 | 9 | 7 |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | 0.12 | REF | NR | NR |
| **Fatal bleeding** | Number of events | 0 | 3 | 1 | 2 |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Critical bleeding** | Number of events | NR | NR | NR | NR |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |

| Trial | | Valkyrie | | RENAL-AF | |
|---|---|---|---|---|---|
| **Intracranial bleeding** | Number of events | NR | NR | 1 | 1 |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Extracranial bleeding** | Number of events | NR | NR | NR | NR |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Hematoma bleeding** | Number of events | NR | NR | NR | NR |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Major gastrointestinal** | Number of events | NR | NR | 4 | 5 |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Gastrointestinal** | Number of events | 9 | 12 | 9 | 12 |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | 0.35 | REF | 0.35 | REF |
| **Clinically relevant bleeding** | Number of events | NR | NR | 14 | 10 |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |

| Trial | | Valkyrie | | RENAL-AF | |
|---|---|---|---|---|---|
| **Other Outcomes** | | | | | |
| **N** | | 46 | 44 | 82 | 72 |
| **All-cause death** | Number of events | 30 | 32 | 21 | 13 |
| | % per year | 33.7 | 28.3 | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | 0.656 | REF | NR | NR |
| **Cardiovascular death** | Number of events | 4 | 5 | 9 | 4 |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | 0.58 | REF | NR | NR |
| **Myocardial infarction** | Number of events | NR | NR | NR | NR |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Pulmonary embolism or deep-vein thrombosis** | N | NR | NR | NR | NR |
| | Number of events | NR | NR | NR | NR |
| | % per year | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Permanent Discontinuation Rates** | Number of events | 9 | 14 | NR | NR |
| | % | 19.6 | 31.8 | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |

| Trial | | Valkyrie | | RENAL-AF | |
|---|---|---|---|---|---|
| **Temporary Discontinuation Rates** | Number of events | NR | NR | NR | NR |
| | % | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR |
| **Not Completed** | | 34 | 37 | 26 | 24 |

BID: twice a day, CI: confidence interval, HR: Hazard ratio, INR: international normalized ratio, mg: milligram, MI: myocardial infarction, N: number, NR: not reported, RR: relative risk, SE: systemic embolism, %: percent

*Ischemic or uncertain type of stroke

†Hemorrhagic stroke of intracerebral bleeding

‡Ischemic or uncertain

§7 Ischemic or uncertain, 2 hemorrhagic

#Stroke, SE, Death, Major Bleeding

¤Composite of cardiovascular death, stroke, cardiac events, other vascular events

**Per 100 patient years

††Major bleed/clinically relevant nonmajor bleed

### Table D3.32. Harms in Valkyrie and RENAL-AF

| Trial | Valkyrie | | RENAL-AF | |
|---|---|---|---|---|
| **Source** | De Vriese et al. 2021[55] | | Pokorney et al. 2022[27] | |
| **Study Arms** | Rivaroxaban (10mg) | VKA (INR: 2-3) | Apixaban (5mg or 2.5mg BID) | Warfarin (INR: 2-3) |
| **N** | 46 | 44 | 82 | 72 |
| **Discontinued due to AE** | NR | NR | NR | NR |
| **Discontinued due to stroke** | NR | NR | NR | NR |
| **Discontinued due to SE** | NR | NR | NR | NR |
| **Discontinued due to bleeding** | 8 (17.4) | 8 (18.2) | NR | NR |
| **Not completed due to AE** | 30 (65.2)* | 32 (72.7)* | NR | NR |
| **All adverse events, n (%)** | NR | NR | 17 (20.7) | 8 (11) |
| **Serious adverse events, n (%)** | NR | NR | 13 (15.9) | 8 (11) |

AE: adverse event, INR: international normalized ratio, mg: milligram, N: number, NR: not reported. %: percent

*Not complete due to death

**Table D3.33. Baseline Characteristics in the Observational Studies (Chan et al., 2022; Lau et al., 2022)**

| Source | | Chan et al. 2022[30] | | | | Lau et al. 2022[29] | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Journal** | | JAMA | | | | Annals of Internal Medicine | | | |
| **Study Arms** | | Dabigatran (110mg or 150mg) | Warfarin | Dabigatran (110mg or 150mg) after PSSW | Warfarin (after PSSW) | Apixaban vs. Dabigatran Comparison: Apixaban (2.5 mg or 5 mg)* | Apixaban vs. Dabigatran Comparison: Dabigatran (110 mg or 150 mg) | Dabigatran vs. Rivaroxaban Comparison: Dabigatran (110 mg or 150 mg) | Dabigatran vs. Rivaroxaban Comparison: Rivaroxaban (15 mg or 20 mg) |
| **N** | | 22,501 | 18,988 | 22,178.67 | 18,469.65 | 281320 | 61008 | 61008 | 172176 |
| **Age** | Median (IQR) | NR | NR | NR | NR | NR | NR | NR | NR |
| | <65 years | 4550 (20.2) | 7536 (39.7) | 4890.67 (22.05) | 4160.75 (22.53) | NR | NR | NR | NR |
| | >65 years | NR | NR | NR | NR | 83.40% | 82.80% | 82.10% | 80% |
| | 65-74 years | 7322 (32.5) | 3906 (20.6) | 6372.68 (28.73) | 5143.34 (27.85) | NR | NR | NR | NR |
| | 75-84 years | 7441 (33.1) | 4715 (24.8) | 7103.54 (32.03) | 5905.56 (31.97) | NR | NR | NR | NR |
| | ≥ 85 years | 3188 (14.2) | 2831 (14.9) | 3811.78 (17.19) | 3260 (17.65) | NR | NR | NR | NR |
| | Mean (SD) | 73.3 (10.9) | 69.4 (14.1) | 73.5 (11.4) | 73.3 (12.2) | NR | NR | NR | NR |
| **Sex** | Female, n (%) | 8912 (39.6) | 8228 (43.3) | NR | NR | 45.70% | 46% | 43.40% | 43.20% |
| | Male, n (%) | 13589 (60.4) | 10760 (56.7) | 12599.74 (56.81) | 10398.16 (56.30) | NR | NR | NR | NR |
| **Race** | White | 0 | 0 | 0 | 0 | NR | NR | NR | NR |
| | Black/AA | 0 | 0 | 0 | 0 | NR | NR | NR | NR |
| | Asian | 22501 (100) | 18988 (100) | 22178.67 (100) | 18469.65 (100) | NR | NR | NR | NR |

| Source | | Chan et al. 2022[30] | | | | Lau et al. 2022[29] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | American Indian/Alaska Native | 0 | 0 | 0 | 0 | NR | NR | NR | NR |
| | Native Hawaiian/Other Pacific Islander | 0 | 0 | 0 | 0 | NR | NR | NR | NR |
| | Other | 0 | 0 | 0 | 0 | NR | NR | NR | NR |
| **Risk factors** | Age ≥75 | 10629 (47.3) | 7546 (39.7) | 10915.32 (49.22) | 9165.56 (49.62) | NR | NR | NR | NR |
| | Prior stroke, TIA, or SE | NR | NR | NR | NR | NR | NR | NR | NR |
| | Prior stroke | 5382 (23.9) | 2459 (13.0) | 4116.23 (10.24) | 3399.75 (10.29) | NR | NR | NR | NR |
| | Prior TIA | NR | NR | NR | NR | NR | NR | NR | NR |
| | Heart failure or reduced LVEF* | 1644 (7.31) | 1769 (9.3) | 1873.72 (8.45) | 1676.5 (9.08) | 14.50% | 14.30% | 12.80% | 12.50% |
| | Diabetes | 7786 (34.6) | 5702 (30.0) | 7703.44 (34.73) | 6430.42 (34.82) | 11.30% | 14.70% | 14.70% | 14.80% |
| | Prior MI | NR | NR | NR | NR | NR | NR | NR | NR |
| | Prior clinical relevant/ spontaneous bleeding | 305 (1.4) | 305 (1.6) | 328.14 (1.48) | 300.86 (1.63) | NR | NR | NR | NR |
| | Hypertension | 10931 (48.6) | 7904 (41.6) | 11071.96 (49.92) | 9214.61 (49.89) | 38.40% | 40.80% | 39.50% | 40% |
| | Active cancer | 1920 (8.5) | 1665 (8.8) | 2142.37 (9.66) | 1825.7 (9.88) | NR | NR | NR | NR |
| **CHADS2 score** | 1 | NR | NR | NR | NR | NR | NR | NR | NR |
| | 2 | NR | NR | NR | NR | NR | NR | NR | NR |
| | 3 | NR | NR | NR | NR | NR | NR | NR | NR |
| | ≥4 | NR | NR | NR | NR | NR | NR | NR | NR |

| Source | | Chan et al. 2022[30] | | | | Lau et al. 2022[29] | | | |
|---|---|---|---|---|---|---|---|---|---|
| **CHA2DS2-VASc score** | Mean (SD) | 3.2 (1.6) | 2.6 (1.9) | 3.2 (1.7) | 3.2 (1.7) | 3.3 | 3.2 | 3.1 | 3.1 |
| **Current medications** | ACE inhibitor or ARB | 13320 (59.2) | 10539 (55.5) | 13069.26 (58.93) | 10936.28 (59.21) | 50.50% | 49.70% | 50.50%‡ | 50.60% |
| | Amiodarone | 5567 (30.7) | 8065 (42.5) | 6910.87 (31.16) | 5911.67 (32.01) | NR | NR | NR | NR |
| | Beta-blocker | 13000 (57.8) | 11739 (61.8) | 13392.62 (60.39) | 11195.55 (60.62) | 55% | 68.10% | 66.70% | 66.30% |
| | Aspirin | NR | NR | NR | NR | NR | NR | NR | NR |
| | Clopidogrel | NR | NR | NR | NR | NR | NR | NR | NR |
| | Digoxin | NR | NR | NR | NR | NR | NR | NR | NR |
| | Calcium blocker | NR | NR | NR | NR | 31.90% | 36.40% | 34.50% | 35.10% |
| | Statin | 7751 (34.5) | 4835 (25.5) | 7433.07 (33.51) | 6037.39 (32.69) | NR | NR | NR | NR |
| | Nonsteroidal anti-inflammatory agent | 5332 (23.7) | 4866 (25.6) | 5460.48 (24.62) | 4548.21 (24.63) | 48.20%§ | 47.50% | 47.70% | 48.80% |
| | Proton-pump inhibitor | 2069 (9.2) | 2551 (13.4) | 2584.31 (11.65) | 2197.1 (11.90) | NR | NR | NR | NR |
| | H2-receptor antagonist | 7140 (31.7) | 6132 (32.3) | 7044.47 (31.76) | 5931.67 (32.12) | NR | NR | NR | NR |
| | Lipid modifying agents | NR | NR | NR | NR | 48.80% | 48% | 47.10% | 47.20% |
| | Antithrombotic agents | NR | NR | NR | NR | 50.40% | 50.50% | 49% | 49.50% |
| | Gastric antacid drugs | NR | NR | NR | NR | 49.40%# | 49.30% | 47% | 47.80% |

| Source | | Chan et al. 2022[30] | | | | Lau et al. 2022[29] | | | |
|---|---|---|---|---|---|---|---|---|---|
| **HAS-BLED score** | Mean (SD) | 2.5 (1.1) | 2.1 (1.3) | 2.5 (1.2) | 2.5 (1.2) | NR | NR | NR | NR |
| | 0-1 | NR | NR | NR | NR | NR | NR | NR | NR |
| | 2 | NR | NR | NR | NR | NR | NR | NR | NR |
| | 3 | NR | NR | NR | NR | NR | NR | NR | NR |
| | ≥4 | NR | NR | NR | NR | NR | NR | NR | NR |
| **Renal Impairment** | | NR | NR | NR | NR | 9.40% | 9.20% | 7% | 7% |

AA: African American, CHADS2-VASc: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female, IQR: interquartile range, N: number, NR: not reported, MI: myocardial infarction, SD: standard deviation, SE: standard error, TIA: transient ischemic attack, HAS-BLED: Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage

*PS stratification

†In past 1-30 days and 31-183 days

‡Agents acting on the renin-angiotensin system

§Anti-inflammatory and antirheumatic products

#Drugs for acid related disorders

**Table D3.34. Baseline Characteristics in the Observational Study (Graham et al., 2015)**

| **Source** | | **Graham et al. 2015[31]** | | |
|---|---|---|---|---|
| **Journal** | | Circulation | | |
| **Study Arms** | | Dabigatran (75mg and 150mg) | Warfarin | Dabigatran (150mg) |
| **N** | | 67207 | 67207 | 56576 |
| **Age** | Median (IQR) | NR | NR | NR |
| | <65 years | NR | NR | NR |
| | >65 years | NR | NR | NR |
| | 65-74 years | 42% | 41% | NR |
| | 75-84 years | 45% | 43% | NR |
| | ≥ 85 years | 16% | 16% | 12% |
| | Mean (SD) | NR | NR | NR |
| **Sex** | Female, n (%) | 51% | 52% | 49% |
| | Male, n (%) | 49% | 48% | NR |
| **Race** | White | 92% | 92% | NR |
| | Black/AA | 3% | 3% | NR |
| | Asian | NR | NR | NR |
| | American Indian/Alaska Native | NR | NR | NR |
| | Native Hawaiian/Other Pacific Islander | NR | NR | NR |
| | Other | 5% | 5% | NR |
| **Risk factors** | Age ≥75 | 59% | 59% | NR |
| | Prior stroke, TIA, or SE | NR | NR | NR |
| | Prior stroke | 3%† | 4% | NR |
| | Prior TIA | 7% | 7% | NR |

| Source | | Graham et al. 2015[31] | | |
|---|---|---|---|---|
| | Heart failure or reduced LVEF* | 18% | 18% | NR |
| | Diabetes | 33% | 34% | 33% |
| | Prior MI | 2%† | 2% | NR |
| | Prior clinical relevant/spontaneous bleeding | 4% | 4% | NR |
| | Hypertension | 87% | 87% | NR |
| | Active cancer | NR | NR | NR |
| **CHADS2 score** | 1 | 28% | 28% | NR |
| | 2 | 40% | 40% | NR |
| | 3 | 21% | 21% | NR |
| | ≥4 | 10% | 11% | 9% |
| **CHA2DS2-VASc score** | Mean (SD) | NR | NR | NR |
| **Current medications** | ACE inhibitor or ARB | 59% | 59% | NR |
| | Amiodarone | 10% | 10% | 9% |
| | Beta-blocker | 70% | 71% | NR |
| | Aspirin | 17% | 17% | NR |
| | Clopidogrel | NR | NR | NR |
| | Digoxin | 17% | 16% | NR |
| | Calcium blocker | 42% | 42% | NR |
| | Statin | 57% | 57% | NR |
| | Nonsteroidal anti-inflammatory agent | 15% | 15% | NR |
| | Proton-pump inhibitor | 26% | 27% | NR |
| | H2-receptor antagonist | 5% | 5% | NR |
| | Lipid modifying agents | NR | NR | NR |
| | Antithrombotic agents | NR | NR | NR |
| | Gastric antacid drugs | NR | NR | NR |

| Source | | Graham et al. 2015[31] | | |
|---|---|---|---|---|
| **HAS-BLED score** | Mean (SD) | NR | NR | NR |
| | 0-1 | 9% | 9% | NR |
| | 2 | 50% | 50% | NR |
| | 3 | 32% | 32% | NR |
| | ≥4 | 9% | 9% | 7% |
| **Renal Impairment** | | NR | NR | NR |

AA: African American, CHADS2-VASc: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female, IQR: interquartile range, N: number, NR: not reported, MI: myocardial infarction, SD: standard deviation, SE: standard error, TIA: transient ischemic attack, HAS-BLED: Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage

*PS stratification

**Table D3.35. Outcomes in the Observational Studies (Chan et al., 2022; Lau et al., 2022)**

| Study | | Chan et al. 2022[30] | | | | Lau et al. 2022*[29] | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Source** | | JAMA | | | | Annals of Internal Medicine | | | |
| **Study Arms** | | Dabigatran (110 mg or 150 mg) | Warfarin | Apixaban† | Rivaroxaban† | Apixaban (2.5 mg or 5 mg) | Dabigatran (110 mg or 150 mg) | Dabigatran (110 mg or 150 mg) | Rivaroxaban (15 mg or 20 mg) |
| **N** | | 22,178.67 | 18,469.65 | 15,386.00 | 36,756.00 | 281320 | 61008 | 61008 | 131616 |
| **Follow-up time** | | Follow-up of at least 2 years | | | | Range: 5-595 days | Range: 4-418 days | Range: 4-418 days | Range: 5-506 days |
| **Person-years follow-up time** | | NR | NR | NR | NR | NR | NR | NR | NR |
| **Ischemic stroke** | Number of events | NR | NR | NR | NR | NR | NR | NR | NR |
| | Incidence rate per pt-yrs | 0.35 (0.30, 0.40)‡ | 0.90 (0.81, 0.98) | NR | NR | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | Absolute rate difference | -0.54 (-0.64, -0.45) | REF | NR | NR | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR | NR | NR | NR | NR |
| **Stroke/SE** | Number of events | NR | NR | NR | NR | 5486 | 906 | 906 | 2920 |
| | Incidence rate per pt-yrs | 1.91 (1.79, 2.02)‡ | 2.55 (2.41, 2.69) | NR | NR | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR | 0.96 (0.77, 1.21) | REF | 0.92 (0.65, 1.31) | REF |
| | Absolute rate difference | -0.64 (-0.82, -0.46) | REF | NR | NR | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR | NR | NR | NR | NR |

| Study | | Chan et al. 2022[30] | | | | Lau et al. 2022*[29] | | | |
|---|---|---|---|---|---|---|---|---|---|
| **All bleeding** | Number of events | NR | NR | NR | NR | NR | NR | NR | NR |
| | Incidence rate per pt-yrs | NR | NR | NR | NR | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR | NR | NR | NR | NR |
| **Major bleeding** | Number of events | NR | NR | NR | NR | NR | NR | NR | NR |
| | Incidence rate per pt-yrs | 1.38 (1.28, 1.47)‡ | 2.39 (2.25, 2.52) | NR | NR | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | Absolute rate difference | -1.01 (-1.17, -0.84) | REF | NR | NR | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR | NR | NR | NR | NR |
| **Intracerebral bleeding** | Number of events | NR | NR | NR | NR | NR | NR | NR | NR |
| | Incidence rate per pt-yrs | NR | NR | NR | NR | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR | NR | NR | NR | NR |

| Study | | Chan et al. 2022[30] | | | | Lau et al. 2022*[29] | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Intracranial bleeding** | Number of events | NR | NR | NR | NR | 465 | 68 | 68 | 262 |
| | Incidence rate per pt-yrs | NR | NR | NR | NR | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR | 0.87 (0.63, 1.21) | REF | 0.96 (0.56, 1.65) | REF |
| | RR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR | NR | NR | NR | NR |
| **Major gastrointestinal** | Number of events | NR | NR | NR | NR | 4188 | 813 | 813 | 3011 |
| | Incidence rate per pt-yrs | 0.94 (0.86, 1.02)‡ | 1.32 (1.22, 1.42) | NR | NR | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR | 0.81 (0.70, 0.94) | REF | 0.87 (0.78, 0.96) | REF |
| | RR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | Absolute rate difference | -0.38 (-0.51, -0.26) | REF | NR | NR | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR | NR | NR | NR | NR |
| **All-cause death** | Number of events | NR | NR | NR | NR | 844 | 92 | 92 | 480 |
| | Incidence rate per pt-yrs | NR | NR | NR | NR | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR | 1.22 (0.94, 1.60) | REF | 0.86 (0.66, 1.12) | REF |
| | RR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR | NR | NR | NR | NR |

| Study | | Chan et al. 2022[30] | | | | Lau et al. 2022*[29] | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Myocardial infarction** | Number of events | NR | NR | NR | NR | NR | NR | NR | NR |
| | Incidence rate per pt-yrs | NR | NR | NR | NR | NR | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR | NR | NR | NR | NR |
| **Interstitial lung disease** | Number of events | NR | NR | NR | NR | NR | NR | NR | NR |
| | Incidence rate per pt-yrs | 0.22 (0.18, 0.26)‡ | 0.17 (0.13, 0.21) | 0.35 | 0.17 | NR | NR | NR | NR |
| | HR (95% CI) | 1.26 (0.96, 1.65) | REF | 1.72 (1.27, 2.31) | 1.48 (1.16, 1.88) | NR | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR | NR | NR | NR | NR | NR |
| | Absolute rate difference | 0.05 (-0.001, 0.10) | REF | NR | NR | NR | NR | NR | NR |
| | P value | NR | NR | NR | NR | NR | NR | NR | NR |

CI: confidence interval, HR: hazard ratio, mg: milligram, NR: not reported, REF: reference, RR: rate ratio, SE: standard error

*Propensity Score–Stratified, On-Treatment Approach. Consistent results with ITT approach.

†Subgroup analysis stratified by each Fxa inhibitor only for incident of ILD. Event rate per 100 patient-years with HR compared to warfarin.

‡incidence 100 patients per year (95% CI)

**Table D3.36. Outcomes in the Observational Study (Graham et al. 2015)**

| **Study** | | **Graham et al. 2015*[31]** | | |
|---|---|---|---|---|
| **Source** | | Circulation | | |
| **Study Arms** | | Dabigatran (75 mg or 150 mg) | Warfarin | Dabigatran (150 mg)† |
| **N** | | 67,207‡ | 67,207 | 56,576 |
| **Follow-up time** | | 6 months - 14 months | | |
| **Person-years follow-up time** | | 18,205 | 19,382 | NR |
| **Ischemic stroke** | Number of events | 205 | 270 | NR |
| | Incidence rate per pt-yrs | 11.3 | 13.9 | NR |
| | HR (95% CI) | 0.80 (0.67, 0.96) | REF | 0.70 (0.57, 0.85) |
| | RR (95% CI) | NR | NR | NR |
| | Absolute rate difference | NR | NR | NR |
| | P value | 0.02 | REF | NR |
| **Stroke/SE** | Number of events | NR | NR | NR |
| | Incidence rate per pt-yrs | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR |
| | Absolute rate difference | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR |
| | P value | NR | NR | NR |
| **All bleeding** | Number of events | 1079§ | 1139 | NR |
| | Incidence rate per pt-yrs | 59.3 | 58.8 | NR |
| | HR (95% CI) | 1.00 (0.92, 1.09) | REF | NR |
| | RR (95% CI) | NR | NR | NR |
| | P value | 0.97 | REF | NR |
| **Major bleeding** | Number of events | 777 | 851 | NR |
| | Incidence rate per pt-yrs | 42.7 | 43.9 | NR |
| | HR (95% CI) | 0.97 (0.88, 1.07) | REF | NR |
| | RR (95% CI) | NR | NR | NR |
| | Absolute rate difference | NR | NR | NR |
| | P value | 0.5 | REF | NR |

| Study | | Graham et al. 2015*[31] | | |
|---|---|---|---|---|
| **Intracerebral bleeding** | Number of events | 44 | 142 | NR |
| | Incidence rate per pt-yrs | 2.4 | 7.3 | NR |
| | HR (95% CI) | 0.33 (0.24, 0.47) | REF | NR |
| | RR (95% CI) | NR | NR | NR |
| | P value | <0.001 | REF | NR |
| **Intracranial bleeding** | Number of events | 60 | 186 | NR |
| | Incidence rate per pt-yrs | 3.3 | 9.6 | NR |
| | HR (95% CI) | 0.34 (0.26, 0.46) | REF | 0.30 (0.21, 0.42) |
| | RR (95% CI) | NR | NR | NR |
| | P value | <0.001 | REF | NR |
| **Major gastrointestinal** | Number of events | 623 | 513 | NR |
| | Incidence rate per pt-yrs | 34.2 | 26.5 | NR |
| | HR (95% CI) | 1.28 (1.14, 1.44) | REF | 1.51 (1.32, 1.73) |
| | RR (95% CI) | NR | NR | NR |
| | Absolute rate difference | NR | NR | NR |
| | P value | <0.001 | REF | NR |
| **All-cause death** | Number of events | 603 | 744 | NR |
| | Incidence rate per pt-yrs | 32.6 | 37.8 | NR |
| | HR (95% CI) | 0.86 (0.77, 0.96) | REF | 0.76 (0.67, 0.86) |
| | RR (95% CI) | NR | NR | NR |
| | P value | 0.006 | REF | NR |
| **Myocardial infarction** | Number of events | 285 | 327 | NR |
| | Incidence rate per pt-yrs | 15.7 | 16.9 | NR |
| | HR (95% CI) | 0.92 (0.78, 1.08) | REF | NR |
| | RR (95% CI) | NR | NR | NR |
| | P value | 0.29 | REF | NR |

| Study | | Graham et al. 2015*[31] | | |
|---|---|---|---|---|
| **Interstitial lung disease** | Number of events | NR | NR | NR |
| | Incidence rate per pt-yrs | NR | NR | NR |
| | HR (95% CI) | NR | NR | NR |
| | RR (95% CI) | NR | NR | NR |
| | Absolute rate difference | NR | NR | NR |
| | P value | NR | NR | NR |

CI: confidence interval, HR: hazard ratio, mg: milligram, NR: not reported, REF: reference, RR: rate ratio, SE: standard error

*incidence per 1000 patients

†Because of covariate imbalances between dabigatran and warfarin cohorts after stratification by dose, patients were rematched within strata defined by daily dabigatran dose, resulting in a total of 67 098 patients in each cohort rather than 67 207 from the primary analysis.

‡52.0% of dabigatran users and 50.2% of warfarin users filled only a single prescription of their anticoagulant

§All hospitalized bleeds

**Table D3.37. Observational Subgroups – Hazard Ratios for ILD for Non-Valvular AF Patients**

| **HR for ILD for non-valvular AF patients treated with dabigatran and warfarin after PSSW** | | Chan et al. 2022[30] | | | |
|---|---|---|---|---|---|
| | | Dabigatran 110 mg or 150 mg (rate per 100-pt-yr) | Warfarin (rate per 100-pt-yr) | HR (95% CI) | P value for interaction |
| **Age** | <75 years | 0.19 | 0.12 | 1.54 (1.06, 2.25) | 0.19 |
| | ≥75 years | 0.27 | 0.25 | 1.08 (0.74, 1.57) | |
| **Sex** | Male | 0.23 | 0.19 | 1.19 (0.86, 1.66) | 0.68 |
| | Female | 0.19 | 0.14 | 1.34 (0.85, 2.12) | |
| **CHADS2-VASc** | <3 | 0.25 | 0.17 | 1.35 (0.93, 1.97) | 0.53 |
| | ≥3 | 0.19 | 0.17 | 1.14 (0.78, 1.66) | |
| **HAS-BLED** | <3 | 0.23 | 0.19 | 1.17 (0.84, 1.62) | 0.43 |
| | ≥3 | 0.21 | 0.14 | 1.47 (0.93, 2.34) | |
| **ACEI/ARB** | No | 0.24 | 0.15 | 1.51 (1.00, 2.28) | 0.23 |
| | Yes | 0.2 | 0.18 | 1.08 (0.76, 1.53) | |
| **Statin** | No | 0.25 | 0.19 | 1.30 (0.97, 1.75) | 0.73 |
| | Yes | 0.13 | 0.11 | 1.15 (0.62, 2.14) | |
| **Beta-blocker** | No | 0.2 | 0.19 | 1.06 (0.70, 1.61) | 0.25 |
| | Yes | 0.22 | 0.15 | 1.46 (1.02, 2.08) | |
| **Amiodarone** | No | 0.18 | 0.13 | 1.38 (0.95, 2.00) | 0.46 |
| | Yes | 0.31 | 0.26 | 1.12 (0.75, 1.68) | |

ACEI/ARB: Angiotensin converting enzyme inhibitors and angiotensin receptor blockers , CHADS2-VASc: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female) CI: confidence interval, HR: hazard ratio, HAS-BLED: Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage, ILD: interstitial lung disease, PT-YR: patients-year.

**Table D3.38. Observational Subgroups – Primary Outcomes by Follow-Up Intervals**

| **Outcomes by intervals of follow-up during continuous use in propensity score matched new user cohort of dabigatran 150 mg compared to warfarin** | | | Graham et al. 2015[31] HR (95% CI) |
|---|---|---|---|
| **Primary Outcomes** | Ischemic stroke | Days 1-90 | 0.70 (0.56, 0.88) |
| | | Days 91-180 | 0.76 (0.40, 1.45) |
| | | ≥ 91 days | 0.66 (0.41, 1.07) |
| | | ≥181 days | 0.56 (0.28, 1.15) |
| | Major GI bleed | Days 1-90 | 1.51 (1.30, 1.76) |
| | | Days 91-180 | 1.60 (1.12, 2.29) |
| | | ≥91 days | 1.50 (1.13, 1.98) |
| | | ≥181 days | 1.35 (0.86, 2.11) |
| | Major intracranial bleed | Days 1-90 | 0.30 (0.20, 0.44) |
| | | Days 91-180 | 0.37 (0.15, 0.95) |
| | | ≥91 days | 0.30 (0.16, 0.57) |
| | | ≥181 days | 0.26 (0.11, 0.61) |
| | Major intracerebral bleed | Days 1-90 | 0.28 (0.17, 0.46) |
| | | Days 91-180 | 0.35 (0.13, 0.95) |
| | | ≥ 91 days | 0.23 (0.11, 0.48) |
| | | ≥181 days | 0.16 (0.06, 0.47) |
| | Acute MI | Days 1-90 | 0.88 (0.71, 1.08) |
| | | Days 91-180 | 0.92 (0.55, 1.55) |
| | | ≥91 days | 0.72 (0.49, 1.06) |
| | | ≥181 days | 0.55 (0.31, 0.97) |
| **Secondary Outcomes** | All hospitalized bleeds | Days 1-90 | 1.13 (1.01, 1.26) |
| | | Days 91-180 | 1.06 (0.82, 1.36) |
| | | ≥91 days | 1.00 (0.83, 1.22) |
| | | ≥181 days | 0.93 (0.69, 1.26) |
| | Mortality | Days 1-90 | 0.80 (0.69, 0.93) |
| | | Days 91-180 | 0.64 (0.46, 0.90) |
| | | ≥91 days | 0.64 (0.50, 0.82 |
| | | ≥181 days | 0.64 (0.44, 0.92) |

CI: confidence interval, GI: gastrointestinal, HR: hazard ratio, MI: myocardial infarction

**Table D3.39. Observational Subgroups – Patients with CKD**

| Lau et al. 2022[29]: Patients with chronic kidney disease* | N Intervention Group | N Comparator Group | Outcome event: Intervention | Outcome event: Comparator | HR (95% CI) |
|---|---|---|---|---|---|
| **Ischemic Stroke/SE** | | | | | |
| **Apixaban vs. dabigatran** | 42270 | 4627 | 1040 | 79 | 0.93 (0.68, 1.28) |
| **Dabigatran vs. rivaroxaban** | 4627 | 15178 | 79 | 312 | 0.93 (0.60, 1.45) |
| **Intracranial bleeding** | | | | | |
| **Apixaban vs. dabigatran** | 42270 | 4627 | 66 | 2 | 0.56 (0.15, 2.05) |
| **Dabigatran vs. rivaroxaban** | 4627 | 15178 | 2 | 15 | 3.67 (0.95, 14.22) |
| **GI bleeding** | | | | | |
| **Apixaban vs. dabigatran** | 42270 | 4627 | 845 | 90 | 0.71 (0.54, 0.94) |
| **Dabigatran vs. rivaroxaban** | 4627 | 15178 | 90 | 334 | 1.04 (0.78, 1.38) |
| **All-cause mortality** | | | | | |
| **Apixaban vs. dabigatran** | 18628 | 1990 | 147 | 5 | 2.04 (0.72, 5.78) |
| **Dabigatran vs. rivaroxaban** | 1990 | 5896 | 5 | 11 | 0.99 (0.28, 3.59) |

CI: confidence interval, GI: gastrointestinal, HR: hazard ratio, N: number, SE: systemic embolism, VS: versus

*Propensity score stratified, on-treatment approach

**Table D3.40. Observational Subgroups – Patients Aged 80 and Older**

| Lau et al. 2022: Patients Aged 80 Years or Older[56] | N Intervention Group | N Comparator Group | Outcome event: Intervention | Outcome event: Comparator | HR (95% CI) |
|---|---|---|---|---|---|
| **Ischemic Stroke/SE** | | | | | |
| **Apixaban vs. dabigatran** | 58852 | 3609 | 1364 | 94 | 1.04 (0.81, 1.34) |
| **Dabigatran vs. rivaroxaban** | 3609 | 19302 | 94 | 433 | 0.97 (0.68, 1.39) |
| **Intracranial bleeding** | | | | | |
| **Apixaban vs. dabigatran** | 58852 | 3609 | 116 | 14 | 0.64 (0.35, 1.17) |
| **Dabigatran vs. rivaroxaban** | 3609 | 19302 | 14 | 55 | 1.38 (0.75, 2.54) |
| **GI bleeding** | | | | | |
| **Apixaban vs. dabigatran** | 58852 | 3609 | 982 | 93 | 0.65 (0.44, 0.95) |
| **Dabigatran vs. rivaroxaban** | 3609 | 19302 | 93 | 460 | 1.02 (0.78, 1.33) |
| **All-cause mortality** | | | | | |
| **Apixaban vs. dabigatran** | 21707 | 2113 | 151 | 9 | 1.04 (0.51, 2.14) |
| **Dabigatran vs. rivaroxaban** | 2113 | 9254 | 9 | 46 | 0.84 (0.40, 1.75) |

CI: confidence interval, GI: gastrointestinal, HR: hazard ratio, N: number, SE: systemic embolism, VS: versus

* Propensity score stratified, on-treatment approach

**Table D3.41. Observational Subgroups – Incidence Rates for Select Outcomes by Age**

| Incidence rates and event counts for selected outcomes stratified by age and gender. Rate per 1000 years (#events) | | Graham et al. 2015[31] | | | |
|---|---|---|---|---|---|
| | | Men | | Women | |
| | | Dabigatran (75mg and 150mg) | Warfarin | Dabigatran (75mg and 150mg) | Warfarin |
| **Ischemic stroke** | 65-74 years | 5.9 (26) | 8.3 (39) | 9.5 (30) | 11.6 (40) |
| | 75-84 years | 11.1 (39) | 11.5 (44) | 14.4 (62) | 16.0 (72) |
| | ≥85 years | 13.2 (12) | 15.0 (15) | 18.9 (36) | 32.0 (60) |
| **Intracranial hemorrhage** | 65-74 years | 2.0 (9) | 6.4 (30) | 0.9 (3) | 7.2 (25) |
| | 75-84 years | 3.4 (12) | 12.8 (49) | 5.4 (23) | 9.1 (41) |
| | ≥85 years | 5.5 (5) | 11.0 (11) | 4.2 (8) | 16.0 (30) |
| **Major GI bleeding** | 65-74 years | 15.2 (67) | 17.8 (84) | 22.4 (71) | 22.6 (78) |
| | 75-84 years | 33.2 (117) | 32.1 (123) | 42.1 (181) | 28.2 (127) |
| | ≥85 years | 62.7 (57) | 41.1 (41) | 68.4 (130) | 32.0 (60) |
| **Mortality** | 65-74 years | 23.1 (103) | 28.0 (134) | 19.6 (63) | 27.1 (95) |
| | 75-84 years | 34.0 (122) | 46.7 (182) | 29.0 (127) | 35.4 (162) |
| | ≥85 years | 57.1 (53) | 62.0 (63) | 69.5 (135) | 56.4 (108) |

GI: gastrointestinal, Mg: milligram

## D4. Previous Systematic Reviews and Technology Assessments

We identified three high-quality NMAs that evaluated the efficacy of therapies of interest for the treatment of NVAF. We compared the results of these previously published NMAs to our NMA and the results were consistent. The three NMAs and the comparison to our results are described below (Table D4.1). A systematic literature review examining observational studies that compared the use of rivaroxaban and warfarin for older adults with NVAF was also consistent with our main results.[57]

**Lopez-Lopez et al. (2017).[58] "Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost-effectiveness analysis"**

Lopez-Lopez et al. (2017)[58] conducted a systematic literature review (N studies = 23) and an NMA (N studies = 13) to evaluate the effectiveness of direct acting oral anticoagulants (DOACs), vitamin K antagonist (warfarin), or antiplatelet drugs for preventing stroke/SE in patients with atrial fibrillation (AF). The DOACs included apixaban, rivaroxaban, dabigatran, and edoxaban. The included RCTs included 94,656 patients, duration ranged from 3 to 30 months, and outcomes included stroke/SE, ischemic stroke, all-cause mortality, and myocardial infarction. The NMA included 13 studies that compared a DOAC with warfarin. The NMA was conducted using a fixed-effects model with results presented as odds ratios with 95% confidence intervals and as rankograms displaying the probability that the intervention was ranked as the highest or second highest. Results of the NMA showed that apixaban, dabigatran, edoxaban, and rivaroxaban reduced the risk of stroke/SE, all-cause mortality, intracranial bleeding compared with warfarin. The risk of stroke/SE was higher with edoxaban and rivaroxaban than with dabigatran. The risk of major bleeding was lower for apixaban, dabigatran, and edoxaban compared with warfarin, although there was a higher risk of major bleeding for dabigatran and rivaroxaban than apixaban. The risk of gastrointestinal bleeding was lower for apixaban as compared to warfarin, but higher for dabigatran and rivaroxaban. Overall, apixaban was ranked highest for most outcomes. There was no evidence of effect modification for age, sex, mean CHADS2 score, or time in warfarin therapeutic range, although data were limited for these analyses. These results of this NMA were consistent with the results of our NMA analyses. However, limitations of this network meta-analysis included: inclusion of short duration trials, subsequent large range of duration across the trials, and the incomplete report of outcomes in some trials that reduced the precision of the estimates.

**Carnicelli et al. (2022).[59] "Direct Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation: Patient-Level Network Meta-Analyses of Randomized Clinical Trials With Interaction Testing by Age and Sex."**

Carnicelli et al. (2022)[59] conducted a patient-level NMA including four trials (including the three trials reported in our main report) evaluating the effectiveness of standard and low-dose DOACs and warfarin on efficacy and safety outcomes in patients with AF. The standard doses included:

dabigatran 150 mg twice daily, rivaroxaban 20 mg (or 15 mg if dose reduction criteria were met) once daily, apixaban 5 mg (or 2.5 mg if dose reduction criteria were met) twice daily, or edoxaban 60 mg once daily. The low doses included: dabigatran 110 mg twice daily or edoxaban 30 mg (or 15 mg if dose reduction criteria were met) once daily. The NMA included 71,683 patients, duration of at least one year (26.6 months), and examined outcomes including: stroke/SE, any stroke, all-cause mortality, cardiovascular mortality, major, fatal, intracranial, or gastrointestinal bleeding, among others. The NMA was conducted using a random-effects model and, for the primary analysis, Kaplan-Meier curves were generated, and univariable stratified Cox proportional hazard models were fitted to allow for cross-trial heterogeneity. Results of the NMA reported that, compared to warfarin, standard-dose DOACs had significantly lower risk for stroke/SE, death, and intracranial bleeding. There was no significant difference for major bleeding, but standard-dose DOACs were associated with a significantly higher risk for major gastrointestinal bleeding. Low-dose DOACs had significantly lower risk for intracranial bleeding, mortality, and major bleeding, but no significant difference for stroke/SE nor major gastrointestinal bleeding. The effects were consistent across age and sex for stroke/SE and mortality. Our NMA only included the standard dose DOACs and the comparisons for the standard dose were consistent with our NMA. This NMA benefitted from the incorporation of patient-level data which enabled the investigators to analyze the data using Kaplan-Meier curves and univariable stratified Cox proportional hazard models and examine the interaction with age and sex. However, the analyses only compared all DOACs with warfarin, limiting our ability to interpret differences in efficacy and safety between the different DOACs.

**Deng et al. (2020).[60] "Efficacy and Safety of Direct Oral Anticoagulants in Elderly Patients With Atrial Fibrillation: A Network Meta-Analysis"**

Deng et al. (2020)[60] aimed to examine the efficacy and safety of DOACs versus warfarin in elderly patients (≥ 75 years) with AF who may be at higher risk of stroke/SE and major bleeding due to comorbidities. The NMA included five RCTs (including the three trials included in this main report) with 28,137 participants, duration ranged from 1.9-2.8 years, and the two primary outcomes were stroke/SE and major bleeding. The DOACs included apixaban, rivaroxaban, dabigatran, and edoxaban, and the included trials must have reported subgroup analyses by age groups (< 75 years and ≥ 75 years). The NMA was conducted using a Bayesian random-effect model assuming a binomial likelihood and using "complementary log-log" as the link function. Results of the NMA showed that for both stroke/SE and major bleeding, apixaban was ranked the most effective among the DOACs compared to warfarin, though the differences in risk were not statistically significant. In terms of ranking among the DOACs, for stroke/SE, apixaban was ranked the highest, followed by rivaroxaban, edoxaban, dabigatran, and warfarin. For major bleeding, apixaban was ranked the highest, followed by edoxaban, dabigatran, warfarin, and rivaroxaban. These results were consistent with the results of the whole sample, results from our NMA, and findings from qualitative synthesis of subgroups.

**Table D4.1. Comparison of Estimates Between Our NMA Results and Published NMAs.**

| | Stroke/SE | Major Bleeding | MI | All-Cause Mortality |
|---|---|---|---|---|
| **NMA Results** | **HR (95% CrI)** | **HR (95% CrI)** | **HR (95% CrI)** | **HR (95% CrI)** |
| Apixaban vs. warfarin | 0.79 (0.66, 0.95) | 0.69 (0.6, 0.8) | 0.88 (0.66, 1.17) | 0.89 (0.79, 1) |
| Apixaban vs. dabigatran | 1.2 (0.9, 1.59) | 0.74 (0.61, 0.91) | 0.64 (0.41, 0.98) | 1.01 (0.85, 1.2) |
| Rivaroxaban vs. warfarin | 0.79 (0.65, 0.96) | 1.04 (0.9, 1.2) | 0.81 (0.62, 1.06) | 0.85 (0.71, 1.02) |
| Rivaroxaban vs. dabigatran | 1.2 (0.89, 1.6) | 1.12 (0.92, 1.37) | 0.59 (0.38, 0.9) | 0.97 (0.77, 1.21) |
| **Lopez-Lopez et al. 2017** | | | | |
| Apixaban vs. warfarin | 0.79 (0.66, 0.94) | 0.71 (0.61, 0.81) | 0.87 (0.66, 1.15) | 0.88 (0.79, 0.98) |
| Apixaban vs. dabigatran* | 1.18 (0.92, 1.38) | 0.67 (0.28, 0.91) | 0.50 (0.22, 1.02) | 1.00 (0.81, 1.16) |
| Rivaroxaban vs. warfarin | 0.88 (0.74, 1.03) | 1.03 (0.89, 1.18) | 0.80 (0.61, 1.04) | 0.83 (0.69, 1.00) |
| Rivaroxaban vs. dabigatran | 1.35 (1.03, 1.78) | 1.10 (0.90, 1.34) | 0.62 (0.41, 0.93) | 0.94 (0.74, 1.18) |
| **Carnicelli et al. 2022** | | | | |
| Standard dose DOAC† vs. warfarin | 0.81 (0.74, 0.89) | 0.86 (0.74, 1.01) | NA | 0.92 (0.87, 0.97) |
| Low dose DOAC‡ vs. warfarin | 1.06 (0.95, 1.19) | 0.63 (0.45, 0.88) | NA | 0.90 (0.83, 0.97) |
| **Deng et al. 2020** | | | | |
| Apixaban vs. warfarin | 0.71 (0.33, 1.50) | 0.64 (0.33, 1.30) | NA | NA |
| Apixaban vs. dabigatran | 0.81 (0.29, 2.30) | 0.64 (0.27, 1.50) | NA | NA |
| Rivaroxaban vs. warfarin | 0.73 (0.40, 1.20) | 1.20 (0.83, 1.90) | NA | NA |
| Rivaroxaban vs. dabigatran | 0.84 (0.32, 1.90) | 1.20 (0.63, 2.40) | NA | NA |

CrI: credible intervals, HR: hazard ratio.
*Lopez-Lopez et al. presented the comparison of dabigatran vs. apixaban. For ease of comparison to our NMA results, we calculated the estimates and 95% CI for apixaban vs. dabigatran.
†Dabigatran 150 mg twice daily, rivaroxaban 20 mg (or 15 mg if dose reduction criteria were met) once daily, apixaban 5 mg (or 2.5 mg if dose reduction criteria were met) twice daily, or edoxaban 60 mg once daily.
‡ Dabigatran 110 mg twice daily or edoxaban 30 mg once daily.

# D5. Heterogeneity and Subgroups

### Subgroups and Heterogeneity

In this supplement, we report the subgroup analyses of interest from the RE-LY trial. There were no data from the RE-LY for individuals with disabilities, those who are terminally ill, or children.

### End-Stage Renal Disease

Two secondary data analyses examined treatment modification by renal function (e.g., creatinine clearance) in the RE-LY trial. Both analyses reported no significant treatment modification for stroke/SE, mortality, or any bleeding event.[26,53] See Tables D3.26-D3.27.

**The Elderly**

There was no effect modification by age reported for the efficacy endpoint (e.g., stroke/SE) in the RE-LY trial.[43,53,54] However, additional secondary data analyses reported effect modification by age for some safety endpoints. For major bleed, one secondary analyses reported increased risk of major bleed and all-cause mortality in older adults; with increase of risk with each increasing age category (e.g., 75-79, 80-84, and 85+).[54] When examining the interaction between age and treatment, Eikelboom et al. (2011)[43] reported a lower risk of major bleeding in those under the age of 75 years who received dabigatran versus warfarin, and no significant difference in major bleeding in those over the age of 75 years who received either of the two treatments. This study also reported an interaction between age and treatment for GI bleeding, with a higher risk of GI bleeding in those over the age of 75 years who received dabigatran compared to those who received warfarin, with no significant difference in GI bleeding in those under 75 years who received either treatment. See Tables D3.28-D3.29. Like the ROCKET AF trial, it appeared that the effect modification for age was for extracranial bleeding.

# E. Comparative Effectiveness and Cost: Supplemental Information

## E1. Detailed Methods

**Table E1.1 Impact Inventory**

| Sector | Type of Impact (Add additional domains, as relevant) | Included in This Analysis from […] Perspective? | | Notes on Sources (if quantified), Likely Magnitude & Impact (if not) |
|---|---|---|---|---|
| | | Health Care Sector | Societal | |
| **Formal Health Care Sector** | | | | |
| **Health Outcomes** | Longevity effects | ☒ | ☒ | |
| | Health-related quality of life effects | ☒ | ☒ | |
| | Adverse events | ☒ | ☒ | |
| **Medical Costs** | Paid by third-party payers | ☒ | ☒ | |
| | Paid by patients out-of-pocket | ☐ | ☐ | |
| | Future related medical costs | ☒ | ☒ | |
| | Future unrelated medical costs | ☐ | ☐ | |
| **Informal Health Care Sector** | | | | |
| **Health-Related Costs** | Patient time costs | NA | ☒ | Warfarin monitoring time costs |
| | Unpaid caregiver-time costs | NA | ☒ | |
| | Transportation costs | NA | ☒ | |
| **Non-Health Care Sector** | | | | |
| **Productivity** | Labor market earnings lost | NA | ☒ | Lost productivity due to acute events (stroke and MI) |
| | Cost of unpaid lost productivity due to illness | NA | ☒ | |
| | Cost of uncompensated household production | NA | ☐ | |
| **Consumption** | Future consumption unrelated to health | NA | ☐ | |
| **Social Services** | Cost of social services as part of intervention | NA | ☐ | |
| **Legal/Criminal Justice** | Number of crimes related to intervention | NA | ☐ | |
| | Cost of crimes related to intervention | NA | ☐ | |
| **Education** | Impact of intervention on educational achievement of population | NA | ☐ | |
| **Housing** | Cost of home improvements, remediation | NA | ☐ | |
| **Environment** | Production of toxic waste pollution by intervention | NA | ☐ | |
| **Other** | Other impacts (if relevant) | NA | ☐ | |

NA: not applicable

Adapted from Sanders et al[61]

## Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Therefore, the evLY complies with the law as described in the Inflation Reduction Act, as described in our public comment letter to CMS regarding its initial program guidance.[62] Below are the stepwise calculations used to calculate the evLY.

1. First, we attributed a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[63]
2. We calculated the evLY for each model cycle.
3. Within a model cycle, if using the intervention resulted in additional life years versus the primary comparator, we multiplied the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator used the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle was calculated by summing steps 3 and 4.
6. The evLY for the comparator arm was equivalent to the QALY for each model cycle.
7. The total evLYs were then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained was the incremental difference in evLYs between the intervention and the comparator arm.

## E1.1 Overview and Model Structure

We developed a *de novo* decision analytic model for this evaluation, informed by an NMA and prior relevant economic models. Costs and outcomes were discounted at 3% per year. The model was developed in Microsoft Excel.

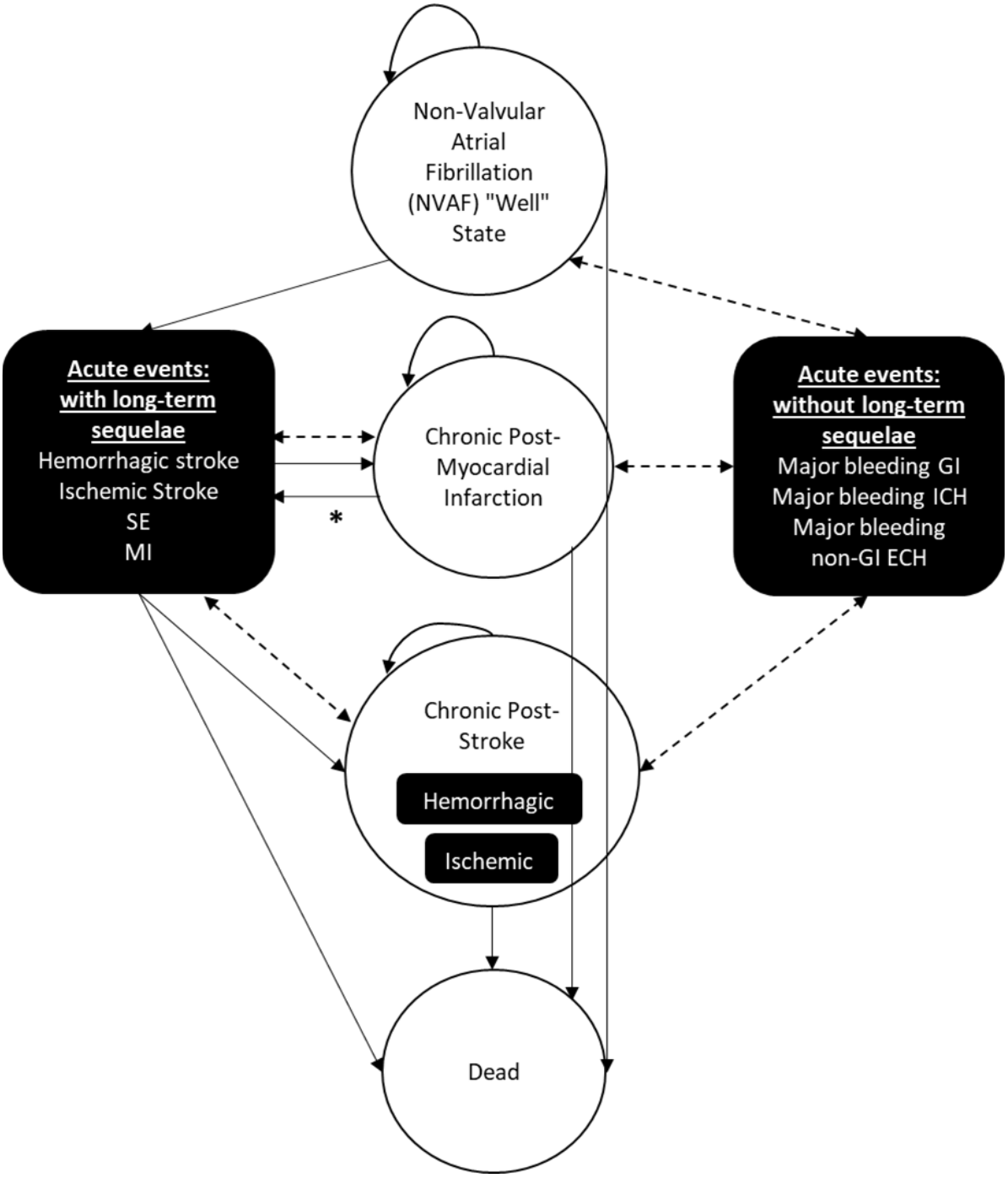
We used a Markov model with monthly cycles to simulate a hypothetical cohort of Medicare patients with NVAF being treated with apixaban, rivaroxaban, or a comparator agent (i.e., dabigatran or warfarin). The model focused on an intention-to-treat analysis, with a model cycle length of one month, based on what was observed in prior published economic models and the clinical data.

Model health states consisted of a NVAF "Well" state, chronic post-stroke (ischemic and hemorrhagic) and post-myocardial infarction (MI) states, and a dead state. Acute events including stroke, MI, and major bleeds (intracranial hemorrhage [ICH], gastrointestinal [GI], and other) were captured as transient events within all living health states. Patients experiencing stroke or MI who survive the event transitioned to a chronic health state with quality-of-life decrements and incurred

costs reflective of individuals experiencing a prior stroke or MI. Patients in the post-stroke state were at risk of subsequent strokes and other events (except MI) and remained in the post-stroke state until they died. Patients in the post-MI state were at risk of subsequent MIs and other events and remained in that state unless they died or experienced a stroke.

Patients remained in the model until they died. All patients transitioned to death from all causes (including background and NVAF-specific mortality) from any of the alive health states. In addition, patients could die from acute events (stroke, MI, major bleeds).

**Figure E1.1. Model Schematic**




ECH: extracranial hemorrhage, GI: gastrointestinal, ICH: intracranial hemorrhage, MI: myocardial infarction, SE: systemic embolism

*Arrow from chronic post-MI represents the % of the cohort experiencing a stroke.

Dotted arrows represent acute events where the patients stay in the original health state but incur cost and utility impacts due to that event.

Solid arrows represent a transition to a new health state and curved arrows indicate staying in that state.

# E2. Key Model Choices and Assumptions

Our model includes several assumptions stated below.

**Table E2.1. Key Model Assumptions**

| Assumption | Rationale |
|---|---|
| Baseline patient characteristics and baseline risk of events were sourced from published US Medicare data (where available) and otherwise supplemented by clinical trials in NVAF. Baseline stroke and bleed risks were calculated using risk equations ($CHA_2DS_2$-VASc and HAS-BLED) informed by baseline patient characteristics from US Medicare data. Other event risks including for MI were taken from Medicare NVAF cohort data, where available. | Published Medicare data best reflects the target population for our analysis and thus those data were preferred to trial-based baseline event risks, where available. Baseline model patient characteristics and event risks were compared to the warfarin arms of the trials included in the NMA, where available. |
| All patients started in the NVAF "well" health state. | We recognize that, in practice, there are likely patients who will initiate treatment in response to an acute stroke or MI. Based on evidence from Graham 2019, the percentage of patients with acute stroke or MI within the prior 6 months of initiation of treatment was small (<6% of patients),[64] and we anticipated that the expected impact of starting a small percentage of patients in a state with a higher risk of recurrence and death was likely to be marginal. |
| The primary cardiovascular events modeled included stroke (ischemic and hemorrhagic), MI, and major bleeds (GI, ICH, non-GI ECH). | Stroke, MI, and major bleeds are considered to be the most influential cardiovascular events for which differential treatment effects from the NMA were observed. There was no evidence of a differential treatment effect between agents for pulmonary embolism (PE), deep vein thrombosis (DVT), transient ischemic attack (TIA), or minor bleeds based on findings from the NMA. We anticipated that the associated costs and disutilities of these events would be small and would be absorbed by the health states included in our model. |
| Treatment effects were assumed to be constant over the lifetime of the model (as long as patients are on treatment) and were applied to an age and prior-event varying baseline event risk. | There was no evidence to suggest that the relative treatment effects varied over time or in response to specific patient characteristics. |
| Patients who experienced a stroke or MI transition to a chronic post-stroke or post-MI health state where they are at increased risk of subsequent events. Patients post-stroke remained in that state until they died, and patients post-MI remained in that state until they died or experienced a stroke (at which point they entered the post-stroke state). All patients in alive health states remained at risk of acute events equal to one cycle length each. | Evidence suggested that patients experiencing a stroke and MI have an increased risk of subsequent events, increased health care costs, and utility decrements for the remainder of their life.[65,66] Given that stroke is likely to have the most burdensome lifetime impact and is more likely to be impacted by different treatments in NVAF, it was deemed reasonable for patients in the post-stroke state to remain in that state until death, and patients experiencing an MI to remain at risk for stroke. |

| Assumption | Rationale |
|---|---|
| All patients remained on treatment following a non-fatal acute event. Patients experiencing a bleed (including a hemorrhagic stroke), experienced a one cycle-long (1 month) discontinuation from active therapy. Upfront added discontinuation rates for DOACs were based on a comparison to pooled warfarin AE-related discontinuation observed in the pivotal DOAC trials included within the NMA. Patients who discontinued from treatment due to an AE were assumed to experience background costs and outcomes that are consistent with a warfarin-treated population. | Clinical practice varies in terms of treatment modifications post-event. Based on discussions with clinical experts and a review of the literature, following an ischemic stroke or MI, it is common for patients to continue receiving their initial treatment[67] and initiate an antiplatelet therapy (e.g., clopidogrel). After acute events, costs of additional treatment and other health care utilization were included. Following a major bleed (and hemorrhagic strokes), all patients discontinued treatment for a one-month washout period and then resumed their initial treatment. Given the short duration of washout, no change in treatment effectiveness was modeled due to washout. The inclusion of trial-based AE discontinuation reflects evidence which suggests that discontinuation from DOACs commonly occurs early on after initiation of treatment (e.g., median time from initiation of therapy to discontinuation of 182 days (IQR: 69–389)[68] and to reflect evidence that suggests differences in discontinuation rates between agents.[69] |
| Acute event cost and disutilities (i.e., stroke, MI, bleeds) were additive. | Individuals with NVAF may experience multiple events throughout their lifetime. These events are expected to be managed as a short-term transient event that incur costs and a reduction in quality of life. Major events (stroke and MI) are expected to incur longer-term costs and reductions in quality of life that will be captured in the respective chronic health state. |

AE: adverse event, DOACs: direct acting oral anticoagulants, MI: myocardial infarction, NMA: network meta-analysis, NVAF: nonvalvular atrial fibrillation

## Target Population

The population of focus for the economic evaluation included Medicare enrollees living with NVAF for whom long-term anticoagulation has been deemed appropriate. A review of best available evidence in Medicare patients suggests that a contemporary FDA- and CMS-led analysis of CV event and bleed rates in patients initiating anticoagulation for NVAF may be most representative of the target population.[64] Those data, along with baseline characteristics of trials included in the ICER NMA for comparison purposes, are reported in Table E2.2. Additional baseline characteristics were sourced on an as needed basis to inform event probabilities in the model (e.g., alcoholic drinks per week, liver function tests). Our primary analysis was based on patient characteristics from the RWD cohort,[64] and all patients started in the NVAF "well" health state.

**Table E2.2. Baseline Population Characteristics Derived from Warfarin Arms of the NMA and Real-World Data**

| | Warfarin arm of RWD | Warfarin Arms of NMA | | | |
|---|---|---|---|---|---|
| **Study** | **Graham 2019** | **Study** | **ARISTOTLE** | **RE-LY** | **ROCKET AF** |
| **Study N** | 183,318 | **Study N (ITT)** | 9,081 | 6,022 | 7,133 |
| **Age, years (mean)** | 75.8 | **Age, years, mean (SD)** | 69.0 (9.74) | 71.6 (8.8) | NR |
| **Female, %** | 48.00% | **Female, n (%)** | 3182 (35.0) | 2213 (36.7) | 2832 (39.7) |
| **Medical comorbidities** | | | | | |
| Diabetes, % | 34.20% | Diabetes, n (%) | 2263 (24.9) | 1410 (23.4) | 2796 (39.2) |
| Hypertension, % | 86.30% | Hypertension, n (%) | 7954 (87.6) | 4750 (78.9) | 6435 |
| Kidney failure | | | | | |
| Acute, % | 4.90% | Moderate kidney impairment (>30 to 50 ml/min), n (%) | 1382 (15.2) | NR | 1459 (20.5) |
| Chronic, % | 12.10% | Severe kidney impairment (≤30 ml/min), n (%) | 133 (1.5) | NR | NR |
| Prior hospitalized bleeding, % | 0.60% | Prior clinically relevant/spontaneous bleeding, n (%) | 1515 (16.7) | NR | NR |
| Smoking, % | 20.50% | Smoking, n (%) | NR | NR | NR` |
| **Cardiovascular disease** | | | | | |
| Acute MI | | Acute MI, n (%) | 1266 (13.9) | 968 (16.1) | 1286 (18.0) |
| Past 1-30 days, % | 1.50% | NR | NR | NR | NR |
| Past 31-183 days, % | 0.80% | NR | NR | NR | NR |
| Coronary revascularization, % | 15.60% | NR | NR | NR | NR |
| Heart failure | | Heart failure or reduced LVEF, n (%) | 3216 (35.4) | 1922 (31.9) | NR |
| Hospitalized, % | 3.60% | NR | NR | NR | NR |
| Outpatient, % | 12.60% | NR | NR | NR | NR |
| Other ischemic heart disease, % | 44.60% | NR | NR | NR | NR |
| **Stroke** | | **Stroke, n (%)** | 1082 (11.9) | NR | NR |
| Past 1-30 days, % | 2.20% | NR | NR | NR | NR |
| Past 31-183 days, % | 1.20% | NR | NR | NR | NR |

| | Warfarin arm of RWD | Warfarin Arms of NMA | | | |
|---|---|---|---|---|---|
| Falls, % | 5.00% | Fall history, n (%) | 367 (4.0) | NR | NR |
| TIA, % | 6.30% | Prior stroke, TIA, or SE, n (%) | 1790 (19.7) | 1195 (19.8) | 3875 (54.3) |
| **$CHA_2DS_2$-VASc score** | | **$CHA_2DS_2$-VASc score, mean (SD)** | 3.7 (1.5) | NR | 4.8 (1.3) |
| 0-1, % | 2.90% | NR | NR | NR | NR |
| 2, % | 14.60% | NR | NR | NR | NR |
| 3, % | 27.90% | NR | NR | NR | NR |
| 4, % | 28.80% | NR | NR | NR | NR |
| 5, % | 16.00% | NR | NR | NR | NR |
| ≥6, % | 9.90% | NR | NR | NR | NR |
| **HAS-BLED score** | | **HAS-BLED score** | | | |
| 1, % | 9.30% | 0-1, n (%) | 3720 (41.0) | NR | 533 (7.5) |
| 2, % | 44.90% | 2, n (%) | 3286 (36.0) | NR | 2079 (29.1) |
| 3, % | 31.00% | ≥3, n (%) | 2075 (24.0) | NR | 4464 (62.2) |
| ≥4, % | 14.80% | NR | NR | NR | NR |
| **Medication use** | | | | | |
| NSAIDs, % | 13.00% | NSAIDs, n (%) | 768 (8.5) | NR | NR |
| Antiplatelets, % | 14.20% | Aspirin, n (%) | 2773 (30.5) | 2442/6017 (40.6) | 2759 (38.72) |
| | | Clopidogrel, n (%) | 168 (1.9) | NR | NR |

ITT: intention-to-treat, MI: myocardial infarction, NR: not reported, NSAIDs: Non-steroidal anti-inflammatory drugs, SD: standard deviation, SE: systemic embolism, TIA: transient ischemic attack.

### Table E2.3. Additional Baseline Patient Characteristics

| | Value | 95% CI | Source | Notes |
|---|---|---|---|---|
| **Drinks per week ≥ 8** | 6.7% | NR | Sterling 2020[70] | Percentage of patients with atrial fibrillation between mid-2018 to early 2020 in a Kaiser Permanente cohort reporting alcohol consumption that exceeds daily limits, weekly limits, or both limits (< 7 drinks per week in patients > 65 years). |
| **Liver disease (cirrhosis)** | 27.6% | 23.42% - 32.46% | UW IHME GHDx GBD[71] | Percentage of Americans 65 – 89 years old with cirrhosis and other chronic liver diseases in 2019 (prevalence value); assumes similar prevalence of cirrhosis across Medicare-aged NVAF and Medicare-aged non-NVAF patients |

CI: confidence interval, NR: not reported

### Treatment Strategies

The full list of interventions is as follows:

- Rivaroxaban (Xarelto®, Janssen Pharmaceuticals, Inc.)
- Apixaban (Eliquis®, Bristol-Myers Squibb Company & Pfizer Inc.)

### Comparators

The Comparator(s) for these interventions were:

- Dabigatran
- Warfarin

## E3. Model Inputs

Clinical inputs including cardiovascular event rates, mortality, and discontinuation rates were derived from the published literature. Treatment efficacy was based on the findings from an ICER-conducted network meta-analysis (NMA). Utility estimates were identified from the published literature, and costs were be derived from the literature as well as from Agency for Healthcare Research and Quality (AHRQ) Healthcare Utilization Project (HCUP) data. Sources, subgroup analyses, and data cuts that reflect a Medicare-specific population were prioritized where possible.

#### *Clinical Inputs*

Key clinical inputs included cardiovascular event risks (thromboembolic and bleeding events), mortality, treatment efficacy, and treatment discontinuation.

#### *Cardiovascular event risks*

Risks of cardiovascular events was derived from published US Medicare data (Graham 2019) using data from patients treated with warfarin. Primary stroke and bleed risk were calculated using risk equations ($CHA_2DS_2$-VASc and HAS-BLED) informed by average baseline patient characteristics from the aforementioned US Medicare data. Since the $CHA_2DS_2$-VASc predicts rates of stroke for patients on aspirin alone (or no anticoagulation), we used a relative risk (RR) of 0.3 (95% CI 0.13 to 0.63) for warfarin vs. aspirin from Mant et al. 2007[72] to derive a baseline risk for a warfarin treated population. The percentage of each subtype of stroke/SE (i.e., ischemic, hemorrhagic, and SE) and major bleeds (GI, ICH, non-GI ECH) was based on observed incidence rates from a Medicare population. In order to capture heterogeneity in baseline characteristics predictive of thromboembolic events and bleeds, we parameterized risk equation inputs and outputs in a continuous fashion over the model time horizon. As part of this exercise, we used best fit equations to predict risk across cohorts in the model calculations. Other event risks including MI were derived

from US Medicare data (warfarin treated), where possible. There was no evidence of a differential treatment effect between agents for pulmonary embolism (PE), deep vein thrombosis (DVT), transient ischemic attack (TIA), or minor bleeds and the impact of these events was expected to be small. As such, we did not plan to include these events in our model and anticipated that their associated costs and disutilities would be absorbed by the health states included in our model. Secondary event risks for stroke and MI were based on risk multipliers from the literature. Risks of events changed over time as a function of age where indicated (e.g., for the calculation of stroke risk via $CHA_2DS_2$-VASc).

**Table E3.1. Event Risks Based on a Warfarin-Treated Population.**

| Parameter | Value | Uncertainty | Source | Notes |
|---|---|---|---|---|
| **Stroke (monthly probability)** | 8.1 per 100 person-years | NA | Calculated using the $CHA_2DS_2$-VASc and baseline patient characteristics described above. | Baseline score calculated as 4.22. 1 year probability (7.82%) and converted to a monthly probability (0.68%). Estimate was adjusted by warfarin RR (0.3).[72] Estimate is updated continuously over model time horizon based on age. |
| **Percentage ischemic** | 71% | +/- 20% | Amin 2020 (US Medicare population with NVAF)[73] | Patients treated with warfarin calculated as the average percentage of all stroke (1.39/1.96 per 100 person-years) |
| **Percentage Hemorrhagic** | 22% | +/- 20% | Amin 2020 (US Medicare population with NVAF)[73] | Average of rivaroxaban and apixaban data calculated as the average percentage of all stroke (0.43/1.96 per 100 person-years) |
| **Percentage systemic embolism** | 7% | +/- 20% | Amin 2020 (US Medicare population with NVAF)[73] | Average of rivaroxaban and apixaban data calculated as the average percentage of all stroke (0.14/1.96 per 100 person-years) |
| **Increased risk of stroke given prior stroke or TIA** | HR 2.17 | 95% CI, 1.80–2.63 | Hacke 2020 (GARFIELD-AF registry)[74] | Adjusted HR |
| **Myocardial infarction** | 1.69 per 100 person-Years | +/- 20% | Graham 2015[31] | Patients enrolled in Medicare with nonvalvular atrial fibrillation. |
| **Increased risk of MI given prior MI** | HR 2.04 | Log normal (1.17, 3.55) | Coyle 2013[75] | Based on Cupples 1993 (prognosis after initial MI) [76] |
| **Major Bleeding** | 0.21% | NA | Baseline score calculated using the HAS-BLED risk equation. | Baseline score calculated as 2.09. 1 year probability (2.44%) and converted to a monthly probability. Estimate is updated continuously over model time horizon based on age. |

| Parameter | Value | Uncertainty | Source | Notes |
|---|---|---|---|---|
| **Percentage GI** | 47% | +/- 20% | Amin 2020 (US Medicare population with NVAF)[73] | Patients treated with warfarin calculated as the average percentage of all major bleeds (2.8/5.94 per 100 person-years) |
| **Percentage intracranial** | 16% | +/- 20% | Amin 2020 (US Medicare population with NVAF)[73] | Patients treated with warfarin calculated as the average percentage of all major bleeds (0.95/5.94 per 100 person-years) |
| **Percentage non-GI extracranial hemorrhage** | 37% | +/- 20% | Amin 2020 (US Medicare population with NVAF)[73] | Patients treated with warfarin calculated as the remaining percentage (i.e., non-GI, non-ICH) of all major bleeds (2.19/5.94 per 100 person-years) |

GI: gastrointestinal, MI: myocardial infarction, TIA: transient ischemic attack

Note: The percentages of each subtype of stroke/SE and major bleed are based on data from a real-world study of a US Medicare population with NVAF. Data were derived from the warfarin-treated group.

### *Treatment efficacy*

The primary measures of treatment efficacy were derived from the NMA. Briefly, the NMA included available Phase III randomized controlled trial evidence on rivaroxaban and apixaban for nonvalvular atrial fibrillation and a targeted search for long-term outcomes and low frequency adverse events for the interventions and comparators. If studies were sufficiently similar in terms of patient populations, outcomes assessed, interventions, and comparators, a restricted maximum likelihood random or fixed effect pairwise meta-analyses or network meta-analyses (NMA) was conducted where feasible. Treatment efficacy was derived from the results of all pairwise comparisons in terms of a point estimate and 95% credible intervals. Preliminary results are reported in Table E2.5 for rivaroxaban and apixaban. The dabigatran comparator trace was based on treatment efficacy estimates compared to warfarin from the NMA. We have outlined the efficacy estimates for dabigatran (vs. warfarin) in Table E2.6, below.

**Table E3.2. Treatment Efficacy for Rivaroxaban and Apixaban (vs. Warfarin and Dabigatran) from NMA Results.**

| Parameter | HR (95% Credible Interval) | | Source/Notes |
|---|---|---|---|
| | **Rivaroxaban** | **Apixaban** | |
| **Stroke and SE** | | | |
| vs. warfarin | 0.79 (0.65, 0.96) | 0.79 (0.66, 0.95) | NMA results<br>Stroke and SE includes hemorrhagic and ischemic stroke. |
| | | | |
| **Myocardial Infarction** | | | |
| vs. warfarin | 0.81 (0.62, 1.06) | 0.88 (0.66, 1.17) | NMA results |
| | | | |
| **PE or DVT** | | | |
| vs. warfarin | No difference | | Based on the clinical review, only one trial (ROCKET AF) had data for both PE and DVT and data suggested that the RRs are very similar with overlapping CrIs. Therefore, no differential effects between treatments are expected for this outcome. |
| | | | |
| **Major Bleed - ICH** | | | |
| vs. warfarin | 0.67 (0.48. 0.93) | 0.42 (0.3, 0.58) | NMA results |
| | | | |
| **Major Bleed - GI** | | | |
| vs. warfarin | 1.46 (1.2, 1.78) | 0.89 (0.69, 1.15) | NMA results |
| | | | |
| **Major Bleed – non-GI ECH** | | | |
| vs. warfarin | 1.04 (0.9, 1.2) | 0.69 (0.6, 0.8) | NMA results<br>Assumes that the treatment efficacy for *Major bleed (non-GI ECH)* is the same as the *"All major bleed (including fatal)"* treatment efficacy estimate from the NMA. |
| | | | |

CrI: credible interval, DVT: deep vein thrombosis, ECH: extracranial hemorrhage, GI: gastrointestinal, ICH: intracranial hemorrhage, NMA: network meta-analysis, PE: pulmonary embolism, RR: relative risk, SE: systemic embolism

**Table E3.3. Treatment Efficacy for Dabigatran vs. Warfarin from NMA Results.**

| Parameter | HR (95% Credible Interval) | Source/Notes |
|---|---|---|
| | | |
| **Stroke and SE** | 0.66 (0.53, 0.82) | NMA results<br>Stroke and SE includes hemorrhagic and ischemic stroke. |
| **Myocardial Infarction** | 1.38 (1, 1.91) | NMA results |
| **PE or DVT** | No difference | Based on the clinical review, only one trial (ROCKET AF) had data for both PE and DVT and data suggested that the RRs are very similar with overlapping CrIs. Therefore, no differential effects between treatments are expected for this outcome. |
| **Major Bleed - ICH** | 0.4 (0.27, 0.6) | NMA results |
| **Major Bleed - GI** | 1.5 (1.19, 1.89) | NMA results |
| **Major Bleed – non-GI ECH** | 0.93 (0.81, 1.07) | NMA results<br>Assumes that the treatment efficacy for *Major bleed (non-GI ECH)* is the same as the "*All major bleed (including fatal)"* estimate from the NMA. |

CrI: credible interval, DVT: deep vein thrombosis, ECH: extracranial hemorrhage, GI: gastrointestinal, ICH: intracranial hemorrhage, NMA: network meta-analysis, PE: pulmonary embolism, RR: relative risk, SE: systemic embolism

### *Discontinuation*

We included a one-time upfront discontinuation from DOAC therapy due to AEs based on trial data. Evidence suggested that discontinuation from DOACs commonly occurs early on after initiation of treatment (e.g., median time from initiation of therapy to discontinuation of 182 days (IQR: 69–389)[68] and that discontinuation rates were likely to vary between agents.[69] Further, there was no evidence to suggest that substantial background discontinuation continued to occur over time. Upfront added discontinuation rates for DOACs were based on a comparison to pooled warfarin AE-related discontinuation observed in the pivotal DOAC trials included within the NMA. DOAC discontinuation in the model occurred on a constant per-cycle basis up to the average follow-up time observed within the same NMA-included trials. Specifically, our starting point to model AE-related discontinuation in DOAC arms of the model was based on rates of discontinuation in the warfarin arms of the NMA-included trials. In the warfarin arms of the trials, 6.55% of patients discontinued therapy due to AEs over approximately 25 months of study follow-up, equating to an unadjusted per-cycle AE-related discontinuation probability of 0.27% for 25 model cycles. Given this warfarin-specific starting point, we calculated any added DOAC discontinuation in the model in excess of that 0.27% probability of AE-related discontinuation per model cycle. Table E2.7 below details the hazard ratios for AE-related discontinuation for apixaban, rivaroxaban, and dabigatran. As is evident in the table below, apixaban is associated with no excess AE-related discontinuation versus warfarin and therefore no upfront AE-related discontinuation occurred in the apixaban arm.

Patients who discontinued from treatment due to an AE were assumed to experience background costs and outcomes that are consistent with a warfarin-treated population.

**Table E3.4. AE-Related Discontinuation Model Inputs and Model Input Derivation**

| Treatment | Background AE-related Discontinuation Rate per Monthly Cycle | HR for AE-related Discontinuation, (95% CI) | HR-adjusted AE-Related Discontinuation per Monthly Cycle (up to cycle 25) |
|---|---|---|---|
| **Warfarin** | 0.27% | N/A | 0% (no excess) |
| **Apixaban** | N/A | 0.9 (0.81, 1) | 0% (no excess) |
| **Rivaroxaban** | N/A | 1.19 (1.06, 1.34) | 0.05% |
| **Dabigatran** | N/A | 1.89 (1.6, 2.24) | 0.24% |

CI: confidence interval, N/A: not applicable.

Following a non-fatal acute event all patients remained on their initial treatment. Patients experiencing a bleed (including a hemorrhagic stroke), experienced a one-cycle (1 month) discontinuation from active therapy. Patients experiencing an ischemic stroke or MI continued with their initial treatment[67] and initiated an antiplatelet therapy (e.g., clopidogrel). Post-event, the costs of additional treatment and other health care utilization were included within post-event health states (e.g., chronic MI health state, chronic ischemic stroke health state). No additional treatment benefit was added for the antiplatelet agent.

*Mortality*

Mortality was modeled based on general population background risk of death with a mortality risk multiplier applied to all alive health states to account for an increased risk of death due to NVAF (Table E2.8). We used a relative effect estimate from the published literature (HR 1.20)[77] to approximate the additional mortality risk associated with NVAF. We assumed that the increased risk of mortality for patients with prior stroke and prior MI were captured with the event rate multipliers (and associated event-related mortality) while patients are in the post-stroke and post-MI health states. Mortality impacts due to treatment efficacy were modeled indirectly by a reduction in overall event risk.

Mortality for acute events in the inpatient setting was taken from the same HCUP dataset describing inpatient costs by MS-DRG (Table E2.9). For GI and non-GI extracranial hemorrhage, acute event mortality rates were taken from Fang 2007.[78] This study included mortality rates for patients with NVAF who experienced warfarin-associated intracranial and extracranial hemorrhages. As mortality data were not stratified by payer (e.g., Medicare), we assumed that general rates in HCUP were applicable to a Medicare population.

**Table E3.5. Mortality Inputs for Chronic Health States**

| Parameter | HR (95% CI) | Source |
|---|---|---|
| Increased risk of mortality for NVAF | 1.20 (1.03 - 1.40) | Wyse 2001[77,79] |
| Increased risk of mortality with prior stroke | 1.0 (NA) | Assume that the increased risk of mortality for patients with prior stroke is captured with the increased risk of recurrent stroke (and associated death) while in the post-stroke health state. |
| Increased risk of mortality with prior MI | 1.0 (NA) | Assume that the increased risk of mortality for patients with prior MI is captured with the increased risk of recurrent MI (and associated death) while in the post-MI health state. |
| All-cause mortality | Varies by age | U.S. Life Tables |

CI: confidence interval, HR: hazard ratio, MI: myocardial infarction, NA: not applicable, RR: relative risk

**Table E3.6. Mortality Inputs for Acute Events**

| Acute Event | Inpatient Mortality Rate | Source |
|---|---|---|
| **Stroke/SE** | | |
| Ischemic | 12.1% | AHRQ HCUPnet (inpatient setting) |
| Hemorrhagic | 25.48% | AHRQ HCUPnet (inpatient setting) |
| SE | 0% | Assumption |
| **Myocardial infarction** | 5.86% | AHRQ HCUPnet (inpatient setting) |
| **Major Bleed** | | |
| Gastrointestinal | 2% | Fang 2007 (inpatient setting; patients with NVAF)[78] |
| Intracranial hemorrhage | 25.48% | AHRQ HCUPnet (inpatient setting) |
| Non-GI extracranial hemorrhage | 2% | Fang 2007 (inpatient mortality; patients with NVAF)[78] |

CEA: cost-effectiveness analysis, GI: gastrointestinal, SE: systemic embolism

*Utilities*

Health state utilities were derived from publicly available literature. Age and sex adjusted utilities were used over the lifetime of the model and disutilities were applied to account for chronic health states and acute events. We used consistent chronic health state and acute event disutility values across treatments evaluated in the model (Table E2.10 and Table E2.11). To account for the quality of life impacts on patients receiving warfarin, we included a disutility of -0.011 for patients on warfarin which was calculated based on the difference in the utility associated with a non-warfarin and warfarin regimen for patients with atrial fibrillation.[80] Disutilities were applied additively to reflect the independence between clinical events. US-based disutilities were prioritized where possible. Acute events with a disutility duration of greater than one month (the cycle length of the model) were accounted for within the cycle that the event was observed (i.e., a stroke event [ischemic] incurred a disutility of -0.3144 during that cycle: -0.0524 x 6 months).

**Table E3.7. Chronic Health State Disutilities**

| Parameter | Mean (SE) | Source |
|---|---|---|
| NVAF "Well" | -0.0190 | Sullivan 2006 (ICD-9 427) Cardiac Dysrhythmias[81] |
| Post-Stroke* | -0.04 (SE 0.0002) | Sullivan 2005[82] |
| Post-MI | -0.012 (SE 0.0002) | Sullivan 2005[82] |

MI: myocardial infarction, NVAF: non-valvular atrial fibrillation, SE: standard error
*Includes ischemic and hemorrhagic stroke based on evidence from Sullivan 2006 suggesting similar event disutilities.[83]

**Table E3.8. Acute Event Disutilities**

| Parameter | Mean (SE, 95% CI) | Duration Applied | Source |
|---|---|---|---|
| **Stroke (ischemic)** | -0.0524 | 1 month* | Sullivan et al 2006 (ICD-9 436 CVA); [81] ICER Sickle Cell Disease Draft Evidence Report. |
| **Stroke (hemorrhagic)** | -0.1511 | 1 month* | Miller 2016[84], assumption (expected to align with major bleed [ICH]) |
| **SE** | -0.0198 | 1 month* | Sullivan et al 2006 (ICD-9 444 Arterial Embolism)[81], assumption |
| **MI** | -0.0409 | 1 month* | Sullivan et al 2006 (ICD-9 410 Acute Myocardial); [81] ICER Sickle Cell Disease Draft Evidence Report. |
| **Major Bleed (GI)** | -0.029 | 1 month | Wang et al 2017 (Based on the ENGAGE AF-TIMI 48 Trial)[85], assumption |
| **Major Bleed (ICH)** | -0.1511 | 1 month* | Miller 2016[84], assumption (expected duration of acute aligns with stroke event) |
| **Major Bleed (non-GI-ECH)** | -0.029 | 1 month | Wang et al 2017[85], assumption |

CI: confidence interval, ECH: extracranial hemorrhage, GI: gastrointestinal, ICH: intracranial hemorrhage, MI: myocardial infarction, SE: systemic embolism
*Acute disutility estimates are applied in the model during the cycle in which they occur. To capture the full disutility during this cycle, the mean evidence-based estimates are multiplied by 6 to account for an assumed acute event impact of 6 months.

*Adverse Events*

All adverse events were assumed to be captured in the health state and event-related probabilities. No additional adverse events were included in the model.

### *Economic Inputs*

All costs used in the model were in 2022 dollars.

*Drug Acquisition Costs*

Our model results are framed as price premiums relative to whatever price CMS determines is paid by Medicare for each comparator, and therefore publicly available prices using external references for each drug are not reported. Dosing and frequency for all agents was informed by the medical literature and are presented in Table E2.12 below.

**Table E3.9. Drug Dosing and Frequency**

| Drug | Dosing and Frequency |
|---|---|
| **Apixaban (Eliquis)** | 5 mg by mouth twice daily* |
| **Rivaroxaban (Xarelto)** | 20 mg by mouth once daily |
| **Dabigatran** | 150 mg by mouth twice daily |
| **Warfarin** | 4 mg total daily dose by mouth** |

WAC: wholesale acquisition cost

* Dose decreased to 2.5 mg twice daily upon reaching an age of 80 years in those patients with kidney failure at baseline [86]

[87]** A 4 mg total daily dose may be a conservative (high) estimate of warfarin acquisition cost. [88]

*Administration and Monitoring Costs*

For patients receiving warfarin therapy, we included costs associated with monitoring the patient's International Normalized Ratio (INR). We assumed patients were stable on warfarin therapy and would incur costs for monthly INR testing (CPT code 85610; $4.29)[89] and one physician office visit every three months (CPT code 99212; $56.93).[80,90]

*Health Care Utilization Costs*

*Acute event costs*

We used a micro-costing analysis of acute CV events and bleeds utilizing AHRQ HCUP data to accurately capture event-related costs to Medicare. Acute event costs included those for emergency department (ED) visits and inpatient stays. We assumed each acute event would be associated with one ED visit and one inpatient stay. ED visits were mapped to the most appropriate corresponding Clinical Classification Software Refine (CCSR) codes available in the HCUP database for which average costs were available for Medicare patients. For example, the acute event of MI was mapped to CCSR code CIR009 (acute myocardial infarction). Inpatient visits were mapped to most appropriate International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10) codes, which were then cross-walked to the corresponding principal Medicare Severity Diagnosis Related Group (MS-DRG) code using version 37.0 of the ICD-10-CM/PCS MS-DRG Definitions Manual.[91] As any given acute event (e.g., MI) may be mapped to a variety of principal MS-DRGs (but only one principal MS-DRG per claim) (e.g., MS-DRG 236: Coronary bypass w/o cardiac cath w/o MCC *vs* MS-DRG 247: Percutaneous CV proc w/DES w/o MCC), we weighted costs

per inpatient event by the rates of various MS-DRG claim submissions available in HCUP. For hemorrhagic stroke specifically, we assumed all events would be associated with an intracranial vascular procedure with a principal diagnosis of hemorrhage (MS-DRGs 20, 21, and 22). In order to tailor these MS-DRG-derived costs to the baseline level of comorbidity (reflective of "Medicare Severity") in the modeled population (as captured by Graham et al, 2019), we calculated the proportion of the cohort assigned the label of MCC (major complication or comorbidity), CC (complication or comorbidity), or no CC/MCC. Using Part 1 of version 37.0 of the ICD-10-CM/PCS MS-DRG v37.0 Definitions Manual[91] we determined that 76% of MS-DRGs would be associated with CC, 0% with MCC, and 24% with no CC/MCC at baseline. All fatal events in the model were assigned a comorbidity classification of MCC (Table 2.12).[92]

*Chronic health state costs*

For costs associated with chronic health states (i.e., "well" NVAF, post-hemorrhagic stroke, post-ischemic stroke, post-MI), we relied on best available estimates within the literature. For background medical costs in NVAF patients, we used a cohort study looking at utilization and costs in patients with and without NVAF (Deshmukh 2022).[93] The average age of the 79,621 NVAF patients included was 74.1 years with a standard deviation of 10.7 years, where 73% of the cohort was aged 70 years or older. Approximately half of the cohort was female, mirroring the baseline characteristics for the model primary analyses (based on Graham 2019).[64] Costs were broken out into all-cause costs and CV-related costs along the domains of inpatient visits, outpatient visits, ED visits, and other medical visits; only non-CV-related costs were included to avoid downstream double-counting. Approximately 35% of all-cause costs in NVAF patients were attributed to CV-related costs, suggesting that substantial utilization and cost burden in NVAF patients is associated with non-CV-related morbidity and comorbidity. Additional costs associated with post-hemorrhagic stroke and post-ischemic stroke health states were taken from a contemporary analysis of allowed (insurer paid) amounts for U.S. Medicare patients initiating anticoagulation for NVAF (Amin 2022).[94] The average age in the matched warfarin cohorts in this analysis ranged from 77 to 78 years old, with one standard deviation equal to 7 years of age, and with approximately half of included warfarin patients being female. Costs were defined as all initial event costs plus additional medical (hospital, outpatient, ED) costs after the initial hospitalization related to the primary event. Patients were followed for close to 6 months across the matched warfarin cohorts, with each cohort consisting of anywhere between approximately 21,000 and 77,000 patients. Finally, chronic health state costs for the post-MI state were imputed from the relationship between acute and chronic ischemic stroke costs.

**Table E3.10. Acute Event and Chronic Health State Costs Derived from Medicare-Specific HCUP Data and Best Available Literature Estimates**

| Health State | Acute Health State Costs | Acute Health State Costs (SE) | Chronic Health State Costs (per month) | Chronic Health State Costs (lower bound - 95% CI) (per month) | Chronic Health State Costs (upper bound - 95% CI) (per month) |
|---|---|---|---|---|---|
| **Gastrointestinal hemorrhage** | $10,625.92 | $86.68 | N/A | N/A | N/A |
| **Hemorrhagic stroke/intracranial hemorrhage** | $73,213.58 | $2,248.58 | $3,813.36 | $3,730.20 | $3,896.64 |
| **Non-gastrointestinal, ECH*** | $10,625.92 | $86.68 | N/A | N/A | N/A |
| **Ischemic stroke** | $33,861.08 | $541.18 | $3,380.34 | $3,306.61 | $3,454.16 |
| **Myocardial infarction** | $23,971.70 | $355.30 | $3,332.43 | $3,259.75 | $3,405.20 |
| **Systemic embolism** | $10,413.60 | $182.47 | N/A | N/A | N/A |
| **"Well" (NVAF)** | N/A | N/A | $3,216.29 | $3,146.14 | $3,286.53 |

CI: confidence interval, ECH: extracranial hemorrhage, N/A: not applicable, NVAF: nonvalvular atrial fibrillation, SE: standard error.

*Costs assumed to be equal to gastrointestinal hemorrhage.

**Table E3.11. Costs for Fatal Acute Events Derived from Medicare-Specific HCUP Data**

| Fatal Event | Fatal Event Costs | SE |
|---|---|---|
| Gastrointestinal hemorrhage | $16,780.88 | $145.74 |
| Hemorrhagic stroke/intracranial hemorrhage | $110,908.05 | $2,771.91 |
| Non-gastrointestinal, ECH* | $16,780.88 | $145.74 |
| Ischemic stroke | $44,964.44 | $730.34 |
| Myocardial infarction | $38,720.27 | $519.14 |

ECH: extracranial hemorrhage, SE: standard error

*Costs assumed to be equal to gastrointestinal hemorrhage

*Adverse Event Costs*

All adverse events were assumed to be captured in the health state and event-related probabilities, disutilities and costs. No additional adverse events were included in the model.

*Indirect Costs (included in modified societal perspective analysis)*

**Warfarin-related management costs**

Costs associated with warfarin management were included in the modified societal perspective analysis. A monthly cost of US$13.98 was included for patients receiving warfarin. This cost was sourced from a 2008-2009 Canadian study which approximated mean costs per patient for warfarin management over a 3-month study time period. Costs included dispensing fees, and costs associated with homecare, travel, and caregiver costs. The CAD estimates were converted to US dollars and inflated to 2022 dollars[95].

**Patient and caregiver productivity costs**

Costs associated with patient and caregiver productivity loss due to cardiovascular events (stroke and MI) were included in the modified societal perspective analysis. These costs were applied for one year following an acute event. Patient productivity costs were estimated based on the number of lost hours of work per month multiplied by the average hourly wage rate in the US. Song et al. 2015 reported an average of 13.6 lost hours of work per month over a one-year period for patients with a cardiovascular event or related clinical procedures [96] compared to a matched cohort without a cardiovascular event. We used an hourly wage rate of $43.06 and 13.6 hours to equate a total annual cost of $7,027 per MI and stroke regardless of patient age.

Caregiver productivity costs for acute MI and stroke were estimated based on a study reporting the average weekly hours of informal caregiving required for patients with a stroke (both with and without health problems) [97] This study reported the percentage of patients with or without health problems following a stroke, the probability of having an informal caregiver, and the weekly average number of hours spent caregiving. Based on these estimates, we assumed that caregivers would spend 3.37 hours per week, on average, providing informal care (Table E3.12). Over the course of one year and at a wage rate of $43.06, we estimated that informal care would cost approximately $7,565 over one year.

**Table E3.12. Weekly Number of Informal Caregiving Hours for Patients with Acute MI and Stroke**

| | % Occurrence of Having Residual Impact | Probability of Informal Caregiving | Average Weekly Hours Caregiving | Total Hours/Week |
|---|---|---|---|---|
| **Stroke with Health Problems** | 43% | 54% | 12.5 | 2.9 |
| **Stroke without Health Problems** | 57% | 33% | 2.5 | 0.47 |
| **Total Hours** | | | | 3.37 |

*Data from Hickenbottom et al. 2022[97]

# E4. Results

## Sensitivity Analyses

## Deterministic Sensitivity Analysis

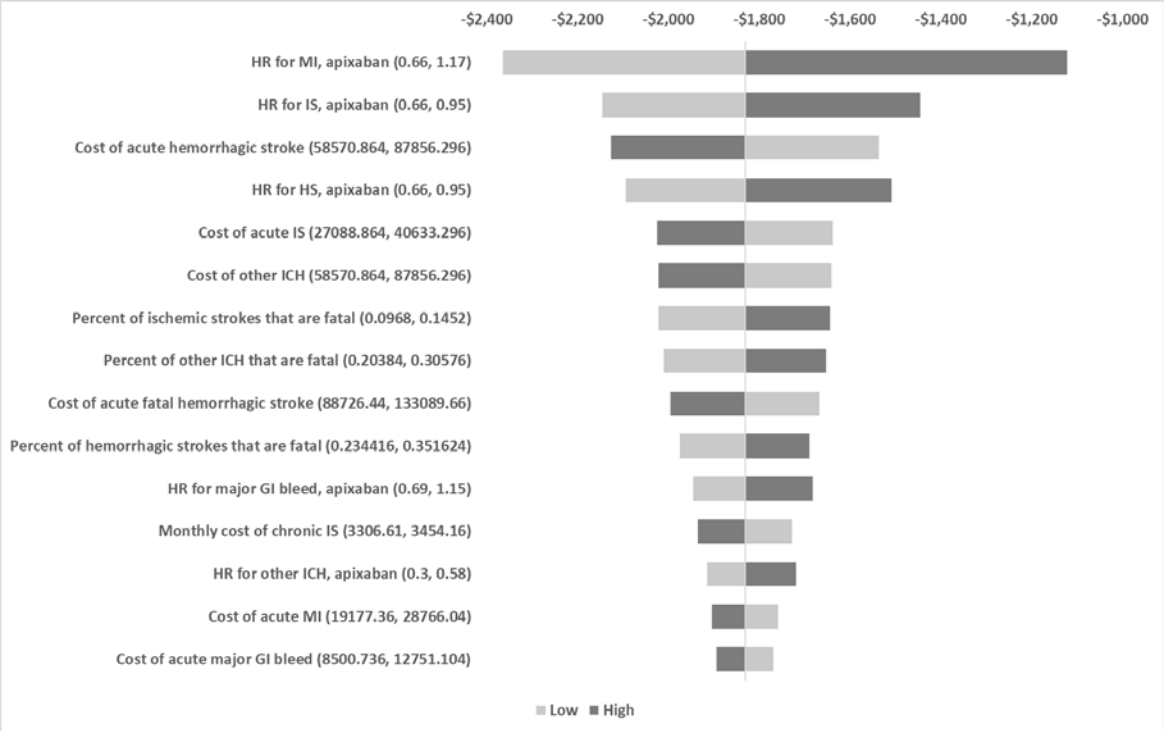
To demonstrate effects of uncertainty on both non-intervention health care system costs and health outcomes (evLYs), we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges. Analyses were conducted for apixaban and dabigatran versus warfarin and dabigatran.

For incremental non-intervention health care system costs, apixaban and rivaroxaban consistently generated incremental non-intervention health care system cost savings compared to both warfarin and dabigatran.

For incremental evLYs, apixaban and dabigatran consistently generated positive incremental evLYs compared to warfarin. When compared to dabigatran, apixaban consistently generated positive incremental evLYs across uncertain parameters, except at the extreme end of the reasonable range of uncertainty for apixaban's treatment efficacy for stroke. For this parameter, there was the potential for less favorable health outcomes (negative incremental evLYs) compared to dabigatran. Results for rivaroxaban vs. dabigatran were less robust, with ten of the top fifteen parameters generating positive incremental evLYs when varied across their reasonable ranges of uncertainty.

***Apixaban vs. Warfarin***

**Figure E4.1. Tornado Diagram (Apixaban vs. Warfarin) for Incremental Non-Intervention Health Care System Costs**




GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

**Table E4.1. Tornado Diagram Inputs and Results for Apixaban vs. Warfarin (Incremental Non-Intervention Health Care System Costs)**

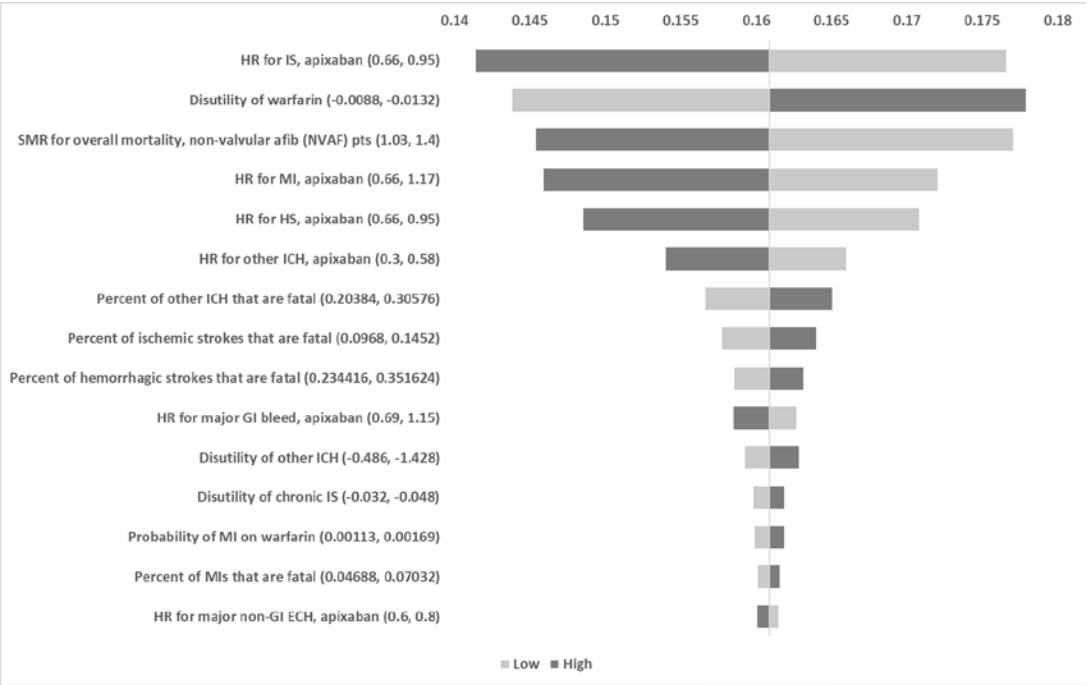
| | Lower Incremental Non-Intervention Health Care System Costs | Upper Incremental Non-Intervention Health Care System Costs | Lower Input* | Upper Input* |
|---|---|---|---|---|
| **HR for MI, apixaban** | -$2,364 | -$1,122 | 0.66 | 1.17 |
| **HR for IS, apixaban** | -$2,145 | -$1,445 | 0.66 | 0.95 |
| **Cost of acute hemorrhagic stroke** | -$1,537 | -$2,125 | $58,571 | $87,856 |
| **HR for HS, apixaban** | -$2,095 | -$1,508 | 0.66 | 0.95 |
| **Cost of acute IS** | -$1,637 | -$2,025 | $27,089 | $40,633 |
| **Cost of other ICH** | -$1,641 | -$2,021 | $58,571 | $87,856 |
| **Percent of ischemic strokes that are fatal** | -$2,022 | -$1,643 | 0.10 | 0.15 |
| **Percent of other ICH that are fatal** | -$2,011 | -$1,652 | 0.20 | 0.31 |
| **Cost of acute fatal hemorrhagic stroke** | -$1,667 | -$1,995 | $88,726 | $133,090 |
| **Percent of hemorrhagic strokes that are fatal** | -$1,975 | -$1,689 | 0.23 | 0.35 |

| | Lower Incremental Non-Intervention Health Care System Costs | Upper Incremental Non-Intervention Health Care System Costs | Lower Input* | Upper Input* |
|---|---|---|---|---|
| **HR for major GI bleed, apixaban** | -$1,946 | -$1,682 | 0.69 | 1.15 |
| **Monthly cost of chronic IS** | -$1,727 | -$1,935 | $3,307 | $3,454 |
| **HR for other ICH, apixaban** | -$1,915 | -$1,719 | 0.30 | 0.58 |
| **Cost of acute MI** | -$1,758 | -$1,904 | $19,177 | $28,766 |
| **Cost of acute major GI bleed** | -$1,768 | -$1,894 | $8,501 | $12,751 |

GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

*Note lower input may reflect either upper or lower incremental non-intervention health care system costs depending on the direction that the input has on the incremental non-intervention health care system costs output.

**Figure E4.2. Tornado Diagram (Apixaban vs. Warfarin) for Incremental evLYs**




evLYs: equal-value life years, GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

**Table E4.2. Tornado Diagram Inputs and Results for Apixaban vs. Warfarin (Incremental evLYs)**

| | Lower Incremental evLYs | Upper Incremental evLYs | Lower Input* | Upper Input* |
|---|---|---|---|---|
| **HR for IS, apixaban** | 0.1414 | 0.1766 | 0.66 | 0.95 |
| **Disutility of warfarin** | 0.1438 | 0.1779 | -0.009 | -0.013 |
| **SMR for overall mortality, non-valvular afib** | 0.1454 | 0.1770 | 1.03 | 1.40 |
| **HR for MI, apixaban** | 0.1459 | 0.1720 | 0.66 | 1.17 |
| **HR for HS, apixaban** | 0.1486 | 0.1708 | 0.66 | 0.95 |
| **HR for other ICH, apixaban** | 0.1540 | 0.1660 | 0.30 | 0.58 |
| **Percent of other ICH that are fatal** | 0.1567 | 0.1650 | 0.20 | 0.31 |
| **Percent of ischemic strokes that are fatal** | 0.1577 | 0.1640 | 0.10 | 0.15 |
| **Percent of hemorrhagic strokes that are fatal** | 0.1586 | 0.1631 | 0.23 | 0.35 |
| **HR for major GI bleed, apixaban** | 0.1585 | 0.1627 | 0.69 | 1.15 |
| **Disutility of other ICH** | 0.1593 | 0.1628 | -0.49 | -1.43 |
| **Disutility of chronic IS** | 0.1599 | 0.1619 | -0.03 | -0.05 |
| **Probability of MI on warfarin** | 0.1599 | 0.1619 | 0.001 | 0.002 |
| **Percent of MIs that are fatal** | 0.1601 | 0.1616 | 0.05 | 0.07 |
| **HR for major non-GI ECH, apixaban** | 0.1601 | 0.1615 | 0.60 | 0.80 |

evLYs: equal-value life years, GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

*Note lower input may reflect either upper or lower incremental evLYs depending on the direction that the input has on the incremental evLYs output.

***Apixaban vs. Dabigatran***

**Figure E4.3. Tornado Diagram (Apixaban vs. Dabigatran) for Incremental Non-Intervention Health Care System Costs**

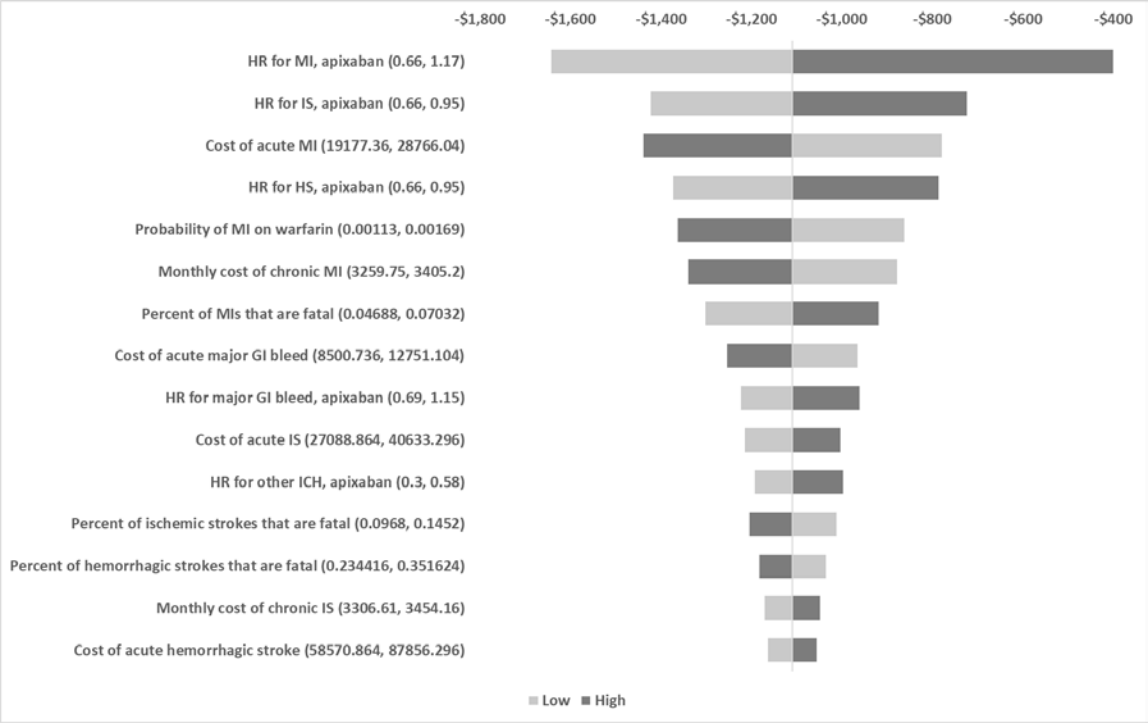


**Table E4.3. Tornado Diagram Inputs and Results for Apixaban vs. Dabigatran (Incremental Non-Intervention Health Care System Costs)**

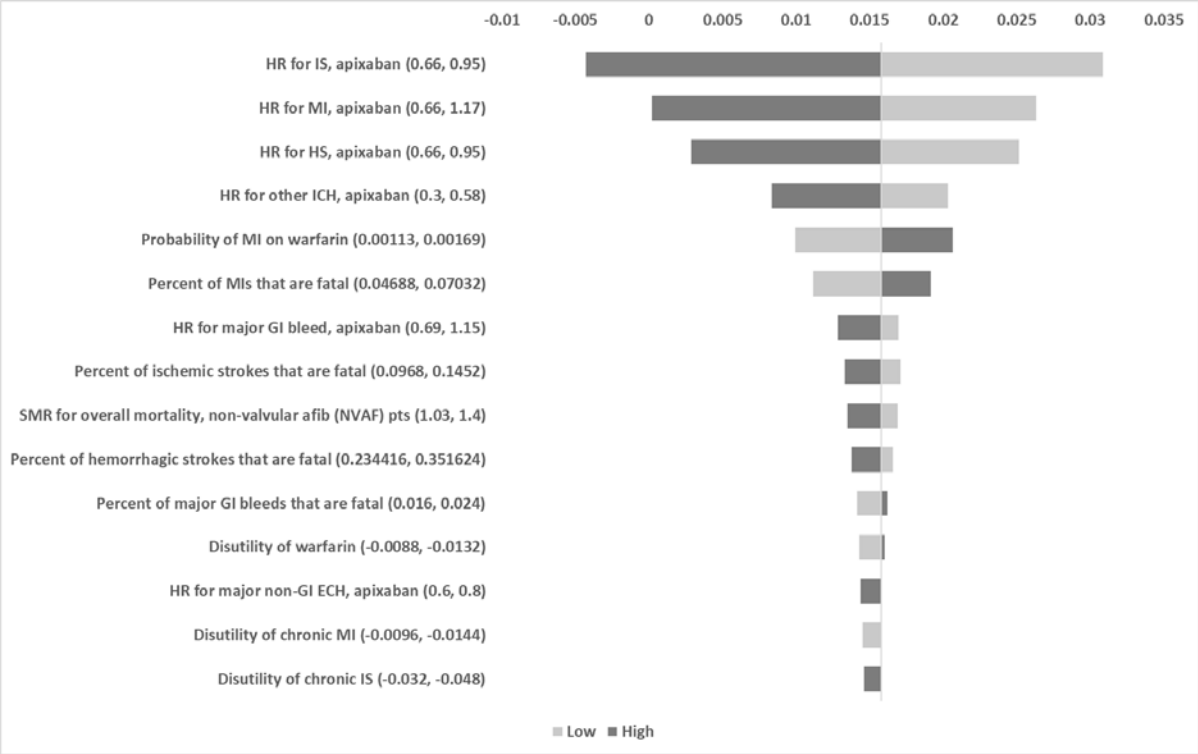
| | Lower Incremental Non-Intervention Health Care System Costs | Upper Incremental Non-Intervention Health Care System Costs | Lower Input* | Upper Input* |
|---|---|---|---|---|
| **HR for MI, apixaban** | -$400 | -$1,642 | 0.66 | 1.17 |
| **HR for IS, apixaban** | -$724 | -$1,423 | 0.66 | 0.95 |
| **Cost of acute MI** | -$779 | -$1,439 | $19,177 | $28,766 |
| **HR for HS, apixaban** | -$786 | -$1,373 | 0.66 | 0.95 |
| **Probability of MI on warfarin** | -$862 | -$1,363 | 0.001 | 0.002 |
| **Monthly cost of chronic MI** | -$878 | -$1,340 | $3,260 | $3,405 |
| **Percent of MIs that are fatal** | -$918 | -$1,301 | 0.05 | 0.07 |
| **Cost of acute major GI bleed** | -$965 | -$1,253 | $8,501 | $12,751 |
| **HR for major GI bleed, apixaban** | -$960 | -$1,224 | 0.69 | 1.15 |
| **Cost of acute IS** | -$1,003 | -$1,215 | $27,089 | $40,633 |
| **HR for other ICH, apixaban** | -$997 | -$1,193 | 0.30 | 0.58 |
| **Percent of ischemic strokes that are fatal** | -$1,012 | -$1,205 | 0.10 | 0.15 |
| **Percent of hemorrhagic strokes that are fatal** | -$1,036 | -$1,182 | 0.23 | 0.35 |
| **Monthly cost of chronic IS** | -$1,048 | -$1,171 | $3,307 | $3,454 |
| **Cost of acute hemorrhagic stroke** | -$1,055 | -$1,163 | $58,571 | $87,856 |

GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

Note: The uncertainty for apixaban efficacy was characterized by a comparison to warfarin. The uncertainty associated with dabigatran efficacy (vs. warfarin) was held at its deterministic value.

*Note lower input may reflect either upper or lower incremental non-intervention health care system costs depending on the direction that the input has on the incremental non-intervention health care system costs output.

**Figure E4.4. Tornado Diagram (Apixaban vs. Dabigatran) for Incremental evLYs**




evLYs: equal-value life years, GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

**Table E4.4. Tornado Diagram Inputs and Results for Apixaban vs. Dabigatran (Incremental evLYs)**

| | Lower incremental evLYs | Upper incremental evLYs | Lower Input* | Upper Input* |
|---|---|---|---|---|
| **HR for IS, apixaban** | -0.004 | 0.031 | 0.66 | 0.95 |
| **HR for MI, apixaban** | 0.000 | 0.026 | 0.66 | 1.17 |
| **HR for HS, apixaban** | 0.003 | 0.025 | 0.66 | 0.95 |
| **HR for other ICH, apixaban** | 0.008 | 0.020 | 0.30 | 0.58 |
| **Probability of MI on warfarin** | 0.010 | 0.021 | 0.001 | 0.002 |
| **Percent of MIs that are fatal** | 0.011 | 0.019 | 0.05 | 0.07 |
| **HR for major GI bleed, apixaban** | 0.013 | 0.017 | 0.69 | 1.15 |
| **Percent of ischemic strokes that are fatal** | 0.013 | 0.017 | 0.10 | 0.15 |
| **SMR for overall mortality, NVAF** | 0.014 | 0.017 | 1.03 | 1.40 |
| **Percent of hemorrhagic strokes that are fatal** | 0.014 | 0.017 | 0.23 | 0.35 |
| **Percent of major GI bleeds that are fatal** | 0.014 | 0.016 | 0.02 | 0.02 |
| **Disutility of warfarin** | 0.014 | 0.016 | -0.01 | -0.01 |
| **HR for major non-GI ECH, apixaban** | 0.014 | 0.016 | 0.60 | 0.80 |
| **Disutility of chronic MI** | 0.015 | 0.016 | -0.01 | -0.01 |
| **Disutility of chronic IS** | 0.015 | 0.016 | -0.03 | -0.05 |

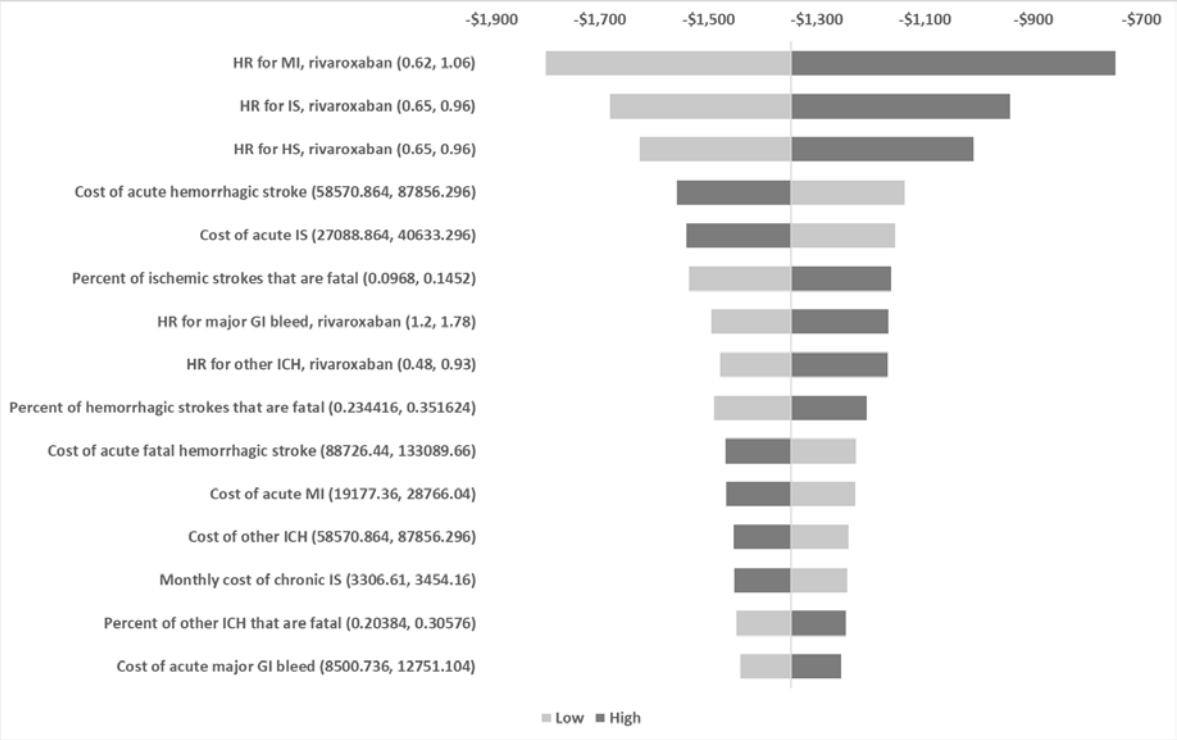
evLYs: equal-value life years, GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

Note: The uncertainty for apixaban efficacy was characterized by a comparison to warfarin. The uncertainty associated with dabigatran efficacy (vs. warfarin) was held at its deterministic value.

*Note lower input may reflect either upper or lower incremental evLYs depending on the direction that the input has on the incremental evLYs output.

***Rivaroxaban vs. Warfarin***

**Figure E4.5. Tornado Diagram (Rivaroxaban vs. Warfarin) for Incremental Non-Intervention Health Care System Costs**




GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

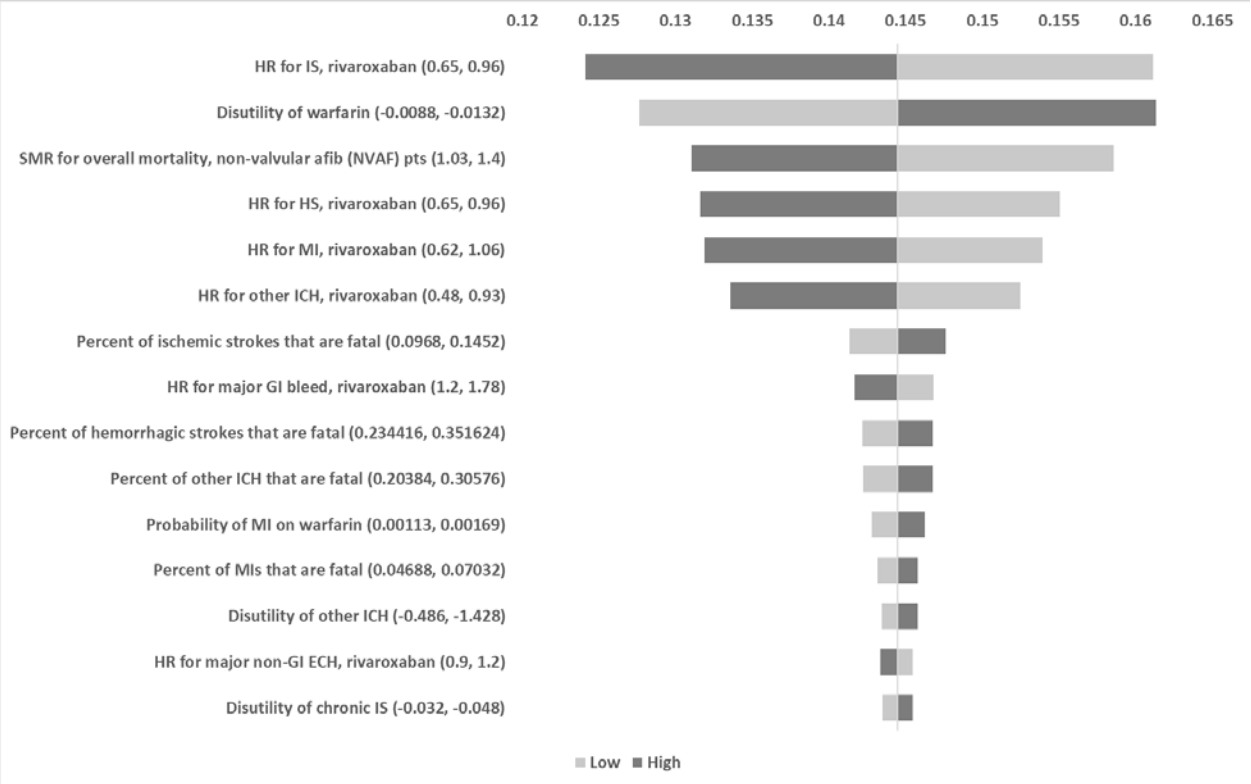
**Table E4.5. Tornado Diagram Inputs and Results for Rivaroxaban vs. Warfarin (Incremental Non-Intervention Health Care System Costs)**

| | Lower Incremental Non-Intervention Health Care System Costs | Upper Incremental Non-Intervention Health Care System Costs | Lower Input* | Upper Input* |
|---|---|---|---|---|
| **HR for MI, rivaroxaban** | -$747 | -$1,799 | 0.62 | 1.06 |
| **HR for IS, rivaroxaban** | -$943 | -$1,681 | 0.65 | 0.96 |
| **HR for HS, rivaroxaban** | -$1,009 | -$1,627 | 0.65 | 0.96 |
| **Cost of acute hemorrhagic stroke** | -$1,137 | -$1,557 | $58,571 | $87,856 |
| **Cost of acute IS** | -$1,154 | -$1,540 | $27,089 | $40,633 |
| **Percent of ischemic strokes that are fatal** | -$1,162 | -$1,535 | 0.10 | 0.15 |
| **HR for major GI bleed, rivaroxaban** | -$1,167 | -$1,494 | 1.20 | 1.78 |
| **HR for other ICH, rivaroxaban** | -$1,169 | -$1,478 | 0.48 | 0.93 |
| **Percent of hemorrhagic strokes that are fatal** | -$1,207 | -$1,489 | 0.23 | 0.35 |
| **Cost of acute fatal hemorrhagic stroke** | -$1,227 | -$1,467 | $88,726 | $133,090 |
| **Cost of acute MI** | -$1,228 | -$1,466 | $19,177 | $28,766 |
| **Cost of other ICH** | -$1,241 | -$1,453 | $58,571 | $87,856 |
| **Monthly cost of chronic IS** | -$1,243 | -$1,451 | $3,307 | $3,454 |
| **Percent of other ICH that are fatal** | -$1,246 | -$1,448 | 0.20 | 0.31 |
| **Cost of acute major GI bleed** | -$1,254 | -$1,440 | $8,501 | $12,751 |

GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

*Note lower input may reflect either upper or lower incremental non-intervention health care system costs depending on the direction that the input has on the incremental non-intervention health care system costs output.

**Figure E4.6. Tornado Diagram (Rivaroxaban vs. Warfarin) for Incremental evLYs**




ECH: extracranial hemorrhage, evLY: equal-value life year, GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

**Table E4.6. Tornado Diagram Inputs and Results for Rivaroxaban vs. Warfarin (Incremental evLYs)**

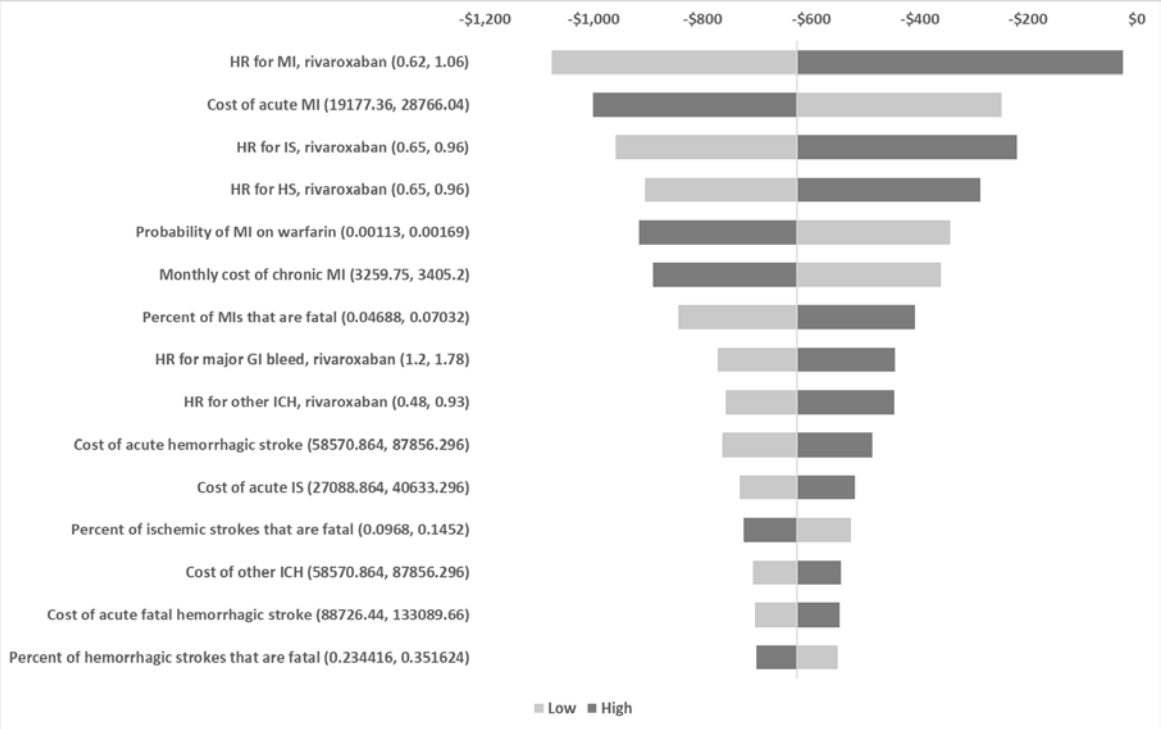
| | Lower Incremental evLYs | Upper Incremental evLYs | Lower Input* | Upper Input* |
|---|---|---|---|---|
| **HR for IS, rivaroxaban** | 0.1241 | 0.1612 | 0.65 | 0.96 |
| **Disutility of warfarin** | 0.1276 | 0.1613 | -0.01 | -0.01 |
| **SMR for overall mortality, NVAF** | 0.1310 | 0.1586 | 1.03 | 1.40 |
| **HR for HS, rivaroxaban** | 0.1316 | 0.1551 | 0.65 | 0.96 |
| **HR for MI, rivaroxaban** | 0.1319 | 0.1539 | 0.62 | 1.06 |
| **HR for other ICH, rivaroxaban** | 0.1336 | 0.1525 | 0.48 | 0.93 |
| **Percent of ischemic strokes that are fatal** | 0.1413 | 0.1476 | 0.10 | 0.15 |
| **HR for major GI bleed, rivaroxaban** | 0.1417 | 0.1468 | 1.20 | 1.78 |
| **Percent of hemorrhagic strokes that are fatal** | 0.1422 | 0.1468 | 0.23 | 0.35 |
| **Percent of other ICH that are fatal** | 0.1422 | 0.1468 | 0.20 | 0.31 |
| **Probability of MI on warfarin** | 0.1428 | 0.1463 | 0.001 | 0.002 |
| **Percent of MIs that are fatal** | 0.1432 | 0.1458 | 0.05 | 0.07 |
| **Disutility of other ICH** | 0.1434 | 0.1458 | -0.49 | -1.43 |
| **HR for major non-GI ECH, rivaroxaban** | 0.1434 | 0.1455 | 0.90 | 1.20 |
| **Disutility of chronic IS** | 0.1435 | 0.1455 | -0.03 | -0.05 |

ECH: extracranial hemorrhage, evLY: equal-value life year, GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

*Note lower input may reflect either upper or lower incremental evLYs depending on the direction that the input has on the incremental evLYs output.

***Rivaroxaban vs. Dabigatran***

**Figure E4.7. Tornado Diagram (Rivaroxaban vs. Dabigatran) for Incremental Non-Intervention Health Care System Costs**




GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

**Table E4.7. Tornado Diagram Inputs and Results for Rivaroxaban vs. Dabigatran (Incremental Non-Intervention Health Care System Costs)**

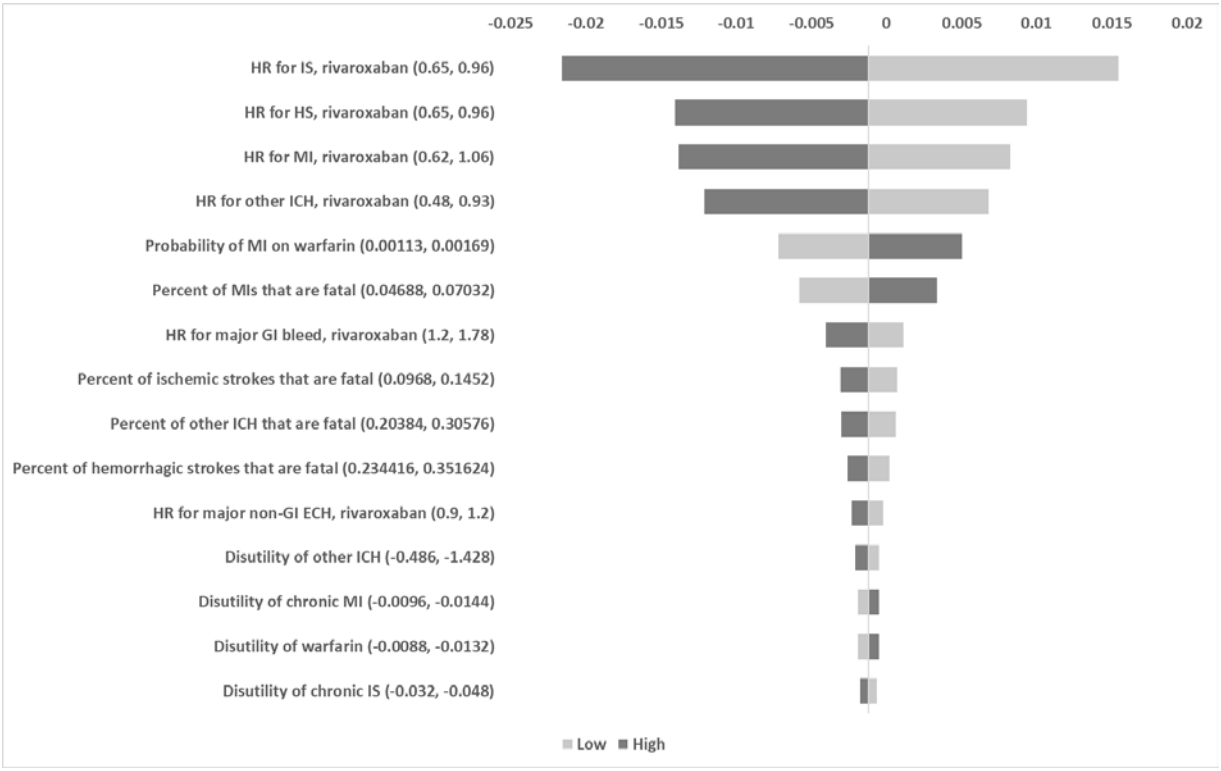
| | Lower Incremental Non-Intervention Health Care System Costs | Upper Incremental Non-Intervention Health Care System Costs | Lower Input* | Upper Input* |
|---|---|---|---|---|
| **HR for MI, rivaroxaban** | -$26 | -$1,077 | 0.62 | 1.06 |
| **Cost of acute MI** | -$249 | -$1,001 | $19,177 | $28,766 |
| **HR for IS, rivaroxaban** | -$221 | -$959 | 0.65 | 0.96 |
| **HR for HS, rivaroxaban** | -$287 | -$905 | 0.65 | 0.96 |
| **Probability of MI on warfarin** | -$343 | -$916 | 0.001 | 0.002 |
| **Monthly cost of chronic MI** | -$361 | -$890 | $3,260 | $3,405 |
| **Percent of MIs that are fatal** | -$409 | -$843 | 0.05 | 0.07 |
| **HR for major GI bleed, rivaroxaban** | -$445 | -$772 | 1.20 | 1.78 |
| **HR for other ICH, rivaroxaban** | -$447 | -$756 | 0.48 | 0.93 |
| **Cost of acute hemorrhagic stroke** | -$487 | -$763 | $58,571 | $87,856 |
| **Cost of acute IS** | -$519 | -$731 | $27,089 | $40,633 |
| **Percent of ischemic strokes that are fatal** | -$526 | -$723 | 0.10 | 0.15 |
| **Cost of other ICH** | -$544 | -$706 | $58,571 | $87,856 |
| **Cost of acute fatal hemorrhagic stroke** | -$547 | -$703 | $88,726 | $133,090 |
| **Percent of hemorrhagic strokes that are fatal** | -$550 | -$700 | 0.23 | 0.35 |

GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

Note: The uncertainty for rivaroxaban efficacy was characterized by a comparison to warfarin. The uncertainty associated with dabigatran efficacy (vs. warfarin) was held at its deterministic value.

*Note lower input may reflect either upper or lower incremental non-intervention health care system costs depending on the direction that the input has on the incremental non-intervention health care system costs output.

**Figure E4.8. Tornado Diagram (Rivaroxaban vs. Dabigatran) for Incremental evLYs**




ECH: extracranial hemorrhage, evLY: equal-value life year, GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

**Table E4.8. Tornado Diagram Inputs and Results for Rivaroxaban vs. Dabigatran (Incremental evLYs)**

| | Lower Incremental evLYs | Upper Incremental evLYs | Lower Input* | Upper Input* |
|---|---|---|---|---|
| **HR for IS, rivaroxaban** | -0.022 | 0.015 | 0.65 | 0.96 |
| **HR for HS, rivaroxaban** | -0.014 | 0.009 | 0.65 | 0.96 |
| **HR for MI, rivaroxaban** | -0.014 | 0.008 | 0.62 | 1.06 |
| **HR for other ICH, rivaroxaban** | -0.012 | 0.007 | 0.48 | 0.93 |
| **Probability of MI on warfarin** | -0.007 | 0.005 | 0.001 | 0.002 |
| **Percent of MIs that are fatal** | -0.006 | 0.003 | 0.05 | 0.07 |
| **HR for major GI bleed, rivaroxaban** | -0.004 | 0.001 | 1.20 | 1.78 |
| **Percent of ischemic strokes that are fatal** | -0.003 | 0.001 | 0.10 | 0.15 |
| **Percent of other ICH that are fatal** | -0.003 | 0.001 | 0.20 | 0.31 |
| **Percent of hemorrhagic strokes that are fatal** | -0.003 | 0.0002 | 0.23 | 0.35 |
| **HR for major non-GI ECH, rivaroxaban** | -0.0002 | -0.002 | 0.90 | 1.20 |
| **Disutility of other ICH** | -0.0005 | -0.002 | -0.49 | -1.43 |
| **Disutility of chronic MI** | -0.0005 | -0.002 | -0.01 | -0.01 |
| **Disutility of warfarin** | -0.001 | -0.002 | -0.01 | -0.01 |
| **Disutility of chronic IS** | -0.001 | -0.002 | -0.03 | -0.05 |

ECH: extracranial hemorrhage, evLY: equal-value life year, GI: gastrointestinal, HR: hazard ratio, HS: hemorrhagic stroke, ICH: intracranial hemorrhage, IS: ischemic stroke, MI: myocardial infarction, SMR: standardized mortality ratio.

Note: The uncertainty for rivaroxaban efficacy was characterized by a comparison to warfarin. The uncertainty associated with dabigatran efficacy (vs. warfarin) was held at its deterministic value.

*Note lower input may reflect either upper or lower incremental evLYs depending on the direction that the input has on the incremental evLYs output.

## Probabilistic Sensitivity Analysis

Probabilistic analyses were conducted for incremental non-intervention health care sector costs versus incremental evLYs.

**Figure E4.9. Probabilistic Sensitivity Analysis (1,000 simulations) for Incremental Non-Intervention Health Care System Costs vs. Incremental evLYs**

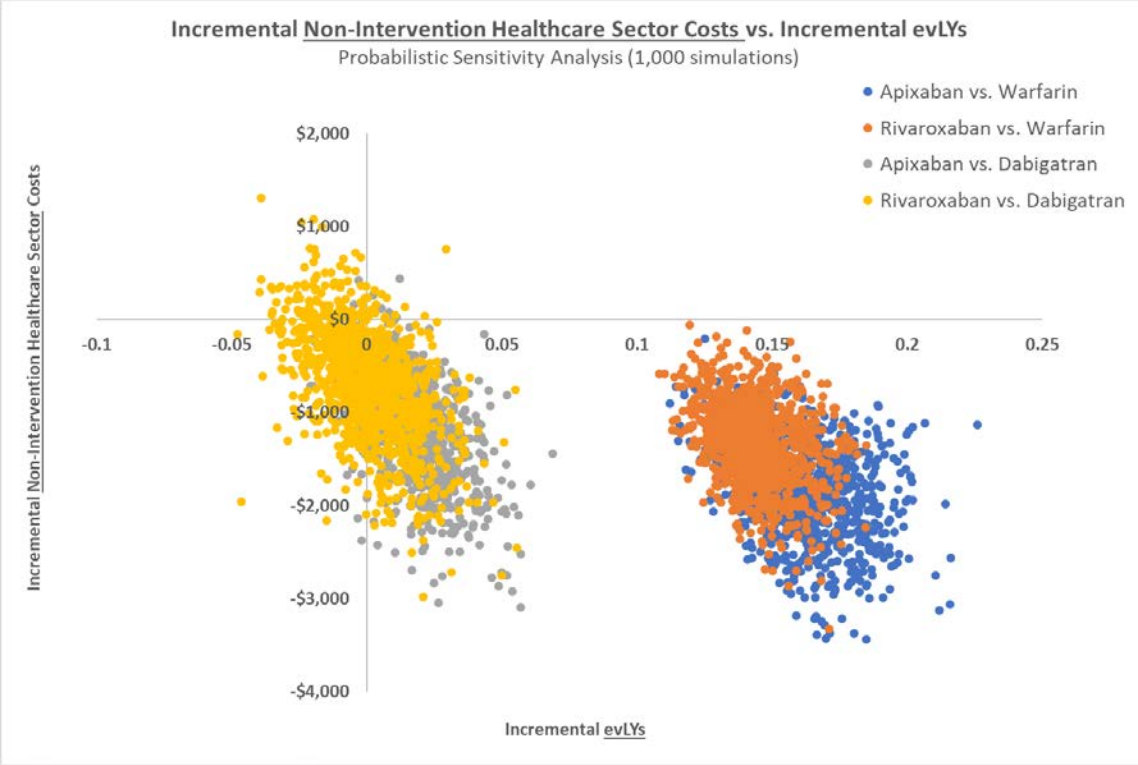



**Table E4.9. Probabilistic Sensitivity Analysis for Incremental Event Related Costs and Incremental evLYs**

| Intervention | Comparator | Percentage of Simulations for Incremental Health Care System Costs <$0 (i.e., Downstream Acute Event and Chronic Condition-Related Cost Savings) | Percentage of Simulations for Incremental evLYs >0 (i.e., Improved Health Outcomes) |
|---|---|---|---|
| **Apixaban** | Warfarin | 100% | 100% |
| **Apixaban** | Dabigatran | 99% | 90% |
| **Rivaroxaban** | Warfarin | 100% | 100% |
| **Rivaroxaban** | Dabigatran | 88% | 49% |

evLYs: equal-value life years

## Scenario Analyses

## Scenario Analysis 1

### *Modified Societal Perspective*

### *Projected Discounted Productivity Costs for Apixaban and Rivaroxaban vs. Warfarin and Dabigatran*

**Table E4.10. Lifetime Discounted Warfarin Time and Productivity Costs for Interventions and Comparators**

| Treatment | Warfarin Time Costs | Patient productivity loss | Caregiver productivity loss |
|---|---|---|---|
| **Apixaban** | $0 | $2,332 | $2,510 |
| **Rivaroxaban** | $14 | $2,245 | $2,417 |
| **Dabigatran** | $65 | $2,757 | $2,968 |
| **Warfarin** | $1,288 | $2,832 | $3,049 |

evLYs: equal value life years, LY: Life year, MI: myocardial infarction

**Table E4.11. Incremental Results for Apixaban versus Warfarin and Dabigatran for Warfarin Time and Productivity Costs**

| | Incremental Costs* | | |
|---|---|---|---|
| **Treatment** | **Warfarin Time Costs** | **Patient productivity loss** | **Caregiver productivity loss** |
| **Apixaban vs. Warfarin** | -$1,288 | -$500 | -$538 |
| **Apixaban vs. Dabigatran** | -$65 | -$425 | -$457 |

*Negative values for costs represent cost savings for intervention vs. comparator.

**Table E4.12. Incremental Results for Rivaroxaban versus Warfarin and Dabigatran for Warfarin Time and Productivity Costs**

| | Incremental costs* | | |
|---|---|---|---|
| **Treatment** | **Warfarin Time Costs** | **Patient productivity loss** | **Caregiver productivity loss** |
| **Rivaroxaban vs. Warfarin** | -$1,274 | -$587 | -$631 |
| **Rivaroxaban vs. Dabigatran** | -$51 | -$512 | -$551 |

*Negative values for costs represent cost savings for intervention vs. comparator.

***Price Premium Threshold Analysis – Scenario Analysis 1: Modified Societal Perspective***

**Table E4.13. Maximum Annualized Price Premium for Apixaban and Rivaroxaban Above Warfarin Pricing to Achieve a Range of Thresholds – Modified Societal Perspective**

| | $50,000/evLY | $100,000/evLY | $150,000/evLY | $200,000/evLY |
|---|---|---|---|---|
| **Apixaban vs. Warfarin** | $1,560 | $2,590 | $3,620 | $4,650 |
| **Apixaban vs. Dabigatran** | $360 | $460 | $550 | $650 |

Note: Annualized price premiums are rounded to the nearest $10.

**Table E4.14. Maximum Annualized Price Premium for Apixaban and Rivaroxaban Above Dabigatran Pricing to Achieve a Range of Thresholds – Modified Societal Perspective**

| | $50,000/evLY | $100,000/evLY | $150,000/evLY | $200,000/evLY |
|---|---|---|---|---|
| **Rivaroxaban vs. Warfarin** | $1,430 | $2,370 | $3,300 | $4,240 |
| **Rivaroxaban vs. Dabigatran** | $230* | $230* | $230* | $230* |

*Annual price premiums are estimated using modeled cost-savings from downstream acute events and chronic health state costs and assume no differences in equal-value life years between rivaroxaban and dabigatran.
Note: Annualized price premiums are rounded to the nearest $10.

## Scenario Analysis 2

### *No MI Treatment Efficacy Applied*

Under a scenario where no MI treatment efficacy is applied to the interventions, both apixaban and rivaroxaban result in fewer evLYs gained and higher non-intervention health care sector costs relative to dabigatran. Under this scenario, findings suggest no price premium for apixaban and rivaroxaban relative to dabigatran. Compared to warfarin, findings suggest a price premium, albeit reduced proportionally by the exclusion of MI treatment.

**Table E4.15. Incremental Results for Apixaban versus Warfarin and Dabigatran**

| | Incremental Outcomes | | | | | |
|---|---|---|---|---|---|---|
| **Treatment** | **Strokes*** | **MIs** | **Major Bleeds**** | **Life Years** | **Equal-Value LYs** | **Non-Intervention Health Care Sector Costs†** |
| **Apixaban vs. Warfarin** | -0.052 | 0.002 | -0.057 | 0.07 | 0.15 | -$1,500 |
| **Apixaban vs. Dabigatran** | 0.028 | -0.001 | -0.084 | -0.01 | -0.01 | $100 |

evLYs: equal-value life years, LY: Life year, MI: myocardial infarction

**Note**: Negative health outcomes represent cardiovascular events averted with apixaban vs. comparators; negative costs represent cost savings for apixaban vs. comparators.

*Includes ischemic and hemorrhagic strokes

**Includes major gastrointestinal bleeds, intracranial hemorrhages, and non- gastrointestinal extracranial hemorrhages.

†Inclusive of acute event and chronic condition costs (excludes intervention costs).

**Table E4.16. Incremental Results for Rivaroxaban versus Warfarin and Dabigatran**

| | Incremental Outcomes | | | | | |
|---|---|---|---|---|---|---|
| **Treatment** | **Strokes*** | **MIs** | **Major Bleeds**** | **Life Years** | **Equal-Value LYs** | **Non-Intervention Health Care Sector Costs†** |
| **Rivaroxaban vs. Warfarin** | -0.052 | 0.002 | 0.042 | 0.05 | 0.13 | -$900 |
| **Rivaroxaban vs. Dabigatran** | 0.028 | -0.001 | 0.015 | -0.03 | -0.03 | $700 |

evLYs: equal-value life years, LY: Life year, MI: myocardial infarction

**Note**: Negative Lys and evLYs represent life years lost with rivaroxaban vs. comparators; negative incremental strokes, Mis, and major bleeds represent events averted with rivaroxaban vs. comparators; negative costs represent cost savings for rivaroxaban vs. comparators.

*Includes ischemic and hemorrhagic strokes

**Includes major gastrointestinal bleeds, intracranial hemorrhages, and non- gastrointestinal extracranial hemorrhages.

†Inclusive of acute event and chronic condition costs (excludes intervention costs).

### *Price Premium Threshold Analyses – Scenario Analysis 2: No MI Treatment Efficacy Applied*

**Table E4.17. Maximum Annualized Price Premium for Apixaban Above Warfarin and Dabigatran Pricing to Achieve a Range of Cost-Effectiveness Price Premium Thresholds**

| | $50,000/evLY | $100,000/evLY | $150,000/evLY | $200,000/evLY |
|---|---|---|---|---|
| **Apixaban vs. Warfarin** | $1,187 | $2,177 | $3,168 | $4,158 |
| **Apixaban vs. Dabigatran** | No price premium* | No price premium* | No price premium* | No price premium* |

evLYs: equal-value life years

*Apixaban resulted in fewer evLYs gained relative to dabigatran

**Table E4.18. Maximum Annualized Price Premium for Rivaroxaban Above Warfarin and Dabigatran Pricing to Achieve a Range of Cost-Effectiveness Price Premium Thresholds**

| | $50,000/evLY | $100,000/evLY | $150,000/evLY | $200,000/evLY |
|---|---|---|---|---|
| **Rivaroxaban vs. Warfarin** | $991 | $1,866 | $2,742 | $3,617 |
| **Rivaroxaban vs. Dabigatran** | No price premium* | No price premium* | No price premium* | No price premium* |

evLYs: equal-value life years

*Rivaroxaban resulted in fewer evLYs gained relative to dabigatran

## Scenario Analysis 3

### *No Treatment Discontinuation*

Under a scenario with no treatment discontinuation applied, results were consistent with base case results for apixaban and rivaroxaban compared to warfarin. When compared to dabigatran, apixaban had fewer incremental evLYs gained and similar cost savings resulting in a lower price premium compared to base case findings. Rivaroxaban had higher incremental evLYs lost and similar cost savings compared in base case findings suggesting no price premium at thresholds greater than $100,000 per evLY gained.

### Table E4.19. Incremental Results for Apixaban versus Warfarin and Dabigatran

| | Incremental Outcomes | | | | | |
|---|---|---|---|---|---|---|
| **Treatment** | **Strokes*** | **MIs** | **Major Bleeds**** | **Life Years** | **Equal-Value LYs** | **Non-Intervention Health Care Sector Costs†** |
| **Apixaban vs. Warfarin** | -0.052 | -0.019 | -0.057 | 0.08 | 0.16 | -$1,800 |
| **Apixaban vs. Dabigatran** | 0.033 | -0.093 | -0.085 | 0.008 | 0.01 | -$1,100 |

evLYs: equal-value life years, LY: Life year, MI: myocardial infarction

**Note**: Negative health outcomes represent cardiovascular events averted with apixaban vs. comparators; negative costs represent cost savings for apixaban vs. comparators.

*Includes ischemic and hemorrhagic strokes

**Includes major gastrointestinal bleeds, intracranial hemorrhages, and non- gastrointestinal extracranial hemorrhages.

†Inclusive of acute event and chronic condition costs (excludes intervention costs).

### Table E4.20. Incremental Results for Rivaroxaban versus Warfarin and Dabigatran

| | Incremental Outcomes | | | | | |
|---|---|---|---|---|---|---|
| **Treatment** | **Strokes*** | **MIs** | **Major Bleeds**** | **Life Years** | **Equal-Value LYs** | **Non-Intervention Health Care Sector Costs†** |
| **Rivaroxaban vs. Warfarin** | -0.052 | -0.032 | 0.043 | 0.06 | 0.15 | -$1,400 |
| **Rivaroxaban vs. Dabigatran** | 0.032 | -0.105 | 0.015 | -0.008 | -0.008 | -$600 |

evLYs: equal-value life years, LY: Life year, MI: myocardial infarction

**Note**: Negative Lys and evLYs represent life years lost with rivaroxaban vs. comparators; negative incremental strokes, Mis, and major bleeds represent events averted with rivaroxaban vs. comparators; negative costs represent cost savings for rivaroxaban vs. comparators.

*Includes ischemic and hemorrhagic strokes

**Includes major gastrointestinal bleeds, intracranial hemorrhages, and non- gastrointestinal extracranial hemorrhages.

†Inclusive of acute event and chronic condition costs (excludes intervention costs).

### *Price Premium Threshold Analyses – Scenario Analysis 3: No Treatment Discontinuation*

**Table E4.21. Maximum Annualized Price Premium for Apixaban Above Warfarin and Dabigatran Pricing to Achieve a Range of Cost-Effectiveness Price Premium Thresholds**

| | $50,000/evLY | $100,000/evLY | $150,000/evLY | $200,000/evLY |
|---|---|---|---|---|
| **Apixaban vs. Warfarin** | $1,263 | $2,292 | $3,321 | $4,350 |
| **Apixaban vs. Dabigatran** | $182 | $227 | $271 | $316 |

evLYs: equal-value life years

**Table E4.22. Maximum Annualized Price Premium for Rivaroxaban Above Warfarin and Dabigatran Pricing to Achieve a Range of Cost-Effectiveness Price Premium Thresholds**

| | $50,000/evLY | $100,000/evLY | $150,000/evLY | $200,000/evLY |
|---|---|---|---|---|
| **Rivaroxaban vs. Warfarin** | $1,111 | $2,048 | $2,985 | $3,922 |
| **Rivaroxaban vs. Dabigatran** | No price premium* | No price premium* | No price premium* | No price premium* |

evLYs: equal-value life years

*Rivaroxaban resulted in fewer evLYs gained relative to dabigatran

## Scenario Analysis 4

### *No Treatment Efficacy Applied where HR CrIs From NMA Cross Null Effect*

Under a scenario where no treatment efficacy is applied to the interventions where inputs derived from the NMA are non-statistically significant (i.e., CrIs of HRs cross 1), both apixaban and rivaroxaban result in fewer evLYs gained and higher non-intervention health care sector costs relative to dabigatran. Under this scenario, findings suggest no price premium for apixaban and rivaroxaban relative to dabigatran. Compared to warfarin, findings suggest that a price premium, albeit reduced proportionally by the exclusion of non-significant findings for non-significant treatment effects.

**Table E4.23. Incremental Results for Apixaban versus Warfarin and Dabigatran – Scenario Analysis 4: No Treatment Efficacy Applied where HR CrIs from NMA Cross no Effect.**

| | Incremental Outcomes | | | | | |
|---|---|---|---|---|---|---|
| **Treatment** | **Strokes*** | **MIs** | **Major Bleeds**** | **Life Years** | **Equal-Value LYs** | **Non-Intervention Health Care Sector Costs†** |
| **Apixaban vs. Warfarin** | -0.052 | 0.002 | -0.045 | 0.07 | 0.15 | -$1,500 |
| **Apixaban vs. Dabigatran** | 0.028 | -0.001 | -0.078 | -0.01 | -0.01 | $100 |

evLYs: equal-value life years, LY: Life year, MI: myocardial infarction

**Note**: Negative health outcomes represent cardiovascular events averted with apixaban vs. comparators; negative costs represent cost savings for apixaban vs. comparators.

*Includes ischemic and hemorrhagic strokes

**Includes major gastrointestinal bleeds, intracranial hemorrhages, and non- gastrointestinal extracranial hemorrhages.

†Inclusive of acute event and chronic condition costs (excludes intervention costs).

**Table E4.24. Incremental Results for Rivaroxaban versus Warfarin and Dabigatran – Scenario Analysis 4: No Treatment Efficacy Applied where HR CrIs from NMA Cross no Effect.**

| | Incremental Outcomes | | | | | |
|---|---|---|---|---|---|---|
| **Treatment** | **Strokes*** | **Mis** | **Major Bleeds**** | **Life Years** | **Equal-Value LYs** | **Non-Intervention Health Care Sector Costs†** |
| **Rivaroxaban vs. Warfarin** | -0.052 | 0.002 | 0.038 | 0.05 | 0.14 | -$900 |
| **Rivaroxaban vs. Dabigatran** | 0.028 | -0.001 | 0.006 | -0.031 | -0.03 | $700 |

evLYs: equal-value life years, LY: Life year, MI: myocardial infarction

**Note**: Negative Lys and evLYs represent life years lost with rivaroxaban vs. comparators; negative incremental strokes, Mis, and major bleeds represent events averted with rivaroxaban vs. comparators; negative costs represent cost savings for rivaroxaban vs. comparators.

*Includes ischemic and hemorrhagic strokes

**Includes major gastrointestinal bleeds, intracranial hemorrhages, and non- gastrointestinal extracranial hemorrhages.

†Inclusive of acute event and chronic condition costs (excludes intervention costs).

***Price Premium Threshold Analyses – Scenario Analysis 4: No Treatment Efficacy Applied where HR CrIs from NMA Cross no Effect.***

**Table E4.25. Maximum Annualized Price Premium for Apixaban Above Warfarin and Dabigatran Pricing to Achieve a Range of Cost-Effectiveness Price Premium Thresholds**

| | $50,000/evLY | $100,000/evLY | $150,000/evLY | $200,000/evLY |
|---|---|---|---|---|
| **Apixaban vs. Warfarin** | $1,173 | $2,157 | $3,141 | $4,126 |
| **Apixaban vs. Dabigatran** | No price premium* | No price premium* | No price premium* | No price premium* |

evLYs: equal-value life years

*Apixaban resulted in fewer evLYs gained relative to dabigatran

**Table E4.26. Maximum Annualized Price Premium for Rivaroxaban Above Warfarin and Dabigatran Pricing to Achieve a Range of Cost-Effectiveness Price Premium Thresholds**

| | $50,000/evLY | $100,000/evLY | $150,000/evLY | $200,000/evLY |
|---|---|---|---|---|
| **Rivaroxaban vs. Warfarin** | $994 | $1,872 | $2,749 | $3,626 |
| **Rivaroxaban vs. Dabigatran** | No price premium* | No price premium* | No price premium* | No price premium* |

evLYs: equal-value life years

*Rivaroxaban resulted in fewer evLYs gained relative to dabigatran

# E5. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings and observational studies. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments. Model findings were also compared to relevant observational study data, where available.

Ray and colleagues 2021[98] reported rates of ischemic and hemorrhagic events, systemic embolism, intracranial hemorrhage, and fatal extracranial bleeding in a retrospective cohort study of US Medicare beneficiaries 65 years of age and older with atrial fibrillation being treated with rivaroxaban and apixaban. Due to differences in the categorization of events between our analysis and Ray 2021, it is difficult to directly compare the results. Ray 2021, for example, reported

unadjusted rates of major ischemic or hemorrhagic events of 14.5 and 14.8 per 1000 person-years, for apixaban and rivaroxaban, respectively. These rates included ischemic and hemorrhagic events and stroke, systemic embolism, other intracranial hemorrhage, and fatal extracranial bleeding. Using an average starting age of 65 years, our model generated rates of ischemic or hemorrhagic stroke of 14.7 and 14.8 per 1000 person-years, for apixaban and rivaroxaban, respectively. For other events, our model generated rates for systemic embolism (1.32 and 1.33 per 1000 patient-years), other ICH (1.2 and 2.0 per 1000 patient-years), and fatal major non-GI extracranial hemorrhage (0.13 and 0.19 per 1000 patient-years), for apixaban and rivaroxaban, respectively.

## Prior Economic Models

There are several published economic models evaluating the cost-effectiveness of DOACs and vitamin-K agonists (including warfarin).[80,84,99,100] Similar to the findings from our analysis, these studies generally favored improved health outcomes and lower costs of the DOACs compared to warfarin, and similar health outcomes when comparing DOACs to each other.

Model structures followed similar approaches using a Markov-model design simulating hypothetical patients or a cohort of patients with NVAF between health states. The majority of studies were conducted from a third-party payer perspective, over a lifetime time horizon and using published literature for clinical data and utility estimates.

Cost-effectiveness studies comparing DOACs (i.e., dabigatran, apixaban, rivaroxaban) varied in how events were modeled (i.e., as chronic vs. transient events), as well as in the classification of events, parameterization of cardiovascular event rates (i.e., using risk-based scores or not), and discontinuation assumptions. Modeled events consistently included ischemic stroke, hemorrhagic stroke, systemic embolism, myocardial infarction, and major bleeds (intracranial hemorrhage, GI bleed, and other major bleeds). Similar to our findings, the incremental health outcomes found in the US cost-effectiveness analyses included in our targeted literature search were marginal between apixaban or rivaroxaban and dabigatran. In the sensitivity analysis results reported, treatment efficacy, drug cost, and discontinuation assumptions were the most influential parameters.

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