



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

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In the development of this report, ICER's researchers consulted with clinical experts, patients, and an expert in health economic evaluation of cardiovascular disease and treatment. The following experts provided input that helped guide the ICER team as we shaped our scope and report.

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None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of this draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

Table of Contents

Executive Summary	1
1. Background and Prescribing Information	1
1.1. Introduction	1
1.2. Prescribing Information	1
2. Unmet Need	4
2.1. Qualitative Discussion	4
2.1.1. Patient and Caregiver Perspectives	4
2.2 Quantitative Discussion	4
3. Comparative Therapeutic Impact	7
3.1. Interventions and Therapeutic Alternatives	7
3.2. Comparative Clinical Effectiveness	7
3.2.1. Methods Overview	7
3.2.2. Results	9
3.2.3. Summary and Comment - Comparative Clinical Effectiveness.....	13
3.3. Comparative Effectiveness and Cost	15
3.3.1. Methods Overview	15
3.3.2. Results	17
3.3.3. Summary and Comment - Comparative Effectiveness and Cost	21
4. Comparative Effectiveness in Specific Populations.....	22
4.1. Comparative Clinical Effectiveness – Subgroup Analyses and Heterogeneity.....	22
4.1.1. End-Stage Renal Disease.....	22
4.1.2. Individuals with Disabilities	26
4.1.3. The Elderly.....	26
4.1.4. Individuals Who Are Terminally Ill	27
4.1.5. Children	27
4.2 Subgroup Uncertainties and Controversies	27
4.3 Comparative Cost Effectiveness – Subgroup Analyses.....	28
References	29

List of Acronyms and Abbreviations Used in this Report

AE	Adverse event
AF	Atrial fibrillation
AHRQ	Agency for Healthcare Research and Quality
BID	Twice a day
CAD	Coronary artery disease
CHADS₂	Congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)
CHA₂DS₂-VASC	Congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female)
CI	Confidence interval
CrI	Credible interval
CKD	Chronic kidney disease
CMS	Centers for Medicare & Medicaid Services
DOAC	Direct-acting oral anticoagulants
DVT	Deep vein thrombosis
ESRD	End-stage renal disease
evLY	Equal-value life years
FDA	Food and Drug Administration
GI	Gastrointestinal
HAS-BLED	Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage
ICH	Intracranial hemorrhage
INR	International normalized ratio
IRA	Inflation Reduction Act
LY	Life year
mg	Milligrams
MI	Myocardial infarction
NMA	Network meta-analysis
NR	Not reported
NVAF	Non-valvular atrial fibrillation
PAD	Peripheral artery disease
PE	Pulmonary embolism
QD	Once a day
RCTs	Randomized controlled trials
SD	Standard deviation
SE	Systemic embolism
VTE	Venous thromboembolic event

Executive Summary

As a result of the Inflation Reduction Act (IRA), the Centers for Medicare & Medicaid Services (CMS) will soon begin negotiating prices for certain high-expenditure drugs. This Special Report examines the direct-acting oral anticoagulants (DOACs) apixaban (Eliquis[®], Bristol Myers Squibb / Pfizer) and rivaroxaban (Xarelto[®], Janssen Pharmaceuticals, Inc.), two of the 10 drugs that CMS has selected for negotiation in the first round. The information in the report is tailored to reflect legislative specifications in the IRA and subsequent CMS guidance. It is not comprehensive but does include sections on multiple elements related to drug value, providing different options for translating evidence into initial offer prices and for assessing counteroffers from drug makers. We focused on the use of these two drugs for non-valvular atrial fibrillation (NVAF) since that represents the vast majority of use for drugs in this class. As clinical and cost comparators, we selected warfarin, an older generic medication that was the standard therapy for atrial fibrillation prior to the DOACs, and dabigatran, which is the first DOAC available as a generic medication, launched in 2022.

We sought patient input and were told of the impact of patients' ongoing fear of having a stroke and the potential for long term disability and loss of independence. We also heard about their lived experience with bleeding, including the time it takes to stop bleeding after cuts and common unsightly bruises without trauma. Some patients worry continually about more significant bleeding, leading them to limit their activities. As a quantitative measure of unmet need, we found the absolute equal value life years (evLY) shortfall for Medicare patients with NVAF was comparable to that observed with living with osteoporosis but substantially less than with chronic depression or Alzheimer's disease. The proportional evLY shortfall was comparable to that observed with ulcerative colitis, but substantially less than that with lupus nephritis or relapsing forms of multiple sclerosis.

To estimate the comparative therapeutic impact of apixaban and rivaroxaban in NVAF, we compared each drug to warfarin and to dabigatran. Both apixaban and rivaroxaban had direct randomized controlled trial evidence versus warfarin, but we needed to conduct a network meta-analysis to assess comparisons with dabigatran. This evidence, consistent with results from observational studies, demonstrates that DOACs improve outcomes for patients with NVAF compared to treatment with warfarin. The DOACs generally provide better protection against stroke and systemic embolism for a similar bleeding risk or equivalent protection with a lower bleeding risk. Across the trials, there was no evidence of effect modification by age in any of the outcomes we examined.

For apixaban, we have rated the evidence on comparative clinical effectiveness as demonstrating a high certainty of a small net benefit compared with warfarin (B rating). In the pivotal randomized trial there were statistically significant benefits for apixaban in preventing strokes/systemic embolism and major bleeding, but the absolute differences were small. There was also a small, but

non-significant trend towards lower total mortality. There were no important differences in adverse events or discontinuation rates. In addition, apixaban has the advantage of not requiring regular laboratory monitoring and dose adjustments that are required for safe and effective use of warfarin.

We judged the evidence on apixaban versus dabigatran to demonstrate moderate certainty of a comparable or small net benefit (C+ rating). There were no randomized trials directly comparing the two therapies, and in our network meta-analyses, there was no significant difference in the prevention of strokes/systemic embolism. There was a small, but statistically significant reduction in major bleeding, a finding also noted in a large, observational real-world study. There were no important differences in adverse events or discontinuation rates.

For rivaroxaban versus warfarin, the evidence was rated as demonstrating high certainty of a small net benefit (B rating). The pivotal randomized trial showed small, but significant benefits in the prevention of strokes/systemic embolism and major bleeding. There was also a small, but non-significant trend towards lower total mortality. There were no important differences in adverse events or discontinuation rates, and rivaroxaban has the advantage of not requiring regular laboratory monitoring and dose adjustments that are required for safe and effective use of warfarin.

For rivaroxaban versus dabigatran, however, we judge the evidence provides high certainty of only a comparable net benefit (C rating). In our network meta-analyses, there were no significant differences in the prevention of strokes/systemic embolism, bleeding rates, or total mortality. Furthermore, our decision-analytic model found the differences between the two DOACs in life-years and evLYs were near zero. In addition, in a large, observational real-world study the bleeding rates for rivaroxaban and dabigatran were similar.

We used decision-analytic modeling to assess the lifetime projected effectiveness and cost of apixaban and rivaroxaban compared to warfarin and dabigatran. Based on their comparative clinical effectiveness, we report price premiums at various cost-effectiveness thresholds for apixaban and rivaroxaban relative to the prices that CMS pays for comparator agents (warfarin and dabigatran) to inform drug price negotiations alongside other considerations. We do not stipulate a specific cost-effectiveness threshold as most appropriate but note for CMS that academic health economics research supports consideration of pricing between \$100,000-\$150,000 per evLYG.

For apixaban, calculated annual price premiums relative to the cost to CMS of warfarin are \$1,260 at a threshold of \$50,000/evLYG; \$2,290 at \$100,000/evLYG; \$3,320 at \$150,000/evLYG; and \$4,350 at \$200,000/evLYG. Annual price premiums for apixaban relative to dabigatran are: \$240 at \$50,000/evLYG; \$340 at \$100,000/evLYG; \$430 at \$150,000/evLYG; and \$530 at \$200,000/evLYG.

For rivaroxaban, annual price premiums relative to the cost to CMS of warfarin are \$1,110 at a threshold of \$50,000/evLYG; \$2,050 at \$100,000/evLYG; \$2,980 at \$150,000/evLYG; and \$3,920 at \$200,000/evLYG. Compared to dabigatran, however, rivaroxaban was not associated with health gains, and therefore decision analytic modeling confirmed that the evidence does not support a price premium for rivaroxaban above CMS pricing for dabigatran.

1. Background and Prescribing Information

1.1. Introduction

As a result of the Inflation Reduction Act (IRA), the Centers for Medicare & Medicaid Services (CMS) will soon begin negotiating prices for certain high-expenditure drugs. This Special Report examines the direct-acting oral anticoagulants (DOACs) apixaban (Eliquis[®], Bristol Myers Squibb / Pfizer) and rivaroxaban (Xarelto[®], Janssen Pharmaceuticals, Inc.), two of the 10 drugs that CMS has selected for negotiation in the first round. The information in the report is tailored to reflect legislative specifications in the IRA and subsequent CMS guidance. It is not comprehensive but does include sections on multiple elements related to drug value, providing different options for translating evidence into initial offer prices and for assessing counteroffers from drug makers. We focused on the use of these two drugs for non-valvular atrial fibrillation (NVAF) since that represents the vast majority of use for drugs in this class. As clinical and cost comparators, we selected warfarin, an older generic medication that was the standard therapy for atrial fibrillation prior to the DOACs, and dabigatran, which is the first DOAC available as a generic medication as of 2022.

These DOACs have several FDA indications. However, data suggest that the vast majority of DOAC use is for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation (NVAF) [IPD Analytics, 2021]. CMS will be able to use its own data to confirm the relative percentage of use of apixaban and rivaroxaban for different indications.

Specialty society guidelines (e.g., the American College of Chest Physicians [CHEST] guidelines) suggest that the use of these medications for NVAF be guided by the risk for stroke using one of two risk prediction tools: the CHADS₂ score (one point for each of congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and one point for stroke) or an updated version: the CHA₂DS₂-VASc score which adds three additional risk factors (vascular disease [coronary artery disease, peripheral artery disease, aortic atherosclerosis], age 65-74 years, and female sex). The benefits of stroke prevention with these medications are balanced by the risk for bleeding, which is most commonly estimated using the HAS-BLED score (one point for each risk factor: hypertension, abnormal renal and liver function, stroke, bleeding, labile INR [international normalized ratio], elderly, drugs or alcohol). For all three risk prediction tools, higher scores correspond to higher risk for the predicted outcome.

1.2. Prescribing Information

The prescribing information for the four drugs is summarized below.

- Apixaban (Eliquis[®], Bristol Myers Squibb / Pfizer)
 - Mechanism of Action: Factor Xa inhibitor

- Dose: 2.5 or 5 mg by mouth twice daily. For NVAF, 5 mg orally twice daily. In patients with at least two of the following characteristics: age greater than or equal to 80 years, body weight less than or equal to 60 kg, or serum creatinine greater than or equal to 1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily.
- Indication:
 - Reduce the risk of stroke and systemic embolism in patients with NVAF
 - Prophylaxis of deep vein thrombosis (DVT) in patients who have undergone knee or hip replacement
 - Treatment of DVT and pulmonary embolism (PE) and to reduce the risk of recurrent DVT and PE
- Rivaroxaban (Xarelto[®], Janssen Pharmaceuticals Inc.)
 - Mechanism of Action: Factor Xa inhibitor
 - Dose: 15 or 20 mg by mouth once daily with food
 - Indications:
 - To reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation
 - For treatment of DVT
 - For treatment of PE
 - For reduction in the risk of recurrence of DVT or PE
 - For the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery
 - For prophylaxis of venous thromboembolism (VTE) in acutely ill medical patients
 - To reduce the risk of major cardiovascular events in patients with CAD
 - To reduce the risk of major thrombotic vascular events in patients with PAD, including patients after recent lower extremity revascularization due to symptomatic PAD
 - For treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years
 - For thromboprophylaxis in pediatric patients two years and older with congenital heart disease after the Fontan procedure
- Warfarin
 - Mechanism of Action: Vitamin K antagonist
 - Dose: By mouth once daily with individualized dosing regimen based on INR results
 - Indications:
 - Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism
 - Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement

- Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction
- Dabigatran
 - Mechanism of Action: Direct thrombin inhibitor
 - Dose: 75 or 150 mg by mouth once daily. For NVAf: 150 mg orally, twice daily for patients with CrCl >30 mL/min or 75mg orally, twice daily for patients with CrCl 15-30 mL/min.
 - Generics first approved on March 11, 2020 (Alkem Labs LTD) and May 6, 2020 (Hetero Labs LTD), and launched in 2022
 - Indications:
 - To reduce the risk of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation
 - For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in adult patients who have been treated with a parenteral anticoagulant for 5-10 days
 - To reduce the risk of recurrence of DVT and PE in adult patients who have been previously treated
 - For the prophylaxis of DVT and PE in adult patients who have undergone hip replacement surgery
 - For the treatment of venous thromboembolic events (VTE) in pediatric patients 8 to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days
 - To reduce the risk of recurrence of VTE in pediatric patients 8 to less than 18 years of age who have been previously treated

2. Unmet Need

2.1. Qualitative Discussion

Revised guidance from CMS defines unmet need as “treating a disease or condition in cases where no other treatment options exist or existing treatments do not adequately address the disease or condition.”¹ DOACs improve outcomes in NVAf compared with warfarin as they generally provide better protection against stroke and systemic embolism for a similar bleeding risk or equivalent protection with a lower bleeding risk. For most patients, warfarin presents more burdens than DOACs, including the requirement for close laboratory monitoring, particularly at initiation. For many patients ongoing monitoring is required every few weeks. Warfarin also requires that patients adhere to a diet with a consistent intake of vitamin K, and initiation or discontinuation of many other medications will require a new phase of close laboratory monitoring and adjustment of warfarin dosing.

Even with the DOACs, however, all patients face a residual risk of strokes and systemic emboli, and all have risks of bleeding events ranging from minor to catastrophic.

2.1.1. Patient and Caregiver Perspectives

Patients told us that they did not like having to go to the laboratory at least once a month to monitor their INR when on warfarin. They also expressed frustration at limiting their intake of leafy green vegetables. Taking a pill once or twice a day without laboratory or dietary monitoring is much easier. However, for all four drugs, patients complained about bleeding, including unsightly bruises arising without trauma and prolonged bleeding after minor cuts. Some patients live in fear of more significant bleeding, leading them to limit activities (e.g., soccer, skiing, biking) that they had previously enjoyed but which now were felt to pose too great a risk. One patient told us about repeated emergency room visits at which he would urinate blood and blood clots due to complications arising from his prior radiation therapy for prostate cancer. Finally, we heard about the fear of having a stroke with its risk of long-term disability and loss of independence. Patients are aware that none of the available drugs are 100% effective at preventing strokes.

2.2 Quantitative Discussion

Decision-analytic models, often used to support estimates of value-based drug pricing, can also produce quantitative findings on unmet need. Calculations of proportional and absolute health “shortfall” are two different ways to estimate the reduction in lifetime health due to a condition compared with health in the age- and sex-matched general US population. Using the decision-

analytic model described in Section 3.3, we calculated proportional and absolute shortfalls in health using the equal value of life years (evLY) measure.²

CMS revised guidance states:

CMS requires respondents submitting information to indicate whether their submission contains information from studies that use measures that treat extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill. CMS also requests that respondents submitting information under 1194(e)(2) provide a short description of any cost-effectiveness measures included in the research they are submitting, and how they believe the data avoids treating extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill.

We attest that all measures of health used throughout this report, and specifically the evLY, do not treat extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill. The evLY treats the value of extended life of all individuals in exactly the same way, with each year of life gained from treatment valued identically. As such, the evLY is a nondiscriminatory alternative to the quality-adjusted life year (QALY). The evLY has served for many years as a bedrock of ICER's drug price benchmarks that are used by the Veterans Administration, Medicaid programs, and private insurers. In our public comments on the CMS draft guidance, we provided further rationale for why the evLY is consistent with the IRA and will be helpful to CMS in its deliberations.³

To quantify unmet need for patients with NVAf, we present evLY shortfall calculations for two treatments: apixaban and dabigatran. We chose to calculate health shortfalls despite apixaban treatment because it is the market leader in utilization and produced the best lifetime health outcomes in analytic modeling (see Section 3.3). We also chose to calculate health shortfalls for patients treated with dabigatran since those shortfalls represent the "unmet need" for patients not treated with one of the two drugs being negotiated.

To calculate the absolute evLY shortfall for each condition, we subtracted the lifetime undiscounted evLYs with apixaban treatment from the evLYs expected for the general population (calculated using age- and sex-adjusted estimates for mortality and a constant utility of 0.851 for quality of life). To calculate the proportional evLY shortfall, we divided the absolute evLY shortfall by the evLY life expectancy for the general population with the same age and sex distribution at baseline.

The undiscounted absolute shortfall for Medicare patients with NVAf treated with apixaban was 2.29 evLYs versus the general age- and sex-adjusted US population. The undiscounted proportional shortfall was $2.29/9.65 = 24\%$. The undiscounted absolute shortfall for Medicare patients with

NVAF treated with dabigatran was 2.31 evLYs versus the general age- and sex-adjusted US population. The undiscounted proportional shortfall was $2.31/9.65 = 24\%$. For context, as shown in Table 2.1, the absolute evLY shortfall for Medicare patients with NVAF treated with apixaban is comparable to that observed with osteoporosis but substantially less than with chronic depression or Alzheimer’s disease. The proportional shortfall was comparable to that for patients living with ulcerative colitis, but substantially less than for patients with lupus nephritis or relapsing forms of multiple sclerosis.

Table 2.1. Absolute and Proportional evLY Shortfall for Medicare Patients with NVAF Treated with Apixaban Compared to Other Conditions.

	Absolute evLY Shortfall	Proportional evLY Shortfall
Lupus nephritis	22.1	56%
Relapsing remitting multiple sclerosis	18.86	52%
Moderate to severe atopic dermatitis	9.92	28%
Chronic depression	9.65	32%
Ulcerative colitis	6.57	19%
Osteoporosis	2.61	19%
Nonvalvular atrial fibrillation	2.29	24%

evLY: equal-value life year

3. Comparative Therapeutic Impact

3.1. Interventions and Therapeutic Alternatives

To estimate the comparative therapeutic impact of apixaban and rivaroxaban in NVAF, we compared each drug to both warfarin and dabigatran.

3.2. Comparative Clinical Effectiveness

3.2.1. Methods Overview

We focused on patient-important outcomes and adverse events, including stroke/systemic embolism (SE), myocardial infarction (MI), bleeding rates, and all-cause mortality. Outcome definitions are reported in Supplement Table A1.⁴ For comparisons with warfarin, we focused on head-to-head randomized controlled trials (RCTs) with the interventions of interest. For comparisons with dabigatran, we conducted Bayesian network meta-analyses (NMAs) of RCTs. We also reviewed evidence from high-quality observational studies on long-term outcomes and harms. The full scope and procedures for the systematic literature review are detailed in the Supplement.

Evidence Base

We examined direct evidence comparing apixaban and rivaroxaban with warfarin from the ARISTOTLE and ROCKET AF trials, respectively. We used the RE-LY trial of dabigatran versus warfarin to conduct indirect analyses comparing the DOACs. These trials are described in the Supplement and in Table 3.1.

Table 3.1. Overview of Main Trials

	Arms	Arm size	Study Duration	Baseline Characteristics					
				Age, mean (SD)	% Male	% White	CHADS ₂ , mean (SD)	CHA ₂ DS ₂ -VASc, mean (SD)	HAS-BLED, mean (SD)
ARISTOTLE	Apixaban§	9120	1.8 years*	69.1 (9.61)	64.5	82.6	2.1 (1.1)	3.7 (1.5)	1.8 (1.05)
	Warfarin‡	9081		69.0 (9.74)	65	82.5	2.1 (1.1)	3.7 (1.5)	1.8 (1.06)
ROCKET AF	Rivaroxaban⌘	7131	1.6 years*	73 (65-78)†	60.3	82.3	3.5 (0.94)	4.8 (1.3)	2.8 (0.9)
	Warfarin‡	7133		73 (65-78)†	60.3	82.9	3.5 (0.95)	4.8 (1.3)	
RE-LY	Dabigatran**	6076	2 years*	71.5 (8.8)	63.2	70.2	2.2 (1.2)	NR	NR
	Warfarin‡	6022		71.6 (8.6)	63.3	69.8	2.1 (1.1)	NR	NR

AF: atrial fibrillation, CHADS₂: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), CHA₂DS₂-VASc: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female), HAS-BLED: Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage, NR: not reported, SD: standard deviation, %: percent

*median

†median(IQR)

‡INR 2-3 dose

§Apixaban 5mg or 2.5 twice daily

⌘Rivaroxaban 20 mg or 15 mg once daily

**Dabigatran 150 mg twice daily

3.2.2. Results

Clinical Benefits

Apixaban

Direct Evidence: Apixaban versus Warfarin

In the ARISTOTLE trial, patients receiving apixaban had a lower rate of stroke/SE (1.27% per year) compared to those in the warfarin group (1.6%) (HR: 0.79; 95% CI: 0.66 to 0.95; p=0.02). Risk of MI with apixaban was not statistically significantly different from that with warfarin (HR: 0.88; 95% CI: 0.66 to 1.17; p=0.37). The rate of all-cause mortality was lower in the apixaban group compared to the warfarin group (HR: 0.89; 95% CI: 0.80 to 0.998; p=0.047).⁵

Indirect Evidence: Apixaban versus Dabigatran

Tables 3.2 and 3.3 provide point estimates of the relative effect of apixaban and rivaroxaban versus dabigatran and warfarin for the NMA outcomes. Risk of stroke/SE with apixaban was not statistically significantly different from that with dabigatran (HR: 1.2; 95% CrI: 0.9 to 1.59). In contrast, apixaban was more efficacious than dabigatran in reducing MI (HR: 0.64; 95% CrI: 0.41 to 0.98). There was no difference in all-cause mortality (HR: 1.01; 95% CrI: 0.85 to 1.2).

Rivaroxaban

Direct Evidence: Rivaroxaban versus Warfarin

In the ROCKET AF trial, patients receiving rivaroxaban had a lower rate of stroke/SE (1.7% per year) compared to those in the warfarin group (2.2%) (HR: 0.79; 95% CI: 0.66 to 0.96; p=0.02). The risk of MI and all-cause mortality were not statistically significantly lower, but the point estimates favored rivaroxaban (MI HR: 0.81; 95% CI: 0.63 to 1.06; p=0.12; mortality HR: 0.85; 95% CI: 0.70 to 1.02; p=0.07).

Indirect Evidence: Rivaroxaban versus Dabigatran

The risk of stroke/SE with rivaroxaban was not statistically significantly different from that with dabigatran (HR: 1.2; 95% CrI: 0.89 to 1.6); however, the risk of MI was lower (HR: 0.59; 95% CrI: 0.38 to 0.9). There was no statistically significant difference in all-cause mortality (HR: 0.97; 95% CrI: 0.77 to 1.21).

All other outcomes are reported in Supplement D.⁴

Table 3.2. Network Meta-Analysis Results for Stroke/Systemic Embolism.

Apixaban (5 mg or 2.5 mg BID)			
1 (0.76, 1.31)	Rivaroxaban (20 mg or 15 mg QD)		
1.2 (0.9, 1.59)	1.2 (0.89, 1.6)	Dabigatran (150 mg BID)	
0.79 (0.66, 0.95)	0.79 (0.65, 0.96)	0.66 (0.53, 0.82)	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 3.3. Network Meta-Analysis Results for Myocardial Infarction.

Apixaban (5 mg or 2.5 mg BID)			
1.09 (0.73, 1.61)	Rivaroxaban (20 mg or 15 mg QD)		
0.64 (0.41, 0.98)	0.59 (0.38, 0.9)	Dabigatran (150 mg BID)	
0.88 (0.66, 1.17)	0.81 (0.62, 1.06)	1.38 (1, 1.91)	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.

Harms

Apixaban

In the ARISTOTLE trial, the rate of major bleeding was lower in the apixaban group compared to the warfarin group (2.13% vs. 3.09% per year, HR: 0.69; 95% CI: 0.60 to 0.80; $p < 0.001$), as was intracranial bleeding (HR: 0.42; 95% CI: 0.30 to 0.58), though absolute rates were small.⁵ Estimates from the NMA reported that the risk of major bleeding was lower with apixaban compared to dabigatran (HR: 0.74; 95% CrI: 0.61 to 0.91), but there was no difference for intracranial bleeding (HR: 1.05; 95% CrI: 0.63 to 1.77). See Table 3.5 and Supplement Table D2.5.⁴

Patients in the apixaban arm of ARISTOTLE were less likely to discontinue the study drug (Table 3.4), but the absolute difference was small. Results of the NMA showed that apixaban had lower total discontinuation and discontinuation due to AEs compared to dabigatran (Supplement Tables D2.9 and D2.10).

Rivaroxaban

In the ROCKET AF trial, the rate of major bleeding was similar in the rivaroxaban and warfarin groups. Patients receiving rivaroxaban had a lower rate of intracranial bleeding (HR: 0.67; 95% CI: 0.47 to 0.93), though absolute rates were small.⁶ The NMA results for rivaroxaban versus dabigatran showed no statistically significant difference in major bleeding (HR: 1.12; 95% CrI: 0.92 to 1.37) or intracranial bleeding (HR: 1.67; 95% CrI: 0.99 to 2.82).

Patients in the rivaroxaban arm of ROCKET AF were more likely to discontinue the study drug and discontinue due to AEs compared with warfarin, though the absolute differences were small. The NMA results for rivaroxaban versus dabigatran showed lower rates for total discontinuation and discontinuation due to AEs for rivaroxaban.

See Supplement D for additional NMA results for harms and discontinuation.

Table 3.4. Discontinuations of DOACs versus Warfarin.

	All discontinuations	Discontinuation due to AEs
ARISTOTLE	Apixaban: 21.4%* Warfarin: 23.4%	Apixaban: 7.6% Warfarin: 8.4%
ROCKET AF	Rivaroxaban: 23.7%* Warfarin: 22.2%	Rivaroxaban: 8.3% Warfarin: 7%
RE-LY	Dabigatran: 17%* Warfarin: 12%	Dabigatran: 6.2% Warfarin: 3.3%

AEs: adverse events, AF: atrial fibrillation

* Difference between the groups met statistical significance, p<0.05.

Table 3.5. Network Meta-Analysis Results for Major Bleeding.

Apixaban (5 mg or 2.5 mg BID)			
0.66 (0.54, 0.81)	Rivaroxaban (20 mg or 15 mg QD)		
0.74 (0.61, 0.91)	1.12 (0.92, 1.37)	Dabigatran (150 mg BID)	
0.69 (0.6, 0.8)	1.04 (0.9, 1.2)	0.93 (0.81, 1.07)	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.

Observational Data

Two large high-quality observational studies were identified that examined long-term safety and effectiveness of apixaban and rivaroxaban.⁷⁻⁹ These studies used propensity scoring to account for confounding, and are described in detail in Supplement D.⁴

Findings in Lau et al. (N=527,226) comparing both drugs to dabigatran in a multinational sample (US, UK, France, and Germany) were generally similar to those in our NMAs with the following exceptions⁷:

- Lower relative major gastrointestinal bleeding risk with apixaban (HR: 0.81; 95% CI: 0.70 to 0.94)

- Higher relative point estimates for all-cause mortality with apixaban (HR: 1.22; 95% CI: 0.94 to 1.60) and with rivaroxaban (HR: 1.16; 95% CI: 0.89-1.59), although these were non-significant with relatively wide confidence intervals.
- Higher relative major gastrointestinal bleeding risk with rivaroxaban (HR: 1.15; 95% CI: 1.04 to 1.28)

Findings in Chan et al. (N=106,044) comparing both drugs to warfarin in a Taiwanese sample found both apixaban and rivaroxaban were associated with a significantly higher risk of interstitial lung disease (ILD) compared to warfarin, though the absolute risk was low (0.29 per 100 person years with DOACs, 0.17 per 100 person years with warfarin).⁸ Observational studies cannot prove causality, but ILD cannot be ruled out as a potential rare complication of DOACs.

Findings from Graham et al. (N=134,414) comparing dabigatran and warfarin (comparators of interest) in a sample of Medicare patients are reported in the supplement.^{4,9}

Uncertainty and Controversies

Indirect analyses were necessary to compare apixaban and rivaroxaban to dabigatran. This increases the uncertainty in the findings. Our NMA results are similar to those observed in the large observational study identified that compares the DOACs, increasing our confidence in the results.⁷

Patients enrolled in the RCTs had some baseline differences compared to a Medicare population. Those in the RCTs had had higher rates of heart failure and prior stroke and MI, and patients in ARISTOTLE and RE-LY were slightly younger than a Medicare population as these trials included patients under the age of 65.¹⁰

Uncertainties regarding findings for key patient subgroups are discussed in Section 4.

3.2.3. Summary and Comment - Comparative Clinical Effectiveness

Summary evidence ratings are shown in Table 3.6. For apixaban, we have rated the evidence on comparative clinical effectiveness as demonstrating a high certainty of a small net benefit compared with warfarin (B rating). In the pivotal randomized trial there were statistically significant benefits for apixaban in preventing strokes/systemic embolism and major bleeding, but the absolute differences were small. There was also a small, but non-significant trend towards lower total mortality. There were no important differences in adverse events or discontinuation rates. In addition, apixaban has the advantage of not requiring regular laboratory monitoring and dose adjustments that are required for safe and effective use of warfarin.

We judged the evidence on apixaban versus dabigatran to demonstrate moderate certainty of a comparable or small net benefit (C+ rating). There were no randomized trials directly comparing the two therapies, and in our network meta-analyses, there was no significant difference in the

prevention of strokes/systemic embolism. There was a small, but statistically significant reduction in major bleeding, a finding also noted in a large, observational real-world study. There were no important differences in adverse events or discontinuation rates.

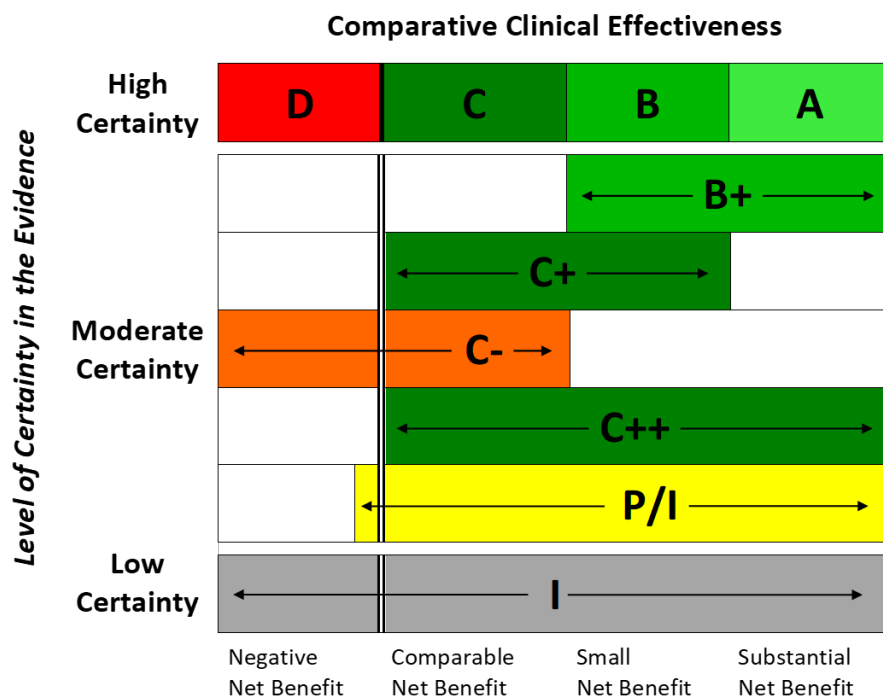
For rivaroxaban versus warfarin, the evidence was rated as demonstrating high certainty of a small net benefit (B rating). The pivotal randomized trial showed small, but significant benefits in the prevention of strokes/systemic embolism and major bleeding. There was also a small, but non-significant trend towards lower total mortality. There were no important differences in adverse events or discontinuation rates, and rivaroxaban has the advantage of not requiring regular laboratory monitoring and dose adjustments that are required for safe and effective use of warfarin.

For rivaroxaban versus dabigatran, however, we judge the evidence provides high certainty of only a comparable net benefit (C rating). In our network meta-analyses, there were no significant differences in the prevention of strokes/systemic embolism, bleeding rates, or total mortality. Furthermore, our decision-analytic model found the differences between the two DOACs in life-years and eVLYs were near zero. In addition, in a large observational real-world study the bleeding rates for rivaroxaban and dabigatran were similar.⁵

Table 3.6 Evidence Ratings

Treatment	Comparator	Evidence Rating
Apixaban	Warfarin	B
Apixaban	Dabigatran	C+
Rivaroxaban	Warfarin	B
Rivaroxaban	Dabigatran	C

Figure 3.1. ICER Evidence Rating Matrix (<https://icer.org/evidence-rating-matrix/>).



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable" - High certainty of a comparable net health benefit
D = "Negative" - High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Incremental" - Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit
C++ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

3.3. Comparative Effectiveness and Cost

3.3.1. Methods Overview

We developed a *de novo* decision-analytic model to assess the lifetime health outcomes and costs of apixaban and rivaroxaban relative to warfarin and dabigatran. If desired, ICER can provide an executable model file to CMS. Health outcomes included cardiovascular events (i.e., number of strokes, MIs, and major bleeds), life years, and equal value life years (evLYs). Importantly, evLYs are a measure of health that captures the impact of treatment on both length of life and quality of life while weighing the value of extended life of all individuals in exactly the same way. In doing so, the

evLY eliminates any risk of valuing extended life lower for conditions in which people are elderly, disabled, or terminally ill. Additional details on the evLY can be found in Section 2.2.

All patients in the model had NVAf and could be in a health state of “well,” chronic post-stroke (ischemic and hemorrhagic), chronic post-MI, or death. 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 a stroke or MI who survived 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. All patients could transition 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). Health outcomes and costs were discounted at 3% per year.

Key model inputs included clinical event probabilities, quality of life values, and health care costs. Where available, Medicare-specific costs based on the Agency for Healthcare Research and Quality’s (AHRQ) Healthcare Cost and Utilization Project (HCUP) were used. Productivity changes and other non-intervention indirect costs were included in a modified societal perspective analysis. Treatment effectiveness was estimated using findings from the clinical review, informed by a network meta-analysis.

The model included non-intervention health care sector costs, including chronic NVAf-related condition costs, acute cardiovascular event-related costs, and chronic condition costs for post-stroke and post-MI-related care. Generic versions of dabigatran were first launched in the US in 2022.¹¹ Because of the recency of launch, no stable data on the effective Medicare price for dabigatran are available publicly. The model results therefore are framed as price premiums and, as such, can be informative regardless of the prices CMS determines are paid by Medicare for warfarin and dabigatran. For the same reason, and because the direction of the treatment efficacy varies by cardiovascular event, the presented model results do not include a cost-consequence analysis (e.g., cost per stroke averted).

Detailed methods and results are presented in the Supplement.⁴

3.3.2. Results

Projected Discounted Lifetime Health Outcomes and Non-Intervention Healthcare Sector Costs for Apixaban and Rivaroxaban versus Warfarin and Dabigatran

Total lifetime discounted health outcomes and non-intervention health care sector costs (inclusive of acute event and chronic condition costs) for each intervention and comparator are shown in Table 3.7.

Apixaban versus Warfarin

Compared to warfarin, apixaban resulted in fewer strokes, MIs, and major bleeds. Overall, apixaban resulted in more life years and evLYs gained and lower non-intervention health care sector costs.

Apixaban versus Dabigatran

Compared to dabigatran, apixaban resulted in fewer MIs and major bleeds, and a greater number of strokes. Overall, apixaban resulted in more life years and evLYs gained and lower non-intervention health care sector costs over the lifetime of the model.

Rivaroxaban versus Warfarin

Compared to warfarin, rivaroxaban resulted in fewer strokes and MIs, and a greater number of major bleeds. Overall, rivaroxaban resulted in more life years and evLYs gained, and lower non-intervention health care sector costs over the lifetime of the model.

Rivaroxaban versus Dabigatran

Compared to dabigatran, rivaroxaban resulted in fewer MIs and a higher number of strokes and major bleeds. Overall, rivaroxaban resulted in the same life years and evLYs gained, with marginally lower non-intervention health care sector costs over the lifetime of the model.

Table 3.7. Lifetime Health Outcomes and Annualized Average Non-Intervention Health Care Sector Costs by Treatment Strategy

Treatment	Strokes*	MIs	Major Bleeds**	Life Years (Discounted)	evLYs (Discounted)	Annualized non-intervention health care sector costs† (Discounted)
Apixaban	0.184	0.148	0.170	7.82	6.15	\$40,600
Rivaroxaban	0.184	0.136	0.269	7.80	6.14	\$40,700
Dabigatran	0.155	0.237	0.253	7.80	6.14	\$40,800
Warfarin	0.236	0.167	0.227	7.74	5.99	\$41,200

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

*Includes ischemic and hemorrhagic strokes

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

†Inclusive of acute event and chronic condition costs estimated over the lifetime of the model and displayed as an annualized average for each treatment strategy (excludes intervention costs).

Table 3.8. Incremental Lifetime Results for Apixaban and Rivaroxaban versus Warfarin and Dabigatran

Treatment	Incremental Lifetime Outcomes					Non-intervention health care sector costs† (Discounted)
	Strokes*	MIs	Major Bleeds**	Life Years (Discounted)	evLYs (Discounted)	
Apixaban vs. Warfarin	-0.052	-0.019	-0.057	0.08	0.16	-\$1,800
Apixaban vs. Dabigatran	0.028	-0.089	-0.083	0.01	0.02	-\$1,100
Rivaroxaban vs. Warfarin	-0.052	-0.032	0.042	0.06	0.14	-\$1,300
Rivaroxaban vs. Dabigatran	0.028	-0.101	0.016	-0.005	-0.001	-\$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

We framed our price threshold calculations as the price premiums for apixaban and for rivaroxaban over whatever the annualized price paid for warfarin and dabigatran may be (Table 3.9).

Considering a range of cost-effectiveness thresholds is recommended, and the most commonly suggested thresholds in the US are \$100,000 and \$150,000 per QALY.^{12,13} We used these same thresholds when substituting the evLYG for the QALY, which would have the effect of increasing the premium prices at each threshold. We have included a wider range of thresholds to provide CMS with additional pricing points for consideration.

Since CMS may want to consider comparative results for apixaban and rivaroxaban versus both warfarin and dabigatran, we present threshold price results versus both these potential comparators. The results are incremental to the price of the comparator agent, and as such, the results remain relevant regardless of whatever price CMS might pay for warfarin or dabigatran.

Annual price premiums are shown in Table 3.9. Thirty-day price premiums above warfarin and dabigatran pricing can be calculated by dividing the annualized price by 12.175. For apixaban, calculated annual price premiums relative to the cost to CMS of warfarin are \$1,260 at a threshold of \$50,000/evLYG; \$2,290 at \$100,000/evLYG; \$3,320 at \$150,000/evLYG; and \$4,350 at \$200,000/evLYG. Annual price premiums for apixaban relative to dabigatran are: \$240 at \$50,000/evLYG; \$340 at \$100,000/evLYG; \$430 at \$150,000/evLYG; and \$530 at \$200,000/evLYG.

For rivaroxaban, annual price premiums relative to the cost to CMS of warfarin are \$1,110 at a threshold of \$50,000/evLYG; \$2,050 at \$100,000/evLYG; \$2,980 at \$150,000/evLYG; and \$3,920 at \$200,000/evLYG. Compared to dabigatran, however, rivaroxaban was not associated with health gains, and therefore decision analytic modeling confirmed that the evidence does not support a price premium for rivaroxaban above CMS pricing for dabigatran.

Table 3.9. Maximum annualized price premium for apixaban and 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
Apixaban vs. Warfarin	\$1,260	\$2,290	\$3,320	\$4,350
Apixaban vs. Dabigatran	\$240	\$340	\$430	\$530
Rivaroxaban vs. Warfarin	\$1,110	\$2,050	\$2,980	\$3,920
Rivaroxaban vs. Dabigatran	No price premium*	No price premium*	No price premium*	No price premium*

evLYs: equal-value life years

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

*Rivaroxaban resulted in fewer evLYs gained relative to dabigatran.

Uncertainty and Controversies

No measure of health gain, including individual cardiovascular events or summary measures such as the evLYG, captures all information important in value considerations. Additional considerations such as unmet need are relevant to consider in discussions on value and pricing negotiations.

We recognize that quality of life associated with acute cardiovascular events and their longer-term sequelae vary across individual patients. Our modeling approach aggregates these impacts to find an average projected lifetime benefit to inform threshold pricing estimates. Given that CMS is seeking a single price for consideration as an initial offer, it is reasonable for an aggregated population-based approach to be used.

No publicly available net price for apixaban and rivaroxaban from the Medicare population was available for our analysis; therefore, we are unable to compare our results to current Medicare prices for these agents.

Sensitivity Analyses

Deterministic and probabilistic sensitivity analyses were conducted. In the Supplement, we present independent tornado diagrams for incremental non-intervention health care sector costs and incremental evLYGs for each intervention versus warfarin and dabigatran.⁴ Based on probabilistic analyses, model findings were robust to uncertainties in parameter estimates.

Scenario Analyses

We conducted a scenario analysis from a modified societal perspective which included warfarin monitoring time and associated costs, and costs related to patient and caregiver productivity loss due to illness. The societal perspective analysis is considered “modified” because it does not include broader societal impacts such as effects on education, tax payments or benefits, or environmental impact. The modified societal perspective analysis supported annual value-based price premiums that were approximately \$120 higher for apixaban when compared to dabigatran across the evaluated thresholds; annual value-based price premiums were \$150 higher for rivaroxaban when compared to dabigatran.

Detailed results from all scenario analyses can be found in the Supplement.⁴

Model Validation

Details related to model validation can be found in the Supplement.⁴

3.3.3. Summary and Comment - Comparative Effectiveness and Cost

We projected lifetime health outcomes and costs for a population of Medicare patients with NVAf receiving apixaban, rivaroxaban, dabigatran, or warfarin. There was an observed health benefit achieved for apixaban and rivaroxaban compared to warfarin, and marginal health gains for apixaban but not for rivaroxaban when compared to dabigatran. The marginal health benefits observed across DOACs is partially explained by the occurrence of competing events. For example, based on the network meta-analysis, dabigatran has a numerically favorable stroke risk profile, and a less favorable MI risk profile compared to apixaban and rivaroxaban. When considering the impact of these events on differences in life years and evLYs (which considers health related quality of life impacts and survival), very similar overall health benefits are observed between DOACs. In addition to the health differences observed, threshold pricing estimates include consideration for the cost-offsets observed between intervention and comparator.

In summary, both apixaban and rivaroxaban have demonstrated clinical benefits over warfarin that support a range of premium pricing options. Modeling of all health and cost effects showed incremental benefits for apixaban (greater evLYs and lower costs) compared to dabigatran, suggesting that a price premium, albeit marginal, would be reasonable. For rivaroxaban, the modeled health outcomes suggest overall comparable clinical effectiveness versus dabigatran, and as such, reference pricing to dabigatran could be considered a reasonable policy application of the cost-effectiveness findings.

4. Comparative Effectiveness in Specific Populations

4.1. Comparative Clinical Effectiveness – Subgroup Analyses and Heterogeneity

To evaluate subgroups of interest and heterogeneity, we evaluated subgroup analyses conducted in the three main trials reported above and one observational study from Lau et al.⁷ Subgroup analyses for the RE-LY trial, comparing dabigatran and warfarin, are reported in the Supplement.⁴ We also identified two trials that specifically enrolled patients with NVAf and end-stage renal disease (ESRD).^{14,15} Ultimately, there are no persuasive findings in the clinical evidence of major differences in the balance of risks and benefits for patients with ESRD, the elderly, or those with terminal illness (e.g., cancer). There is currently no reported evidence that examined differences in risk and benefits for children or those with disabilities. The studies are described in detail below.

4.1.1. End-Stage Renal Disease

Comparative Clinical Effectiveness - Trials in Patients with ESRD

Evidence informing our review of the interventions of interest in those with ESRD were derived from two Phase IV clinical trials: RENAL AF and Valkyrie.^{14,15} Both ESRD trials were small and underpowered to detect comparative efficacy of the intervention of interest versus the comparator. Overall, there are no persuasive findings in the clinical evidence to suggest major differences in the balance of risks and benefits for patients with ESRD. The studies are described in detail below.

RENAL AF was a Phase IV open-label, blinded-outcome RCT that evaluated the efficacy of oral apixaban 5 mg twice daily (2.5 mg twice daily if weight ≤ 60 kg or age ≥ 80 years) versus warfarin (INR 2-3) in those with AF and ESRD in the US.¹⁴ RENAL AF was designed to test for noninferiority on the primary outcome (major or clinically relevant nonmajor bleeding) and superiority for primary and secondary outcomes, including stroke/SE and death. There were challenges with participant recruitment and this study was ultimately terminated early, which meant that the study was underpowered to detect a statistical effect. Patients were followed for a median of 330 (apixaban) or 340 (warfarin) days. See Supplement D2 for further description of the planned analysis and termination. Full inclusion and exclusion criteria for both ESRD trials are described in Supplement Table D3.1., and baseline characteristics are outlined in Table 4.1. and Supplement Table D3.30. Like ARISTOTLE, a greater proportion of patients were younger (37% were <65 years of age). Patients were more racially diverse (45% identified as Black) and were more likely to have heart failure, hypertension, and diabetes as compared to the three RCTs and the other ESRD trial.

Rates of stroke, SE, and bleeding-related mortality were similar among those in the apixaban or warfarin group at one year.¹⁴ In contrast, rates of major or non-major clinically relevant bleeding were high overall and numerically higher in the apixaban group (32%) versus warfarin group (26%) as was all-cause mortality (26% vs. 18% in apixaban versus warfarin, respectively). See Supplement Tables D3.31 and D3.32. However, due to the small sample size (N=154), the authors were not able to draw any conclusions from the clinical data.

Valkyrie was a Phase IV open-label RCT that evaluated the efficacy of oral rivaroxaban 10 mg once daily versus warfarin (INR 2-3) in those with NVAF on chronic hemodialysis.¹⁵ There was an additional group who received rivaroxaban and menquinone-7 (MK-7). As this intervention was not one of our interventions of interest, we did not include the results of this group in our report. 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 at a median of 1.8 years. Compared to the RCTs, patients were older with a median age of 80, were more likely to have had a prior stroke or MI, and had a higher CHA₂DS₂-VAS score; although the mean was comparable to the ROCKET AF trial.

The primary clinical endpoint for the Valkyrie study was a composite of fatal cardiovascular disease and nonfatal stroke, cardiac events, and other vascular events at a median of 1.8 years. The rate of the composite outcome was significantly lower in the rivaroxaban compared to the warfarin group (HR: 0.34; 95% CI: 0.19 to 0.61; p=0.0003).¹⁶ The rate of all-cause death and any bleeding events was numerically lower in the rivaroxaban group compared to the warfarin group. Stroke did not differ between the groups. See Supplement Table D3.31. Major bleeding outcomes were only available for the two rivaroxaban groups combined (rivaroxaban alone and rivaroxaban plus vitamin K2). Like RENAL AF, the study was not powered to detect clinical benefit and thus results of these two ESRD trials should be interpreted with caution.

As noted above, both ESRD trials were small and underpowered to detect comparative efficacy of the intervention of interest versus the comparator. There are no persuasive findings in the clinical literature suggesting major differences in the overall balance of risks and benefits for patients with ESRD.

Table 4.1. Overview of ESRD Studies

	Arms	Arm size	Study Duration	Baseline Characteristics					
				Age, mean (SD)	% Male	% White	CHADS ₂ , mean (SD)	CHA ₂ DS ₂ -VASc, mean (SD)	HAS-BLED, mean (SD)
Valkyrie	Rivaroxaban α	46	1.88 years*	79.9 (74.4-83.9) \ddagger	76.1	NR	NR	4.7 (1.4)	4.7 (1.4)
	Warfarin \ddagger	44		80.3 (71.5-84.3) \ddagger	56.8	NR	NR	4.8 (1.5)	4.8 (1.5)
RENAL-AF	Apixaban $\#$	82	0.93 years* \dagger	69.0 (61.0, 76.0) \ddagger	58.5	52.4	NR	NR	NR
	Warfarin \S	72		68.0 (60.5, 72.5) \ddagger	69.4	50	NR	NR	NR

AF: atrial fibrillation, CHADS₂: congestive heart failure, hypertension, age \geq 75 (doubled), diabetes, stroke (doubled), CHA₂DS₂-VASc: congestive heart failure, hypertension, age \geq 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female), HAS-BLED: Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage, NR: not reported, SD: standard deviation, %: percent

*median

\dagger Treatment was planned for up to 15 months but the study was terminated early due to a lower recruitment rate.

\ddagger median(IQR)

\S INR 2-3 dose

$\#$ Apixaban 5mg or 2.5 twice daily

α Rivaroxaban 10 mg once daily

Within-Trial Subgroups for ESRD

Within-trial subgroup analyses examined the effect of renal function or chronic kidney disease, as a proxy for ESRD, on treatment benefit. There were no consistent subgroup effects for renal function. This was especially true when using a continuous assessment of renal function, which may be considered a more sensitive variable than a categorical assessment.

There was no effect modification by renal function reported across subgroup analyses of stroke/SE, MI, or all-cause mortality of the ARISTOTLE trial.^{5,17-19} See Supplement Tables D3.5-6, and D3.11-12. There was a suggestion of a greater reduction in major bleeding in patients with moderate or severe renal impairment (creatinine clearance [CrCl] \leq 50 ml/min) in those who received apixaban versus warfarin (p value for interaction = 0.03).⁵ In a subsequent analyses of those with advanced chronic kidney disease (CrCl 25 to 30 mL/min), there were fewer major bleeding events in those in the apixaban group, compared to warfarin, but no difference in intracranial bleeding.¹⁷ However, a secondary data analysis that used worsening renal function as a continuous independent variable reported no effect modification by renal function on any of the outcomes.¹⁸ Renal function as a continuous variable could be considered a more sensitive measure to examine treatment modification and overcomes the issue of interpreting different categories of renal function that have been used across analyses.

Differences in results when using categories versus continuous variables were also found in subgroup analyses of the ROCKET AF trial. In several analyses that categorized patients into renal function groups (e.g., 30-49, > 50; or < 50, 50-80, > 80 CrCl mL/min), there was no interaction between renal function and treatment group for major or non-major bleeding, major bleeding alone, stroke/SE, and ischemic or hemorrhagic stroke.^{6,20,21} However, when median CrCl was used as a variable, Piccini et al. (2014) reported that those in the warfarin group who had a major bleed had lower CrCl at baseline as compared to patients in the rivaroxaban group.²² This effect modification was not replicated by Fordyce et al. (2016).²³ Fordyce et al. identified patients who experienced a worsening of renal function during the study (> 20% decrease in CrCl from screening to any point in the trial) and reported no treatment modification by worsening renal function for any bleeding, MI, or death. However, those who had worsening renal function and were given rivaroxaban had a larger reduction in stroke/SE compared to those given warfarin (HR: 0.50; 95% CI: 0.27 to 0.93; p=0.05). See Supplement Tables D3.15, D.17, and D3.21-D3.25. The subgroup analyses from this trial were inconsistent. There are also issues with interpretation when including independent variables that change over the course of a study (e.g., worsening renal function) as it is unclear how the intervention or other uncontrolled factors in the trial may influence this relationship.

The observational study from Lau et al. (2022) examined the primary endpoint (stroke/SE) and safety endpoints (bleeding and all-cause mortality) in patients with chronic kidney disease (CKD) for the comparisons of interest (apixaban versus dabigatran; dabigatran versus rivaroxaban).⁷ See

Supplement Table D3.39. Consistent with the overall sample of the Lau et al. study, the authors reported similar rates of stroke/SE, intracranial hemorrhage, and all-cause mortality in those with CKD. For GI bleeding, the findings were consistent with the overall sample for the apixaban versus dabigatran comparison. However, when comparing dabigatran versus rivaroxaban, the rates of GI bleeding were similar in those with CKD, suggesting less benefit from dabigatran in reducing GI bleeding in those with CKD. The authors note that apixaban may be more favorable in reducing the risk of GI bleeding in those with CKD.

4.1.2. Individuals with Disabilities

No reported evidence examined the efficacy and safety of the interventions of interest in individuals with disabilities with NVAf.

4.1.3. The Elderly

Within-trial subgroup analyses examined the effect of age on treatment benefit. There were no clear subgroup effects by age, except a potential signal for lower risk of extracranial bleeding, particularly GI bleeding, in older adults prescribed DOACs as compared to warfarin.

There was no effect modification by age reported across multiple analyses of primary and secondary outcomes from the ARISTOTLE trial.^{5,24} See Supplement Tables D3.5, D3.6, and D3.13.

In the main trial publication, there was no effect modification by age for stroke/SE nor major bleed in the ROCKET AF trial, which was confirmed in a secondary analysis.^{6,21} Additional secondary data analyses reported that there was no treatment modification for major bleeding, fatal bleeding, and intracranial hemorrhage alone.^{21,25} However, when examining major and non-major clinically relevant bleeding, there was a significant effect modification by age ($p=0.009$).²¹ There was a higher risk of bleeding in those 75 years and older in the rivaroxaban group versus warfarin (HR: 1.13; 95% CI: 1.02 to 1.25) but, in those less than 75 years, there was no significant difference in the bleeding risk between the groups (HR: 0.93; 95% CI: 0.84 to 1.04). See Supplement Tables D3.15-20 and D3.24. Given these results, it is likely that the subgroup effect, if real, may be driven by non-major clinically relevant bleeding and, as noted in the study, extracranial bleeding. Gastrointestinal bleeding was more common in those over 75 years in the rivaroxaban group as compared to the warfarin group.

The observational study conducted by Lau et al. (2022) examined the effect of age in the comparisons of interest.⁷ Similar to the subgroup analyses for CKD, the results for stroke/SE, intracranial hemorrhage, and all-cause mortality in those 80 years or older were consistent with the overall sample. See Supplement Table D3.40. Again, the rates of GI bleeding were similar in those 80 years or older when comparing dabigatran versus rivaroxaban, inconsistent with the overall

sample. The authors noted that apixaban may be more favorable in reducing the risk of GI bleeding for older adults.

4.1.4. Individuals Who Are Terminally Ill

A within-trial subgroup analysis of the ARISTOTLE trial examined the efficacy and safety of apixaban versus warfarin in those with AF and active cancer (N=157), history of (remote) cancer (N=1,079), or no cancer (N=16,947).²⁶ Those with active or remote cancer were older (74 vs. 70) and had a slightly higher CHA₂DS₂-VASc score compared to those with no cancer. Those with active cancer had a higher rate of all-cause mortality compared to those with no or remote cancer. See Supplement Tables D3.7 to D3.9. When examining the effect on the primary efficacy and safety outcomes for apixaban versus warfarin according to cancer status, the results were consistent in patients with and without cancer. Apixaban versus warfarin was associated with fewer thrombotic events in patients with active cancer (HR: 0.30; 95% CI: 0.11 to 0.83) compared to those with no cancer (HR: 0.86; 95% CI: 0.78 to 0.95). There was also a trend towards greater reduction in mortality with apixaban versus warfarin in those without cancer. With further investigation, the authors noted that this effect was mostly driven by high rates of non-cardiovascular death in those with remote cancer who received apixaban versus those treated with warfarin.

4.1.5. Children

No reported evidence examined the efficacy and safety of the interventions of interest in children with NVAf.

Subgroups for the RE-LY trial are reported in Section D5 of the Supplement.⁴

4.2 Subgroup Uncertainties and Controversies

There are uncertainties around the comparative effectiveness of the drugs in patients with ESRD. Both trials in this patient population were underpowered: one because it was a pilot study and the other stopped enrolling patients due to challenges in recruitment. However, an individual patient-level NMA that combined the results of four trials including the three in our NMA found that the DOACs were safer and more effective than warfarin in patients with NVAf at 5 levels of renal function down to a creatine clearance of 25-29.9 ml/min.²⁷ Dabigatran is renally cleared with dose reduction indicated for patients with a creatine clearance of 15-30 ml/min.²⁸

Older patients are a major subgroup of interest as they comprise most patients covered by Medicare. As noted above, there was no evidence of effect modification by age in any of the randomized trials included in our analyses. In addition, an individual patient-level NMA that combined the results of four trials including the three in our NMA found that the DOACs were safer

and more effective than warfarin in patients without effect modification by age (<65, 65-75, and >75 years) for the outcomes of stroke / systemic embolism, major bleeding, and total mortality.²⁹

4.3 Comparative Cost Effectiveness – Subgroup Analyses

There was no clinical evidence to support subgroup analyses within the cost-effectiveness model.

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