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Comparing Direct Factor Xa Inhibitors and Warfarin in the Prevention of Stroke in Patients with Atrial Fibrillation

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Abstract

Objective: To evaluate the overall efficacy, advantages, and disadvantages of treatment with direct factor Xa inhibitors as compared to warfarin in the prevention of stroke in patients with atrial fibrillation. *Methods:* A quantitative meta-analysis was performed on three separate studies, each of which evaluated the efficacy and safety outcomes of a direct factor Xa inhibitor versus warfarin in preventing stroke in patients with atrial fibrillation. The direct factor Xa inhibitors that were evaluated included apixaban, edoxaban, and rivaroxaban. *Results:* The direct factor Xa inhibitors were found to be as effective, and in some cases more effective, than warfarin in preventing stroke in patients with atrial fibrillation. In addition, the direct factor Xa inhibitors were associated with a significantly decreased rate of major bleeding events, as compared to warfarin.

Introduction

Cerebrovascular accidents, also known as strokes, are currently the second leading cause of death worldwide with over 6 million deaths and another 5 million patients left with permanent disabilities.[1] A stroke is a condition in which the brain is deprived of oxygen and important nutrients needed for normal functioning. An ischemic stroke occurs when there is decreased blood flow to the brain, due to a thrombus or arterial stenosis. A hemorrhagic stroke occurs when an artery ruptures within the brain, resulting in decreased delivery of blood to the brain. In both types of stroke, deprivation of oxygen and nutrients may manifest as confusion, numbness, weakness, or tingling in the extremities, an inability to speak, and lack of coordination. Early recognition and treatment of stroke is key to minimizing the degree of brain cell death and regaining full capacity. However, in many cases, patients still suffer from permanent disabilities.[2]

While there are many factors associated with an increased risk of stroke, atrial fibrillation is the most prominent, particularly in ischemic stroke.[3] Normally, the atria are passively filled with blood from the venous system throughout the cardiac cycle. A single electrical impulse generated from the sinoatrial (SA) node within the right atrium, causes simultaneous depolarization and contraction of the right and left atria. Upon contraction, blood within the atria is forcefully pushed into the ventricles, effectively emptying the atria. Atrial fibrillation is a type of cardiac arrhythmia where there are multiple electrical impulses conducted from various automaticity foci at independent times within the atria. This pattern of unorganized impulse generation causes the atria to quiver rather than contract as a single unit. This quivering hinders the atria from emptying blood into the ventricles, causing blood to pool and become stagnant within the atria. Blood stasis within the atria results in thrombus formation, which can become dislodged and enter the systemic circulation, ultimately resulting in a stroke.[4,5]

In 2001, a risk assessment tool called the $CHADS_2$ score was created to assess the risk of stroke in individual patients with atrial fibrillation. This assessment tool, outlined in figure 1, allocates points based on the presence of congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, as well as a history of previous stroke or transient ischemic attack (TIA). A patient's overall score then determines whether or not they receive anti-platelet (i.e. aspirin) or anti-coagulant (i.e. warfarin) therapy to prevent stroke.[6]

Figure 1 : $CHADS_2$ Stroke Risk Assessment with Corresponding Recommended Therapy

Condition		**Points**
C : congestive heart failure		1
H : blood pressure consistently > 140/90 (or hypertension treated with medication)		1
A : age ≥ 75 years		1
D : diabetes mellitus		1
S_2 : prior stroke, transient ischemic attack, or thromboembolism		2
Overall Risk of Stroke and Recommended Treatment		
$CHADS_2$ Score	**Risk**	**Anticoagulation Therapy**
0	Low	None or daily aspirin
1	Moderate	Daily aspirin or warfarin (with INR 2 – 3)
2 or more	High	Warfarin with INR 2 - 3

Figure 1 displays the $CHADS_2$ risk assessment tool used to predict the risk of stroke in patients with atrial fibrillation. Recommended anti-platelet or anti-coagulant therapy, corresponding to calculated risk, is also displayed.

Warfarin has been approved by the Food and Drug Administration (FDA) for the use of stroke prevention in patients with atrial fibrillation since 1954.[6] However, there are many limitations to its use.

Some of these limitations include a slow onset of action, a narrow therapeutic range that requires regular prothrombin time/international normalized ratio (PT/INR) monitoring and subsequent dose adjustments, numerous drug and food interactions, as well as an increased risk of serious bleeding, such as intracranial bleeding, gastrointestinal bleeding, as well as other forms of internal bleeding.[6]

Recently, a newer class of anticoagulants, the direct factor Xa inhibitors, have been approved by the FDA for preventing stroke in patients with atrial fibrillation. These drugs are known to have a quicker onset of action, less drug and food interactions, and do not require coagulation monitoring or dose adjustments. The major disadvantages to the use of these drugs are that they are more expensive than warfarin and there are currently no known agents for drug reversal.[7,8,9]

Since the direct factor Xa inhibitors are a novel method of preventing stroke in patients with atrial fibrillation, many physicians may not be familiar with them or may be hesitant to use them, as warfarin has been an effective and established mainstay of therapy for the past six decades. With this research, we hope to define a new method of preventing stroke with the use of direct factor Xa inhibitors, while evaluating the overall efficacy, advantages, and disadvantages as compared to that of warfarin.

Clinical Question

In male and female patients 45 years and older with atrial fibrillation, is oral direct factor Xa inhibitor anti-coagulant therapy as effective in preventing stroke, as compared to oral warfarin anti-coagulant therapy?

Methods

An initial search of PudMed and Scopus databases was performed in August 2015 using the terms "factor Xa inhibitors", "atrial fibrillation", and "stroke", which produced 1,459 results. The search was then narrowed, based on the following limitations: full-text articles, English, published within the previous 5 years, human subjects, and age ≥ 45 years. This narrowed the search results produced to 223. After removal of duplicates, there were 219 results that were evaluated for eligibility.

To evaluate the search results for eligibility, articles were first excluded if the study involved a population that was non-comparable to the target population in question (ex. studies solely focusing on a Japanese population were excluded, as this was not representative of the U.S. population). Studies were also excluded if patients with atrial fibrillation were not the focus of the study, the prevention of cerebrovascular events was not evaluated, an adverse event of bleeding was not considered, and the efficacy of the study drug was not directly compared to that of warfarin. Lastly, studies were excluded if the efficacy and safety of dabigatran in preventing stroke in patients with atrial fibrillation was assessed, or if the study design involved evaluation of interruption-based therapy or anti-platelet therapy. After completion of the evaluation for eligibility, 89 results remained. The process of article selection is detailed in figure 2 below.

Figure 2: Article Selection Criteria

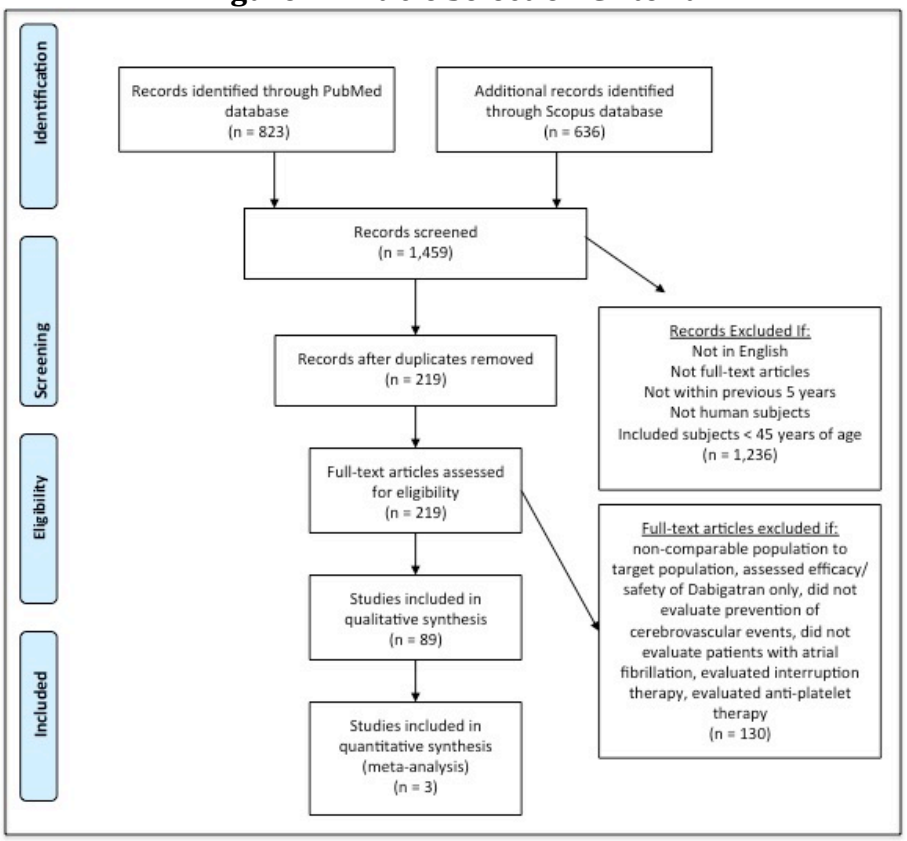

Figure 2 displays a PRISMA flow diagram that outlines the process used to select the final 3 studies to be included in the quantitative analysis.

A qualitative synthesis was performed on the 89 articles identified through the literature search, ultimately producing 3 articles to be included in the quantitative synthesis. The inclusion and exclusion criteria involved in the qualitative synthesis is outlined in table 1 below.

Table 1: Inclusion and Exclusion Criteria for Qualitative Synthesis

Inclusion Criteria	Exclusion Criteria
• Randomized controlled trials	• Meta-analyses • Systematic reviews • Cohort studies • Retrospective and prospective case control studies

Table 1 outlines the inclusion and exclusion criteria used to perform the qualitative synthesis on the 89 articles produced during the initial literature search.

A meta-analysis was performed for the quantitative analysis of the remaining three articles. In order to perform a meta-analysis, the hazard ratios reported in each of the studies were first converted to relative risks, with associated 95% confidence intervals and p-values, using a free, online statistical program, MedCalc.[10] A second free, online statistical program, OpenMeta[Analyst], was then used to perform meta-analyses on all of the recalculated data. The parameters utilized within the program included proportional data (data on two or more groups per study), risk ratio (also referred to as relative risk), and a binary fixed-effect using the Mantel Haenszel method with a 95% confidence interval and a default correction factor of 0.5 applied to all data values. The OpenMeta[Analyst] program reported hetero/homogeneity as chi-squared (X^2) values with degrees of freedom (df), statistical significance as p-values, and produced corresponding Forest plots.[11] All values calculated from the free, online statistical programs were rounded to the nearest hundredth.

The data points calculated via the MedCalc and OpenMeta[Analyst] programs were spot checked using manual calculations. All values reported by the programs were identical to manual calculations to the thousandth decimal value, ensuring a negligible margin of error and program accuracy.

Results

Study #1

Apixaban versus Warfarin in Patients with Atrial Fibrillation. Granger et al.[7]

Objective:

To compare the efficacy of apixaban versus warfarin in the prevention of stroke or systemic embolism in patients with atrial fibrillation and at least one other risk factor for stroke.

Study Design

This was a randomized controlled double blind, double-dummy study design, with 18,201 patients recruited from North America, Latin America, Europe, and the Asian Pacific. Inclusion and exclusion criteria are outlined in table 2. Patients were randomized to receive either apixaban (n = 9,120) or warfarin (n = 9,081), with each group balanced based on baseline characteristics, some of which included age, sex, and mean $CHADS_2$ score. Patients received 5 mg of apixaban twice daily (or matching placebo) or 2 mg of warfarin once daily (or matching placebo). Patients receiving warfarin were dose-adjusted to achieve a target INR of 2.0 to 3.0 throughout the duration of the study. A 2.5 mg dose of apixaban twice daily was used in a subset of patients, in order to adjust for kidney dysfunction. These individuals met at least two of the following criteria: at least 80 years of age, body weight less than or equal to 60 kg, or serum creatinine of greater than or equal to 1.5 mg/dL. Duration of treatment was defined as beginning on the day of randomization and ending on January 30, 2011. The median follow-up duration was 1.8 years. Patients received monthly visits for INR monitoring and dose-adjustment, if necessary. In addition to monthly visits, patients also received visits every 3 months to assess clinical outcomes and any adverse events associated with treatment.

Table 2: Inclusion and Exclusion Criteria for Apixaban vs. Warfarin Study

Inclusion Criteria	Exclusion Criteria
Atrial fibrillation or flutter at enrollment OR ≥ 2 episodes of atrial fibrillation or flutter at least 2 weeks apart in the 12 months prior to enrollment	• Atrial fibrillation due to reversible cause • Moderate or severe mitral stenosis • Conditions other than atrial fibrillation that require anti-coagulation therapy • Stroke within previous 7 days of enrollment • Need for aspirin at a dose > 165 mg/day • Need for aspirin AND clopidogrel daily • Serum creatinine > 2.5 mg/dL • Calculated creatinine clearance < 25 mL/min
At least one of the following: • Age ≥ 75 years • Previous stroke, TIA, or systemic embolism • Symptomatic heart failure within previous 3 months • Left ventricular ejection fraction ≤ 40% • Diabetes mellitus • Hypertension that requires pharmacologic treatment	

Table 2 outlines the inclusion and exclusion criteria for the apixaban versus warfarin efficacy study.

The primary efficacy outcome evaluated was overall rate of stroke or systemic embolism, which included both ischemic and hemorrhagic stroke The primary safety outcome evaluated was the rate of major bleeding, which was defined by the International Society on Thrombosis and Haemostasis (ISTH).

The ISTH defines major bleeding as a decrease in hemoglobin of at least 2 g/dL or requiring transfusion of at least 2 units of packed red blood cells, occurring at a critical site, or resulting in death.

Statistical analyses, which included hazard ratios, confidence intervals, and p-values, were performed using the Cox proportional-hazards model. These values are outlined in tables 3 and 5 below. Analyses included all patients who underwent randomization (intention-to-treat population), as well as all events that occurred from the time of randomization to the study cut off date (defined as January 30, 2011). A modified intention-to-treat analysis was performed for the primary safety outcome. This modified analysis included all patients that received at least one dose of study drug and experienced a major bleeding event from the time of randomization to the study cut off date.

For the purpose of performing a meta-analysis, we performed a separate statistical analysis to include relative risks, confidence intervals, and p-values. These values are outlined in tables 4 and 6 below.

Study Results

Table 3 outlines the hazard ratios associated with the primary efficacy outcomes of treatment with apixaban as compared to warfarin, as reported by the study authors. Apixaban was associated with a significantly decreased rate of stroke overall, but particularly hemorrhagic, in patients with atrial fibrillation, as compared to that of warfarin. However, there was no significant difference between apixaban and warfarin in the rate of ischemic stroke or systemic embolism.

Table 3: Hazard Ratios Associated with Primary Efficacy Outcomes of Apixaban vs. Warfarin

Outcome	Apixaban (n = 9,120) # Patients with event	Warfarin (n = 9,081) # Patients with event	Hazard Ratio (95% CI)	P value
Stroke (overall)	199	250	0.79 (0.65 – 0.95)	0.01
Hemorrhagic stroke	40	78	0.51 (0.35 – 0.75)	< 0.001
Ischemic stroke	162	175	0.92 (0.74 – 1.13)	0.42
Systemic embolic event	15	17	0.87 (0.44 – 1.75)	0.70

Table 3 outlines the primary efficacy outcomes, stroke or systemic embolism, in the comparison of apixaban versus warfarin. Primary efficacy outcomes are displayed as hazard ratios, as reported by the study authors. P-value < 0.05 indicates statistical significance.

Table 4 outlines the relative risks associated with the primary efficacy outcomes of treatment with apixaban as compared to warfarin. The statistically significant trends observed with the primary efficacy outcome hazard ratios were the same for those associated with the corresponding relative risks.

Table 4: Relative Risks Associated with Primary Efficacy Outcomes of Apixaban vs. Warfarin

Outcome	Apixaban (n = 9,120) # Patients with event	Warfarin (n = 9,081) # Patients with event	Relative Risk (95% CI)	P value
Stroke (overall)	217	270	0.80 (0.67 – 0.95)	0.013
Hemorrhagic stroke	40	78	0.51 (0.35 – 0.75)	< 0.001
Ischemic stroke	162	175	0.92 (0.75 – 1.14)	0.45
Systemic embolic event	15	17	0.88 (0.44 – 1.76)	0.71

Table 4 outlines the primary efficacy outcomes, stroke or systemic embolism, in the comparison of apixaban versus warfarin. Primary efficacy outcomes are displayed as relative risks, as recalculated for the purposes of performing a meta-analysis. P-value < 0.05 indicates statistical significance.

Table 5 outlines the hazard ratios associated with the primary safety outcomes of treatment with apixaban as compared to warfarin, as reported by the study authors. Apixaban was associated with a

significantly decreased rate of intracranial bleeding, as well as bleeding in other locations, as compared to that of warfarin. However, there was no difference between treatment with apixaban and warfarin in the rate of gastrointestinal bleeding.

Table 5: Hazard Ratios Associated with Primary Safety Outcomes of Apixaban vs. Warfarin

Outcome	Apixaban (n = 9,088) # Patients with event	Warfarin (n = 9,052) # Patients with event	Hazard Ratio (95% CI)	P value
Intracranial bleeding	52	122	0.42 (0.30 – 0.58)	< 0.001
Gastrointestinal bleeding	105	119	0.89 (0.70 – 1.15)	0.37
Bleeding (other location)	275	340	0.79 (0.68 – 0.93)	0.004

Table 5 outlines the primary safety outcomes, major bleeding events, in the comparison of apixaban versus warfarin. Primary safety outcomes are displayed as hazard ratios, as reported by the study authors. Major bleeding events included intracranial bleeding, gastrointestinal bleeding, and major bleeding in other locations. P-value < 0.05 indicates statistical significance.

Table 6 outlines the relative risks associated with the primary safety outcomes of treatment with apixaban as compared to warfarin. The statistically significant trends observed with the primary safety outcome hazard ratios were the same for those associated with the corresponding relative risks.

Table 6: Relative Risks Associated with Primary Safety Outcomes of Apixaban vs. Warfarin

Outcome	Apixaban (n = 9,088) # Patients with event	Warfarin (n= 9,052) # Patients with event	Relative Risk (95% CI)	P value
Intracranial bleeding	52	122	0.42 (0.31 – 0.59)	< 0.001
Gastrointestinal bleeding	105	119	0.88 (0.68 – 1.14)	0.33
Bleeding (other location)	275	340	0.81 (0.69 – 0.94)	0.001

Table 6 outlines the primary safety outcomes, major bleeding events, in the comparison of apixaban versus warfarin. Primary safety outcomes are displayed as relative risks, as re-calculated for the purposes of performing a meta-analysis. Major bleeding events included intracranial bleeding, gastrointestinal bleeding, and major bleeding in other locations. P-value < 0.05 indicates statistical significance.

After study completion, the authors concluded that apixaban was superior to warfarin in preventing stroke or systemic embolism, in addition to decreasing major bleeding, in patients with atrial fibrillation.

Study Critique

Strengths of this study included large sample sizes, sample groups with similar baseline characteristics, a diverse patient population, and a low loss to follow-up (0.4% of patients in both the apixaban and warfarin groups). Another strength of this study included the use of a double blind, double-dummy study design, to further reduce any possible bias.

Weaknesses of this study included patients within the warfarin group only falling within a therapeutic INR range 62.2% of the time throughout the duration of the study. An INR outside of this therapeutic range could significantly decrease or increase the risk of stroke and major bleeding, with a lower or higher therapeutic INR respectively. Another weakness of this study included allowing patients to remain on low-dose aspirin therapy throughout the duration of the study, as it was not addressed how aspirin therapy may affect primary efficacy or safety outcomes. However, at the study conclusion there was no statistically significant difference in major bleeding between patients receiving or not receiving aspirin in combination with apixaban as compared to that of warfarin.

Study #2

Edoxaban versus Warfarin in Patients with Atrial Fibrillation. Giugliano et al.[8]

Objective:

To compare the efficacy of low-dose and high-dose edoxaban versus warfarin in the prevention of stroke or systemic embolism in patients with atrial fibrillation and a $CHADS_2$ score of at least 2.

Study Design

This study was a randomized controlled double-blind, double-dummy study design consisting of 21,105 patients recruited from North America, Latin America, Europe, South Africa and Pacific Asia. Inclusion and exclusion criteria are outlined in table 7. The enrollment period took place from November 2008 to November 2010. Treatment exposure spanned 907 days, with a median follow-up of 2.8 years.

Table 7: Inclusion and Exclusion Criteria for Edoxaban vs. Warfarin Study

Inclusion Criteria	Exclusion Criteria
• Age ≥ 21 years • Atrial fibrillation confirmed via 12-lead EKG or Holter monitoring within 12 months prior to randomization • Paroxysmal, persistent, or permanent atrial fibrillation • $CHADS_2$ score ≥ 2 • Anti-coagulation therapy planned for the duration of the study	• Atrial fibrillation due to reversible cause • Estimated creatinine clearance < 30 mL/min • High risk of bleeding • Treatment plan including rhythm control with discontinuation of anti-coagulation if sinus rhythm restored • Moderate to severe mitral stenosis • Other indications requiring anti-coagulation therapy • Acute coronary syndromes, coronary revascularization, or stroke within 30 days prior to randomization

Table 7 outlines the major inclusion and exclusion criteria for the edoxaban versus warfarin efficacy study. A complete, detailed list of inclusion and exclusion criteria can be found in the study's supplemental material.

Patients were randomized to receive warfarin (n = 7,036), high-dose edoxaban (n = 7,035), or low-dose edoxaban (n = 7,034). Each treatment group had equal representation of various demographic and clinical characteristics, such as age, sex, risk factors and $CHADS_2$ scores. Patients in the high-dose edoxaban group received 60 mg once daily, and patients in the low-dose group received 30 mg once daily. The edoxaban dose was halved if any of the following criteria were met: estimated creatinine clearance of 30 – 50 mL/min, body weight of 60 kg or less, or concomitant use of verapamil or quinidine at any point throughout the duration of the study. Patients in the warfarin group received a dose that was individually adjusted to maintain an INR between 2.0 and 3.0. Each patient returned monthly for blinded INR monitoring and dose-adjustment as necessary. Follow-up visits were also scheduled every 3 months to assess clinical outcomes and any adverse events associated with treatment.

The primary efficacy outcome evaluated was the overall rate of stroke or systemic embolism, which included ischemic and hemorrhagic stroke. The primary safety outcome evaluated was the rate of major bleeding, which was defined by the ISTH as a decrease in hemoglobin of at least 2 g/dL, requiring transfusion of at least 2 units of packed red blood cells, occurring at a critical site such as the head or gastrointestinal tract, or resulting in death.

Statistical analyses on these outcomes, which included hazard ratios, confidence intervals and p-values, were performed using the Cox proportional hazards model. These values are outlined in tables 8 and 10 below. An intention-to-treat population analysis was performed, which included all patients who underwent randomization, as well as any events pertaining to the primary efficacy and safety outcomes

that occurred from the time of randomization to the study end date. A modified intention-to-treat analysis was also performed, which included all patients that received at least one dose of study drug.

For the purpose of performing a meta-analysis, we performed a separate statistical analysis to include relative risks, confidence intervals, and p-values. These values are outlined in tables 9 and 11 below.

Study Results

Table 8 outlines the hazard ratios associated with the primary efficacy outcomes of treatment with high-dose and low-dose edoxaban versus warfarin, as reported by the study authors. High-dose edoxaban was found to have a significantly decreased rate of hemorrhagic stroke, but a similar rate of ischemic stroke as compared to warfarin. This resulted in a non-significant decrease in the rate of overall stroke in patients treated with high-dose edoxaban as compared to warfarin. Low-dose edoxaban was found to have a significantly decreased rate of hemorrhagic stroke as compared to warfarin, but a significantly increased rate of ischemic stroke. This resulted in an increase in the rate of overall stroke in patients treated with low-dose edoxaban as compared to warfarin, although the results were non-significant. Lastly, a non-significant increase in the rate of systemic embolism was also observed in patients receiving low-dose edoxaban as compared to treatment with warfarin.

Table 8: Hazard Ratios Associated with Primary Efficacy Outcomes of Edoxaban vs. Warfarin

Outcome	Warfarin (n = 7,036) # Patients with event	High-dose Edoxaban (n = 7,035) # Patients with event	Hazard Ratio (95% CI) Warfarin vs. high-dose Edoxaban	P value	Low-dose Edoxaban (n = 7,034) # Patients with event	Hazard Ratio (95% CI) Warfarin vs. low-dose Edoxaban	P value
Stroke (overall)	317	281	0.88 (0.75 – 1.03)	0.11	360	1.13 (0.97 – 1.31)	0.12
Hemorrhagic stroke	90	49	0.54 (0.38 – 0.77)	< 0.001	30	0.33 (0.22 – 0.50)	< 0.001
Ischemic stroke	235	236	1.00 (0.83 – 1.19)	0.97	333	1.41 (1.19 – 1.67)	< 0.001
Systemic embolic event	23	15	0.65 (0.34 – 1.24)	0.19	29	1.24 (0.72 – 2.15)	0.43

Table 8 outlines the primary efficacy outcomes, stroke or systemic embolism, in the comparison of high-dose and low-dose edoxaban versus warfarin. Primary efficacy outcomes are displayed as hazard ratios, as reported by the study authors. P-value < 0.05 indicates statistical significance.

Table 9 outlines the relative risks associated with the primary efficacy outcomes of treatment with high-dose and low-dose edoxaban versus warfarin. The statistically significant trends observed with the primary efficacy outcome hazard ratios were the same for those associated with the corresponding relative risks.

Table 9: Relative Risks Associated with Primary Efficacy Outcomes of Edoxaban vs. Warfarin

Outcome	Warfarin (n = 7,036) # Patients with event	High-dose Edoxaban (n = 7,035) # Patients with event	Relative Risk (95% CI) Warfarin vs. high-dose Edoxaban	P value	Low-dose Edoxaban (n = 7,034) # Patients with event	Relative Risk (95% CI) Warfarin vs. low-dose Edoxaban	P value
Stroke (overall)	348	300	0.86 (0.74 – 1.00)	0.054	392	1.2 (0.97 – 1.29)	0.11
Hemorrhagic stroke	90	49	0.54 (0.39 – 0.77)	0.001	30	0.33 (0.22 – 0.50)	< 0.001
Ischemic stroke	235	236	1.00 (0.84 – 1.20)	0.96	333	1.42 (1.20 – 1.67)	< 0.001
Systemic embolic event	23	15	0.65 (0.34 – 1.25)	0.20	29	1.26 (0.73 – 2.18)	0.41

Table 9 outlines the primary efficacy outcomes, stroke or systemic embolism, in the comparison of high-dose and low-dose edoxaban versus warfarin. Primary efficacy outcomes are displayed as relative risks, as recalculated for the purposes of performing a meta-analysis. P-value < 0.05 indicates statistical significance.

Table 10 outlines the hazard ratios associated with the primary safety outcomes associated with the treatment of high-dose and low-dose edoxaban versus warfarin, as reported by the study authors. High-dose edoxaban was shown to have a significantly decreased rate of intracranial bleeding and bleeding in other locations, but was associated with a significantly increased rate of gastrointestinal bleeding when compared to warfarin. Low-dose edoxaban was shown to have a significantly decreased rate of bleeding in all categories as compared to warfarin.

Table 10: Hazard Ratios Associated with Primary Safety Outcomes of Edoxaban vs. Warfarin

Outcome	Warfarin (n = 7,036) # Patients with event	High-dose Edoxaban (n = 7,035) # Patients with event	Hazard Ratio (95% CI) Warfarin vs. high-dose Edoxaban	P value	Low-dose Edoxaban (n = 7,034) # Patients with event	Hazard Ratio (95% CI) Warfarin vs. low-dose Edoxaban	P value
Intracranial bleeding	132	61	0.47 (0.34 – 0.63)	< 0.001	41	0.30 (0.21 – 0.43)	< 0.001
Gastrointestinal bleeding	190	232	1.23 (1.02 – 1.50)	0.03	129	0.67 (0.53 – 0.83)	< 0.001
Bleeding (other location)	211	131	0.62 (0.50 – 0.78)	< 0.001	87	0.40 (0.31 – 0.52)	< 0.001

Table 10 outlines the primary safety outcomes, major bleeding events, in the comparison of high-dose and low-dose edoxaban versus warfarin. Primary safety outcomes are displayed as hazard ratios, as reported by the study authors. Major bleeding events included intracranial bleeding, gastrointestinal bleeding, and major bleeding in other locations. P-value < 0.05 indicates statistical significance.

Table 11 outlines the relative risks associated with the primary safety outcomes of treatment with high-dose and low-dose edoxaban versus warfarin. The statistically significant trends observed with the primary safety outcome hazard ratios were the same for those associated with the corresponding relative risks.

Table 11: Relative Risks Associated with Primary Safety Outcomes of Edoxaban vs. Warfarin

Outcome	Warfarin (n = 7,036) # Patients with event	High-dose Edoxaban (n = 7,035) # Patients with event	Relative Risk (95% CI) Warfarin vs. high-dose Edoxaban	P value	Low-dose Edoxaban (n = 7,034) # Patients with event	Relative Risk (95% CI) Warfarin vs. low-dose Edoxaban	P value
Intracranial bleeding	132	61	0.46 (0.34 – 0.62)	< 0.001	41	0.31 (0.22 – 0.44)	< 0.001
Gastrointestinal bleeding	190	232	1.22 (1.01 – 1.47)	0.04	129	0.68 (0.55 – 0.85)	0.001
Bleeding (other location)	211	131	0.62 (0.50 – 0.77)	< 0.001	87	0.41 (0.32 – 0.53)	< 0.001

Table 11 outlines the primary safety outcomes, major bleeding events, in the comparison of high-dose and low-dose edoxaban versus warfarin. Primary safety outcomes are displayed as relative risks, as re-calculated for the purposes of performing a meta-analysis. Major bleeding events included intracranial bleeding, gastrointestinal bleeding, and major bleeding in other locations. P-value < 0.05 indicates statistical significance.

Overall, the authors concluded that both edoxaban regimens were non-inferior to warfarin therapy, with high-dose edoxaban more effective than low-dose edoxaban. It was also concluded that both edoxaban regimens showed consistently lower rates of major bleeding events, as compared to warfarin.

Study Critique

Strengths of this study included a large study population with equal representation given to each treatment group, long period of follow-up, as well as a diverse patient population that corresponds with patients that may be seen in the general population. Another strength includes the comparison of a high and low-dose of edoxaban. The data collected may be beneficial in providing evidence to support the use of low-dose edoxaban to prevent stroke in patients with atrial fibrillation if a high-dose regimen is not well tolerated.

In addition to the strengths, the study also had several weaknesses. One weakness was the median time the warfarin group remained in the therapeutic INR range, which was only 68.4% of the time throughout the duration of the study. While the researchers believed this was a strength of the study, we feel it is a large discrepancy that could have artificially increased or decreased either the rate of stroke or the rate of major bleeding in the warfarin group. Another weakness was inclusion of data from patients who were randomized and received at least one dose of treatment. Administration of only a single dose of study drug would yield different stroke and major bleeding outcomes, as compared to individuals who completed the study as it was intended. Therefore, study results may have been significantly skewed based on these inclusion criteria. Lastly, the study also included data from individuals that were taking aspirin or amiodarone throughout the duration of the study. The authors mentioned that combining either of these medications with low-dose edoxaban appeared to result in a synergistic effect in preventing stroke. However, the final results may have been confounded by integrating these results with the results of individuals who did not take aspirin or amiodarone.

Study #3

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. Patel et al.[9]

Objective:

To compare the efficacy of rivaroxaban versus warfarin in the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation who are at moderate to high risk of stroke.

Study Design

This was a randomized controlled double blind, double-dummy study design, with 14,264 patients recruited from 45 countries. Inclusion and exclusion criteria are outlined in table 12. Patients were randomized to receive either rivaroxaban (n = 7,131) or warfarin (n = 7,133), with each group balanced based on baseline characteristics, some of which included age, sex, and mean $CHADS_2$ score. Patients received 20 mg of rivaroxaban once daily (or matching placebo) or warfarin once daily (or matching placebo). Patients receiving warfarin were dose-adjusted to achieve a target INR of 2.0 to 3.0 throughout the duration of the study. Patients with a creatinine clearance of 30 – 49 mL/min received 15 mg of rivaroxaban once daily (or matching placebo), to adjust for kidney dysfunction. The median duration of treatment was 590 days and the median follow-up duration was 707 days. Follow-up visits occurred at weeks 1, 2, and 4, and then every 4 weeks thereafter throughout the duration of the study. INR monitoring, dose-adjustment if necessary, and assessment of clinical outcomes and any adverse events associated with treatment was performed at each follow-up visit. Additional laboratory assessment was performed as needed throughout follow-up, which is outlined in the study's supplemental material.

Table 12: Inclusion and Exclusion criteria for Rivaroxaban vs. Warfarin Study

Inclusion Criteria	Exclusion Criteria
• Nonvalvular atrial fibrillation (documented via EKG) with moderate to high risk for stroke • Age ≥ 18 years	• Significant mitral valve stenosis • Atrial fibrillation due to a reversible cause • Active internal bleeding • Platelet count < 90,000/μL at time of screening • Sustained, uncontrolled hypertension (≥180 systolic or ≥100 diastolic) • Need for anti-coagulant therapy for condition other than atrial fibrillation • Need for aspirin > 100 mg/day • Calculated creatinine clearance < 30 mL/min at time of screening
Moderate to high risk for stroke determined by (at least one of following): • History of stroke, TIA, or systemic embolism OR • At least two of the following: o Heart failure OR left ventricular ejection fraction ≤ 35% o Hypertension o Age ≥ 75 years o Diabetes mellitus	

Table 12 outlines the major inclusion and exclusion criteria for the rivaroxaban versus warfarin efficacy study. A complete, detailed list of inclusion and exclusion criteria can be found in the study's supplemental material.

The primary efficacy outcome evaluated was the overall rate of stroke and systemic embolism, which included ischemic, hemorrhagic, and uncertain types of stroke. The primary safety outcome evaluated was the rate of major and non-major clinically relevant bleeding events. Major bleeding was defined as bleeding associated with a decrease in hemoglobin ≥ 2 mg/dL, requiring a transfusion of ≥ 2 units of packed red blood cells or whole blood, occurring at a critical site (ex. intracranial, pericardial, intra-articular), or having a fatal outcome. Non-major clinically relevant bleeding was defined as bleeding that did not meet the criteria for major bleeding, but required medical intervention. A detailed list of criteria for major and non-major bleeding events is outlined in the study's supplemental material.

Statistical analyses, which included hazard ratios, confidence intervals, and p-values, were performed using the Cox proportional-hazards model. These values are displayed in tables 13 and 15 below. A primary analysis was performed on the per-protocol population, with a secondary analysis

performed on the intention-to-treat population. The per-protocol population included patients who received at least one dose of study drug, did not have a major protocol violation, and who were followed for efficacy and safety outcomes while receiving a study drug or within 2 days after discontinuation.

For the purpose of performing a meta-analysis, we performed a separate statistical analysis to include relative risks, confidence intervals, and p-values. These values are outlined in tables 14 and 16 below.

Study Results

Table 13 outlines the hazard ratios associated with the primary efficacy outcomes of treatment with rivaroxaban as compared to warfarin. A statistically significant decrease in rate of overall stroke, hemorrhagic stroke, and systemic embolic event was observed with treatment of rivaroxaban as compared to that of warfarin. However, there was no difference in the rate of ischemic stroke between treatment with rivaroxaban and warfarin.

Table 13: Hazard Ratios Associated with Primary Efficacy Outcomes of Rivaroxaban vs. Warfarin

Outcome	Rivaroxaban (n = 7,081) # Patients with event	Warfarin (n = 7,090) # Patients with event	Hazard Ratio (95% CI)	P value
Stroke (overall)	184	221	0.85 (0.70 – 1.03)	0.092
Hemorrhagic stroke	29	50	0.59 (0.37 – 0.93)	0.024
Ischemic stroke	149	161	0.94 (0.75 – 1.17)	0.581
Systemic embolic event	5	22	0.23 (0.09 – 0.61)	0.003

Table 13 outlines the primary efficacy outcomes, stroke or systemic embolism, in the comparison of rivaroxaban versus warfarin. Primary efficacy outcomes are displayed as hazard ratios, as reported by the study authors. P-value < 0.05 indicates statistical significance.

Table 14 outlines the relative risks associated with the primary efficacy outcomes of treatment with rivaroxaban versus warfarin. The statistically significant trends observed with the primary efficacy outcome hazard ratios were the same for those associated with the corresponding relative risks.

Table 14: Relative Risks Associated with Primary Efficacy Outcomes of Rivaroxaban vs. Warfarin

Outcome	Rivaroxaban (n = 7,081) # Patients with event	Warfarin (n = 7,090) # Patients with event	Relative Risk (95% CI)	P value
Stroke (overall)	183	233	0.79 (0.65 – 0.95)	0.013
Hemorrhagic stroke	29	50	0.58 (0.37 – 0.92)	0.02
Ischemic stroke	149	161	0.93 (0.74 – 1.16)	0.50
Systemic embolic event	5	22	0.23 (0.10 – 0.60)	0.003

Table 14 outlines the primary efficacy outcomes, stroke or systemic embolism, in the comparison of rivaroxaban versus warfarin. Primary efficacy outcomes are displayed as relative risks, as recalculated for the purposes of performing a meta-analysis. P-value < 0.05 indicates statistical significance.

Table 15 outlines the hazard ratios associated with the primary safety outcomes of treatment with rivaroxaban as compared to warfarin. There was no statistically significant difference between rivaroxaban and warfarin in regards to major and non-major clinically relevant bleeding.

Table 15: Hazard Ratios Associated with Primary Safety Outcomes of Rivaroxaban vs. Warfarin

Outcome	Rivaroxaban (n = 7,111) # Patients with event	Warfarin (n = 7,125) # Patients with event	Hazard Ratio (95% CI)	P value
Major and non-major clinically relevant bleeding	1475	1449	1.03 (0.96 – 1.11)	0.44
Major bleeding (any type)	395	386	1.04 (0.90 – 1.20)	0.58
Non-major bleeding	1185	1151	1.04 (0.47 – 0.93)	0.35

Table 15 outlines the primary safety outcomes in the comparison of rivaroxaban versus warfarin. Primary safety outcomes are displayed as hazard ratios, as reported by the study authors. Hazard ratios were only reported for the types of bleeding displayed in the table above. The authors further categorized major bleeding events in the supplemental material, without reporting specific hazard ratios, which was used to calculate the relative risks outlined in table 16. P-value < 0.05 indicates statistical significance.

Table 16 outlines the relative risks associated with the primary safety outcomes of treatment with rivaroxaban versus warfarin. A statistically significant reduction in intracranial bleeding and gastrointestinal bleeding was observed with treatment of rivaroxaban, as compared to warfarin. However, there was no statistically significant difference in major bleeding in other locations with treatment of rivaroxaban, as compared to warfarin.

Table 16: Relative Risks Associated with Primary Safety Outcomes of Rivaroxaban vs. Warfarin

Outcome	Rivaroxaban (n = 7,111) # Patients with event	Warfarin (n = 7,125) # Patients with event	Relative Risk (95% CI)	P value
Intracranial bleeding	55	84	0.66 (0.47 – 0.92)	0.015
Gastrointestinal bleeding	224	154	1.46 (1.19 – 1.78)	< 0.001
Bleeding (other location)	91	106	0.86 (0.65 – 1.14)	0.29

Table 16 outlines the primary safety outcomes, major bleeding events, in the comparison of rivaroxaban versus warfarin. Primary safety outcomes are displayed as relative risks, as re-calculated for the purposes of performing a meta-analysis. Major bleeding events included intracranial bleeding, gastrointestinal bleeding, and major bleeding in other locations, which the authors outlined in their supplemental material. P-value < 0.05 indicates statistical significance.

After study completion, the authors concluded that rivaroxaban was non-inferior to warfarin in the prevention of stroke and systemic embolism, as well as in the risk of major and non-major clinically relevant bleeding, in patients with atrial fibrillation who are at increased risk of stroke.

Study Critique

Strengths of this study included large sample sizes, sample groups with similar baseline characteristics, and a diverse patient population. This study also included the use of a double blind, double-dummy study design, to further reduce any possible bias. To further support the study's statistical findings, both a per-protocol and intention-to-treat analysis was performed.

Weaknesses of this study included a high loss to follow-up (14.3%), as well as allowing patients to remain on low-dose aspirin therapy. In addition, patients within the warfarin group only fell within a therapeutic INR range 55% of the time throughout the duration of the study. Both continuance of low-dose aspirin and falling outside of the therapeutic INR range may have significantly affected primary efficacy and safety outcomes.

Discussion

Table 17 displays the meta-analysis results for the rate of overall stroke in the comparison of treatment with direct factor Xa inhibitors and warfarin. The rate of overall stroke significantly favored

treatment with direct factor Xa inhibitors, as the overall confidence interval did not cross the line of no effect, even though warfarin was superior to treatment as compared to low-dose edoxaban.

Table 17: Meta-Analysis of Overall Stroke

Study	Intervention n/N	Control n/N	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI)
Study #1	217/9,120	270/9,081		22.56%	0.80 (0.67 – 0.96)
Study #2					
High-dose	300/7,035	348/7,036		29.01%	0.86 (0.74 – 1.00)
Low-dose	392/7,034	348/7,036		29.01%	1.13 (0.98 – 1.30)
Study #3	183/7,081	233/7,090		19.42%	0.79 (0.65 – 0.95)
Total	1,092/30,270	1,199/30,243	0.65 0.91 1.3	100%	0.91 (0.84 – 0.99)

Table 17 displays the meta-analysis for rate of overall stroke with treatment of direct factor Xa inhibitors versus warfarin. Overall stroke includes hemorrhagic stroke, ischemic stroke, and systemic embolism. Study #1 refers to treatment with apixaban. Study #2 refers to treatment with high-dose and low-dose edoxaban. Study #3 refers to treatment with rivaroxaban. The overall effect is considered non-significant if the symbol crosses the line of no effect (equal to 1). Overall effect p-value = 0.022. X^2 = 13.635 with df = 3, indicating heterogeneity.

Table 18 displays the meta-analysis results for the rate of hemorrhagic stroke in the comparison of treatment with direct factor Xa inhibitors and warfarin. The overall rate of hemorrhagic stroke favors treatment with direct factor Xa inhibitors over warfarin and was also found to be statistically significant, as the overall confidence interval does not cross the line of no effect.

Table 18: Meta-Analysis of Hemorrhagic Stroke

Study	Intervention n/N	Control n/N	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI)
Study #1	40/9,120	78/9,081		25.37%	0.51 (0.35 – 0.75)
Study #2					
High-dose	49/7,035	90/7,036		29.21%	0.55 (0.39 – 0.77)
Low-dose	30/7,034	90/7,036		29.20%	0.33 (0.22 – 0.50)
Study #3	29/7,081	50/7,090		16.22%	0.58 (0.37 – 0.92
Total	148/30,270	308/30,243	0.22 0.44 0.48 0.92	100%	0.48 (0.40 – 0.58)

Table 18 displays the meta-analyses for rate of hemorrhagic stroke with treatment of direct factor Xa inhibitors versus warfarin. Study #1 refers to treatment with apixaban. Study #2 refers to treatment with high-dose and low-dose edoxaban. Study #3 refers to treatment with rivaroxaban. The overall effect is considered non-significant if the symbol crosses the line of no effect (equal to 1). Overall effect p-value < 0.001. X^2 = 4.273 with df = 3, indicating heterogeneity.

Table 19 displays the meta-analysis results for the rate of ischemic stroke in the comparison of treatment with direct factor Xa inhibitors and warfarin. The overall rate of ischemic stroke appears to favor treatment with warfarin, although the results were not statistically significant, as the confidence interval crosses the line of no effect. However, even though it appears that low-dose edoxaban is a significant outlier, removing it from the analysis did not statistically change the overall effect (meta-analysis results not displayed).

Table 19: Meta-Analysis of Ischemic Stroke

Study	Intervention n/N	Control n/N	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI)
Study #1	162/9,120	175/9,081		21.75%	0.92 (0.75 – 1.14)
Study #2					
High-dose	236/7,035	235/7,036		29.15%	1.00 (0.84 – 1.20)
Low-dose	333/7,034	235/7,036		29.14%	1.42 (1.20 – 1.67)
Study #3	149/7,081	161/7,090		19.96%	0.93 (0.74 – 1.16)
Total	880/30,270	806/30,243		100%	1.09 (0.99 – 1.20)

Table 19 displays the meta-analyses for rate of ischemic stroke with treatment of direct factor Xa inhibitors versus warfarin. Study #1 refers to treatment with apixaban. Study #2 refers to treatment with high-dose and low-dose edoxaban. Study #3 refers to treatment with rivaroxaban. The overall effect is considered non-significant if the symbol crosses the line of no effect (equal to 1). Overall effect p-value = 0.069. X^2 = 15.177 with df = 3, indicating heterogeneity.

Table 20 displays the meta-analysis results for the rate of systemic embolic events in the comparison of treatment with direct factor Xa inhibitors versus warfarin. Even though the overall rate of systemic embolic events appears to be reduced with treatment of direct factor Xa inhibitors, this reduction is not statistically significant, as the overall effect crosses the line of no effect.

Table 20: Meta-Analysis of Systemic Embolic Event

Study	Intervention n/N	Control n/N	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI)
Study #1	15/9,120	17/9,081		20.04%	0.88 (0.44 – 1.76)
Study #2					
High-dose	15/7,035	23/7,036		27.05%	0.65 (0.34 – 1.25)
Low-dose	29/7,034	23/7,036		27.05%	1.26 (0.73 – 2.18)
Study #3	5/7,081	22/7,090		25.86%	0.23 (0.09 – 0.60)
Total	64/30,270	85/30,243		100%	0.75 (0.54 – 1.04)

Table 20 displays the meta-analyses for rate of systemic embolic event with treatment of direct factor Xa inhibitors versus warfarin. Study #1 refers to treatment with apixaban. Study #2 refers to treatment with high-dose and low-dose edoxaban. Study #3 refers to treatment with rivaroxaban. The overall effect is considered non-significant if the symbol crosses the line of no effect (equal to 1). Overall effect p-value = 0.085. X^2 = 9.394 with df = 3, indicating heterogeneity.

However, if treatment with low-dose edoxaban is removed from the meta-analysis, the rate of systemic embolic events with treatment of direct factor Xa inhibitors is significantly reduced as compared to warfarin. The overall effect no longer crosses the line of no effect, as displayed in table 21 below.

Table 21: Meta-Analysis of Systemic Embolic Event, without Low-Dose Edoxaban

Study	Intervention n/N	Control n/N	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI)
Study #1	15/9,120	17/9,081		27.47%	0.88 (0.44 – 1.76)
Study #2					
High-dose	15/7,035	23/7,036		37.08%	0.65 (0.34 – 1.25)
Study #3	5/7,081	22/7,090		35.45%	0.23 (0.09 – 0.60)
Total	35/23,236	62/23,207		100%	0.56 (0.37 – 0.85)

Table 21 displays the meta-analyses for rate of systemic embolic event with treatment of direct factor Xa inhibitors versus warfarin, excluding treatment with low-dose edoxaban. Study #1 refers to treatment with apixaban. Study #2 refers to treatment with high-dose edoxaban. Study #3 refers to treatment with rivaroxaban. The overall effect is considered non-significant if the symbol crosses the line of no effect (equal to 1). Overall effect p-value = 0.007. X^2 = 4.960 with df = 2, indicating heterogeneity.

Table 22 displays the meta-analysis results of the rate of major bleeding events that occurred with treatment of direct factor Xa inhibitors, as compared to warfarin. Even though the rate of major bleeding events was lower in the warfarin treated group as compared to the rivaroxaban treated group, the overall rate of major bleeding events was significantly reduced with the use of direct factor Xa inhibitors, as compared to warfarin.

Table 22: Meta-Analysis of Major Bleeding

Study	Intervention n/N	Control n/N	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI)
Study #1	432/9,088	581/9,052		29.23%	0.74 (0.66 – 0.84)
Study #2					
High-dose	424/7,012	533/7,012		26.77%	0.80 (0.70 – 0.90)
Low-dose	257/7,002	533/7,012		26.75%	0.48 (0.42 – 0.56)
Study #3	370/7,111	344/7,125		17.25%	1.08 (0.93 – 1.24)
Total	1,483/30,213	1,991/30,201		100%	0.75 (0.70 – 0.80)

Table 22 displays the meta-analyses for rate of major bleeding with treatment of direct factor Xa inhibitors versus warfarin. Major bleeding includes intracranial bleeding, gastrointestinal bleeding, and major bleeding in other locations, as described by the study authors. Study #1 refers to treatment with apixaban. Study #2 refers to treatment with high-dose and low-dose edoxaban. Study #3 refers to treatment with rivaroxaban. The overall effect is considered non-significant if the symbol crosses the line of no effect (equal to 1). Overall effect p-value < 0.001. X^2 = 60.921 with df = 3, indicating heterogeneity.

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Conclusion

Overall, the direct factor Xa inhibitors were found to be at least as effective, and in some cases more effective, than warfarin in preventing stroke and systemic embolism in patients with atrial fibrillation. In addition, the direct factor Xa inhibitors were associated with a significantly decreased rate of major bleeding events, as compared to warfarin. Apixaban was the most effective treatment in reducing the rate of overall stroke and ischemic stroke. Low-dose edoxaban was the most effective treatment in reducing the rate of both hemorrhagic stroke and major bleeding, which would be expected due to the lower dose being administered. However, if evaluating the "standard" doses of direct factor Xa inhibitors, apixaban was the most effective treatment in reducing the rate of hemorrhagic stroke and major bleeding, as compared to high-dose edoxaban and rivaroxaban. In contrast, rivaroxaban was the most effective treatment in reducing the risk of systemic embolic events, as compared to the other factor Xa inhibitors. Ultimately, apixaban was found to be the most effective factor Xa inhibitor, as compared to treatment with warfarin.

The decision of whether to prescribe a direct factor Xa inhibitor or warfarin involves the consideration of several factors. The direct factor Xa inhibitors appear to be a better choice of

anticoagulant therapy, especially in regards to their quicker onset of action, less drug and food interactions, and no need for PT/INR monitoring or dose adjustments. Unfortunately, the lack of familiarity with the use of effective reversal agents at this time, in addition to the enormous expense associated with these medications, as outlined in table 23 below, are major disadvantages that must be considered prior to use.

Table 23: Per Tablet Medication Costs

Medication (PO tablets)	Cost per tablet
Warfarin (2 mg)	$2.15
Apixaban (5 mg)	$6.67
Edoxaban (60 mg)	$11.09
Rivaroxaban (20 mg)	$13.33

Table 23 outlines the cost, per tablet, of each of the direct factor Xa inhibitors, as compared to warfarin.

Ultimately, the decision to prescribe either a direct factor Xa inhibitor or warfarin is just as much a consideration of the patient's and clinician's comfort, as it is the overall efficacy and safety of the treatment.

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