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Comparison of Rivaroxaban and Warfarin in the Prevention of Recurrent Venous Thromboembolism

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by

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Abstract

The purpose of this systematic literature review is to determine the efficacy and safety of rivaroxaban (Xarelto) compared to warfarin (Coumadin), for the long term prophylaxis of recurrent venous thromboembolism (VTE). Rivaroxaban was chosen as the primary representative of factor Xa inhibitors because of its simplistic once a day dosing regimen. The PubMed database was extensively searched, using a variety of key terms, from September 10 to November 30, 2018. Works chosen include propensity-matched cohorts, retrospective studies, systematic reviews, and meta-analyses. All of which were published within the last 10 years; sources dated prior to 10 years were excluded. Studies with poor design or dual antiplatelet therapies were also grounds for exclusion. For this review, 11 resources were selected for analysis; 7 additional resources were included for contextual information. Much of the research revealed that rivaroxaban is an adequate alternative for VTE prophylaxis, but the purpose of this research was to determine if its efficacy and safety is superior to that of warfarin. Despite statistically superior results for several aspects of rivaroxaban, an absence of distinct recommendations remain. The following results are intended to make the difficult decision of choosing an anticoagulant clearer for medical professionals and patients.

Introduction

Venous thromboembolism (VTE) refers to the formation of a blood clot in a vein. The term VTE encompasses two types, deep vein thrombosis (DVT) and pulmonary embolism (PE). When a clot forms in a deep vein, usually in a leg or arm, it is referred to as a DVT. These clots may be stationary, blocking venous blood flow, or it may break free. If freed, it will travel until it gets lodged into a narrower vessel, which is typically in the lung, blocking some or all of the blood supply. Despite an increased prevalence of VTE in adults 60 and older, individuals of any age are susceptible. (American Heart Association, 2017)

Virchow's triad is a theory that helps describe the pathogenesis of VTE. The triad consists of alterations in blood flow (i.e. stasis), vascular endothelial injury, and alterations in the constituents of the blood (i.e. inherited or acquired hypercoagulable state). One or more of these risk factors can be identified in 80% of patients with VTE. For those with inherited thrombophilia, 50% of VTEs are additionally linked with an acquired risk factor, such as surgery, prolonged bed rest, pregnancy, or oral contraceptives. It is also thought that over 50% of VTE patients have at least three of the following risk factors; hospital admission, surgery, malignancy, infection in the past three months, current hospitalization, or greater than 48 hours of immobility in the preceding month. A provoked VTE is associated with a clinical risk factor; a VTE without an identifiable risk factor is considered unprovoked. (Bauer & Lip, 2018)

Nearly 900,000 individuals in the United States are impacted by VTE each year, equaling about 1 to 2 per 1,000 individuals. Overall incidence is slightly higher in men (0.13%) than women (0.11%), although a slight increase is present in women of reproductive age. The estimated total annual healthcare cost for VTE can range from $7,594 to $16,644. To give a perspective of severity, it is thought that 60,000-100,000 will die from a VTE each year. For a

PE specifically, sudden death will be the first symptom for about 25% of these individuals. For those who have experienced a DVT, there is a risk for long-term complications, known as post-thrombotic syndrome; about half will experience swelling, pain, discoloration, and scaling in the affected limb. Also, about 33% of people who have had a VTE will have a recurrence within 10 years. Genetic risk factors or inherited thrombophilias play a role for approximately 5-8% of individuals, increasing their risk for thrombosis. (Beckman, Hooper, Critchley, & Ortel, 2010)

Anticoagulation is a crucial aspect of treatment and prophylaxis for individuals who have suffered from a VTE. Warfarin has been the mainstay for VTE prophylaxis for many years, which can burden the patients with many drug and dietary interactions, as well as routine international normalized ratio (INR) testing to monitor therapeutic levels (Kreutz, 2014). A newer class of medications, called factor Xa inhibitors or novel oral anticoagulants (NOACs), have been challenging warfarin. NOACs do not require regular therapeutic monitoring and have far fewer drug and dietary interactions (Kreutz, 2014). For the purpose of this review, rivaroxaban (Xarelto) will be the NOAC that is compared to warfarin because of the simplistic dosing regimen, requiring just once daily oral administration; other NOACs require twice daily oral administration. Warfarin also follows once daily oral administration.

Statement of the Problem

The choice of agent for VTE prophylaxis, warfarin or NOACs, is a collective decision between the patient and provider. In the end, the choice of agent is often in the hands of the patient, and the decision is commonly based on cost and number of required clinic visits. There is general knowledge amongst most prescribing providers about the efficacy and safety of the two types of medications, but it often remains difficult to give a recommendation for one versus

the other. Therefore, providers need to be informed on the latest studies to help differentiate which treatment is the best fit for a specific patient.

Research Questions

When treating patients with anticoagulants for prophylaxis of recurrent VTE, is there a statistical difference in efficacy and safety with rivaroxaban versus warfarin?

When treating patients with anticoagulants for prophylaxis of recurrent VTE, is there a statistical difference in cost and adherence of therapy with rivaroxaban versus warfarin?

When treating patients with anticoagulants, is there a statistical difference in potential drug and dietary interactions with rivaroxaban versus warfarin?

Review of Literature

In this review, the PubMed database was searched from September 10 to November 30, 2018. A variety of key terms were used when searching. In PubMed, searches were conducted using a variety of combinations of the MeSH headings rivaroxaban, warfarin, NOAC, DOAC, VKA, cost, efficacy, effectiveness, bleeding, safety, adherence, interactions, recurrent, VTE, and thromboembolism. Filters were added to only include human studies published within the last 10 years. Sources that were excluded comprised those published greater than 10 years ago, non-human studies, poor study design, dual antiplatelet therapies, and comparisons to antiplatelet agents. Those that did not include VTE as an indication for anticoagulation or isolate individual NOAC agents were also excluded. The Cochrane Database was examined, but it did not contain a systematic review that encompassed the purpose of this study.

Pharmacology of Rivaroxaban and Warfarin

Warfarin and other vitamin K antagonists (VKAs) block the function of vitamin K epoxide reductase complex in the liver. In doing so, it depletes the formation of the reduced form of vitamin K that serves as a cofactor for gamma carboxylation of vitamin K-dependent coagulation factors. Without gamma carboxylation, the vitamin K-dependent factors are immunologically detectable but cannot carry out their hemostatic function. This does not impact the previously synthesized clotting factors, so these have to be cleared from circulation before VKAs produce an effect. Depletion of factors II and X are important for efficacy, with II having the longest half-life of about 3 days. Therefore, it takes about 3 days to attain the desired anticoagulation effect. Gamma carboxylation also inhibits protein C and S, which inhibit factors V and VIII. This inhibition causes a transient procoagulant effect during the first couple of days,

until the other factors are inhibited, but this effect is rarely significant. (Hull, Garcia, & Vazquez, 2018)

Rivaroxaban has a bioavailability of 80-100% and has a much quicker onset of action compared to warfarin, achieving maximal plasma concentration in 2-4 hours (Kreutz, 2014). By direct, selective, and reversible inhibition of factor Xa in the intrinsic and extrinsic coagulation pathways, rivaroxaban inhibits platelet activation and fibrin clot formation ("Rivaroxaban: Drug information," n.d.). It targets free and clot-bound factor Xa, as well as factor Xa in the prothrombinase complex (Kreutz, 2014). The prothrombinase complex catalyzes the conversion of prothrombin to thrombin, which activates platelets and catalyzes the conversion of fibrinogen to fibrin ("Rivaroxaban: Drug information," n.d.).

Theme One: Comparison of costs between warfarin and rivaroxaban

Amin, Bruno, Trocio, Lin, and Lingohr-Smith (2015) obtained data from literature and health care claims databases for a retrospective analysis of patient costs of treatment after a VTE. Specifically, NOACs and warfarin based treatments were compared in this analysis. The agents were examined to determine efficacy and safety, as VTE recurrence and major bleeding events may impact medical costs. Through retrospective analysis, the population consisted of 112,885 patients diagnosed with VTE. Examination of published literature provided cost for recurrent VTE. A retrospective analysis of the MarketScan database was used to determine annual costs of major bleeding is those with a diagnosis of VTE between January 1, 2008 to December 31, 2011. All costs were inflation adjusted, using the CPI Medical Care Index, to 2013 cost levels. The collected data was used to estimate differences in total medical costs. Clinical outcomes were strictly used to determine medical costs. Costs of the drugs and additional monitoring were excluded. (Amin et al., 2015)

Real-world event rates in NOACs and warfarin were compared. For the purpose of this review, only rivaroxaban and warfarin were compared. Rates of recurrent VTE were reduced by -1.23% (95% CI -3.81% to -2.13%) and major bleeding events were reduced by -4.97% (95% CI -6.80% to -2.27%) in those treated with rivaroxaban compared to warfarin. Regarding expenses, the annual total medical cost avoidances were reduced by -$2,971 US per patient year in those treated with rivaroxaban compared to warfarin. Further breakdown, with a Univariate sensitivity analysis, showed a reduction range of -$4,469 to -$1,016 US per patient year for variations in VTE event rate. Similarly, a reduction range of -$3,803 to -$1,746 US per patient year was shown for variations in major bleeding event rates. The mean medical cost reduction for those treated with rivaroxaban was -$2979 US per patient year (95% CI -$5014 to -$980), based on Monte Carlo multivariate analyses. Of the 10,000 random Monte Carlo simulation cycles for rivaroxaban, 99.8% had a cost reduction of <$0 US. (Amin et al., 2015)

Despite the substantial population size, selection of the VTE prophylactic agent was based on that individuals' circumstance and not randomized, which may impact rates of VTE and major bleeding. Also, the costs used for comparison were not reported figures by patients, instead they were theoretical numbers acquired through analysis of data from databases and other literature. (Amin et al., 2015)

A study by Seaman, Smith, and Ragni (2013) directly compared the cost effectiveness of rivaroxaban and warfarin for prevention of recurrent VTE, using a Markov state-transition model over a 10-year time horizon. The population consisted of a hypothetical cohort, which was comprised of 60-year-old patients who had an initial diagnosis of VTE, either provoked or unprovoked. The age was based on the mean of clinical trial patients and VTE diagnosis. The hypothetical population received secondary prophylaxis with rivaroxaban or warfarin, after in-

hospital anticoagulation with standard heparin or low-molecular-weight heparin. Prophylactic treatment was for 3-12 months, and warfarin patients were dose-adjusted to an INR of 2.0-3.0. Patients with underlying malignancy or hypercoagulable state were excluded. Costs were estimated with the use of the Healthcare and Utilization Project medical literature, warfarin at $39 per month and rivaroxaban at $205 per month. Probabilities of complications were based on the EINSTEIN-PE study, which consisted of 4832 subjects with acute symptomatic PE, with or without DVT. Using appropriate literature, a meta-analysis was conducted to determine the probability of bleeding events for each medication, which were utilized in determining added costs. The U.S. Consumer Price Index was used to inflate the costs to 2011 USD, and cost ranges were expressed as ± 50% of base-case estimates. The total cost of prophylactic treatment was calculated to include medication and downstream costs. (Seaman et al., 2013)

The total cost of warfarin was estimated at $6,188, and rivaroxaban was estimated to be more cost effective at $3,195. The decreased costs for rivaroxaban were the result of increased effectiveness and safety compared to warfarin (9.29 QALYs vs. 9.14 QALYs). A one-way sensitivity analyses was conducted for further evaluation. Rivaroxaban dominated with individual variation of all parameters over plausible ranges; the only exceptions were the variation of quality-of-life and bleeding risk estimates for rivaroxaban. In addition, rivaroxaban was not more cost effective in two scenarios, when its utility was less than 0.978 (base case estimate: 0.994) or risk of major bleeding exceeded 3.8% (base case estimate: 0.96%). A two-way sensitivity analysis compared rivaroxaban and warfarin simultaneously, finding a 91.8% likelihood that rivaroxaban would be more cost effective, using a willingness to pay threshold of $100,000 per QALY gained. (Seaman et al., 2013)

Even with the use of medical literature and databases, the results are based on statistical calculations and a hypothetical cohort, thus eliminating any possible use of reported figures from real-world patients. However, the creation of a hypothetical cohort allows for equal distribution of the two treatment choices, while disregarding possible comorbidities that may impact treatment choices and/or risk of adverse bleeding events. (Seaman et al., 2013)

Theme Two: Comparison of efficacy and safety between warfarin and rivaroxaban

In a propensity-matched cohort study by Larsen et al. (2017), data was accessed and analyzed from the Danish health registries. The population encompassed new users of rivaroxaban or warfarin, who had a first inpatient diagnosis of unprovoked VTE. Patients with an outpatient diagnosis of VTE, other indications for anticoagulation, previous use of other anticoagulants, and those who did not have a prescriptions for either anticoagulant within 7 days of diagnosis, were excluded. After exclusions, 5004 oral anticoagulant-naive patients with incident VTE were identified, of which 3253 (65%) were prophylactically treated with warfarin and 1751 (35%) with rivaroxaban. Propensity score matching was performed to compared matched cohorts, demonstrating excellent compatibility; all absolute standardized differences were below 0.062. (Larsen et al., 2017)

In comparison of the two anticoagulants, rivaroxaban was associated with shorter hospital stays after their first VTE; 2.0 days (SE 2.8) with rivaroxaban and 3.0 days (SE 4.9) with warfarin. Additionally, rates of recurrent VTE after 3 months were lower with rivaroxaban (16.4%) compared to warfarin (21.8%), with a hazard ratio (HR) of 0.75 (95% CI 0.56-1.01). After 6 months, rates of recurrent VTE were also lower with rivaroxaban (9.9%) compared to warfarin (13.1%), with a HR of 0.74 (95% CI 0.56-0.96). Of patients that had a confirmed recurrent VTE with imaging, 46 were on rivaroxaban and 111 were on warfarin. Bleeding rates

were compared with cox regression analysis, indicating similar bleeding rates at amongst rivaroxaban and warfarin users, at 3 months (HR 0.99, 95% CI 0.47–2.07) and 6 months (HR 1.19, 95% CI 0.66–2.13). Cox regression analysis was also conducted for mortality rates per 100 person-years, resulting in no significant difference between rivaroxaban and warfarin at 3 months (HR 1.24, 95% CI 0.79–1.96) and 6 months (HR 1.03, 95% CI 0.72–1.49). In total, 125 patients died within the 6 months. Overall, rivaroxaban was associated with a lower risk of recurrent VTE when compared to warfarin, with a similar risk of bleeding and death. (Larsen et al., 2017)

Again, treatment randomization was not possible for this type of study. This causes medical treatment to be patient specific, possibly allowing for prescriber preferences and patient differences to impact the decision. Another aspect to be considered is the Denmark resident only population, which may not directly translate to a U.S. based population. Also, patients were only studied until their 6 month follow up; however, prophylactic treatment often extends to a year or longer. Patients with a provoked VTE were excluded from the study, eliminating a population that may need prophylactic treatment as well. Regarding length of inpatient treatment, the transition from heparin to warfarin was considered in the analysis, which was likely a major cause of the longer hospital stays. Additionally, their use of ICD coding may have resulted in misclassification, and limited data was available for specific location of the thrombus or lifestyle factors (i.e. alcohol, tobacco, exercise). (Larsen et al., 2017)

A retrospective study was carried out by Coleman, Peacock, Bunz, and Beyer-Westendorf (2018). This study used US MarketScan claims from January 2012 to December 2016. The population consisted of adults that had a primary diagnosis of an unprovoked VTE. To be included, these patients had to be initiated on warfarin or rivaroxaban within 30 days of

diagnosis, and treatment had to be at least 12 months in length. Patients with a provoked VTE were excluded from this study. After exclusions, 10,489 rivaroxaban users and 26,364 warfarin users were identified. The Cunningham algorithm was used to identify major bleeding episodes. (Coleman et al., 2018)

At 6 months, rivaroxaban was associated with lower rates of recurrent VTE (HR 0.60, 95% CI 0.54–0.67) and major bleeding (HR 0.80, 95% CI 0.66–0.98), when compared to warfarin. Also at 6 months, rivaroxaban was associated with reduced rates of gastrointestinal bleeding, or GIB, (HR 0.81, 95% CI 0.63–1.05) and markedly lower incidence of intracranial hemorrhage, or ICH, (HR 0.21, 95% CI 0.09–0.62). Similar results were seen at 3 month evaluation, recurrent VTE (HR 0.61, 95% CI 0.54–0.68), major bleeding (HR 0.77, 95% CI 0.60–0.98), GIB (HR 0.64, 95% CI 0.46–0.90), and ICH (HR 0.29, 95% CI 0.09–0.92). Evaluation at 12 months for recurrent VTE and major bleeding exhibited even lower rates for the rivaroxaban group; (HR 0.53, 95% CI 0.47–0.61) and (HR 0.71, 95% CI 0.56–0.89), respectively. (Coleman et al., 2018)

The Danish study conducted by Larsen et al. (2017) had similar results. However, the study failed to demonstrate a significant difference in bleeding, but this may be a result of different billing codes that were used to identify major bleeding. In contrast, the study performed by Coleman et al. (2018) used the Cunningham algorithm, instead of billing codes. (Coleman et al., 2018)

Limitations were similar to the study by Larsen et al. (2017). Treatment randomization was not possible for this type of study, causing patient specific treatment and prescriber preferences to impact the decision. Patients with a provoked VTE were also excluded from the study, eliminating a population that may need prophylactic treatment as well. In comparison, this

study used data for one year of prophylactic care versus 6 months, but it still often extends past one year. Regarding warfarin, the time spent in therapeutic range was not calculated because of inadequate data. Recurrent VTE may be miscoded by medical staff, but this would likely occur at the same rates for warfarin and rivaroxaban users; i.e. the recycling of VTE codes in the patient's chart, instead of appropriately selecting recurrent VTE. These recycled codes would not be included in the statistics because they were not labeled as recurrent. Also, there may have been misclassification of unprovoked VTE because of minor provoking factors. Additionally, patients without health insurance may not have been included, due to use of US claims data. (Coleman et al., 2018)

Prins et al. (2013) executed a prespecified analysis of the EINSTEIN-PE and EINSTEIN-DVT studies to demonstrate non-inferiority of rivaroxaban to standard anticoagulation therapy. Standard anticoagulation therapy consisted of low-molecular-weight heparin, followed by a VKA, with titration to an INR of 2.0-3.0. Patients were prophylactically treated for 3, 6, or 12 months. The margin for non-inferiority was set at 1.75. The total population consisted of 8282 patients, 4151 received rivaroxaban and 4131 received standard anticoagulation therapy. Overall adherence was at least 80% in 93.5% of patients on rivaroxaban, and the mean percentage of time in a therapeutic INR (2.0-3.0) was 61.7% for patients on warfarin. (Prins et al., 2013)

Results from the pooled analysis displayed a lower risk of recurrent VTE (HR 0.89, 95% CI 0.66–1.19) and major bleeding (HR 0.54, 95% CI 0.37–0.79) for rivaroxaban users, compared to warfarin users. A lower risk was also observed combining nonmajor clinically relevant and major bleeding (HR 0.93, 95% CI 0.81–1.06). Net clinical benefit similarly favored rivaroxaban (HR 0.77, 95% CI 0.61–0.97). The study concluded that rivaroxaban is noninferior ($p < 0.001$) compared to standard anticoagulation therapy, for the treatment of acute symptomatic DVT

and/or PE. It went further to say that rivaroxaban provides an important safety advantage, but superiority was not demonstrated ($p = 0.41$). (Prins et al., 2013)

Other comorbidities were not excluded from this study, without performing a propensity analysis or multiple regression, which may impact the results. Also, the population included provoked and unprovoked VTEs; the previous studies above separated the two cohorts. Additionally, this study was supported by Bayer HealthCare, the developers of Xarelto (rivaroxaban), and Janssen Pharmaceuticals, who market the drug. The companies were involved with trial design, data collection, and data analysis. However, the pooled analysis of randomized controlled trials (RCTs) strengthen this study. (Prins et al., 2013)

Raschi, Bianchin, Ageno, R. D. Ponti, and F. D. Ponti (2016) executed systematic reviews with meta-analysis of RCTs and observational studies to compare NOACs with VKAs. MEDLINE and PubMed was accessed to acquire sources, which were individually assessed for quality by applying the 11 items of the validated AMSTAR tool. Efficacy and bleeding risk were analyzed from high strength evidence within the selected sources, regardless of clinical relevance and severity of the bleeding events. Efficacy and safety endpoints were extracted, along with consideration of heterogeneity. (Raschi et al., 2016)

Rivaroxaban was found to have a significantly lower risk of recurrent VTE when compared to warfarin, both at the upper limit (HR 0.33, 95% CI 0.21–0.53) and at the lower limit of the confidence intervals (HR 0.91, 95% CI 0.54–1.54). In contrast to most studies, rivaroxaban provided no statistically significant protective effect for ICH, compared to warfarin (HR 1.17, 95% CI 0.66–2.05). However, NOACs as a collective group reduced the risk of ICH across meta-analyses (RR 0.43, 95% CI 0.37–0.50) and observational studies (adjusted HR 0.08, 95% CI 0.01–0.40). Results provided no statistically significant differences in risk of GIB, major

bleeding, fatal bleeding, and clinically relevant bleeding, due to lack of consistency amongst studies. (Raschi et al., 2016)

This study included RCTs for comparison of anticoagulants, eliminating bias and providing an advantage over other study designs. Due to an extensive review of numerous studies and combination of data, individual quality analysis is not feasible. Although a lower risk of ICH was displayed for NOACs as a whole, similar results were not specifically shown for rivaroxaban. This difference may contradict other results that were found in this literature review. No other information was able to be provided for other risks because of inconsistencies and inadequate presentation of the results. (Raschi et al., 2016)

Skaistis and Tagami (2015) conducted a meta-analysis of 20 RCTs comparing NOACs to VKA therapy. The intention was to determine relative odds of major and fatal bleeding events, as well as explore the outcomes after the major bleeds have occurred. Selected studies were assessed for validity using the Cochrane Collaboration's risk of bias assessment tool. Data obtained was combined by a random effects model and analyzed by RevMan 5.3. To be considered significant, the two tailed p-values were <0.05. (Skaistis & Tagami, 2015)

Of the 20 reviewed studies, 4 compared relative odds of fatal ICH events with rivaroxaban and VKA therapy; rivaroxaban therapy resulted in 65 events, causing 34 deaths, and VKA therapy resulted in 108 events, causing 61 deaths (OR 0.84, 95% CI 0.20–3.51). Three studies that compared relative odds of fatal extracranial bleeding events with rivaroxaban and VKA therapy. Patients on rivaroxaban had 36 extracranial bleeding events, resulting in 1 death; 60 of such cases were reported with VKA therapy, resulting in 5 deaths (OR 0.45, 95% CI 0.08–2.56). Results of the meta-analysis displayed statistically reduced deaths from major bleeds with NOAC therapy versus VKA therapy, mainly because of the reduction of ICH with NOACs.

However, events at any anatomical site showed no detectable difference between the two therapies. Despite the poorly understood reversibility of NOACs during the time of this study, no increase in mortality was discovered compared to VKAs. (Skaistis & Tagami, 2015)

Despite these results, comparison of individual NOAC agents remains difficult because of the limited population size. Although analysis of RCTs provides an advantage to this study, there are many other limitations. As with the majority of all completed studies, the reversal agent for factor Xa inhibitors had not been released yet, which may greatly change the treatment plan for those individuals experiencing major bleeding when on NOAC therapy. In addition, there are no concrete recommendations for management NOAC associated bleeding, which may result in significant treatment variation. Most significantly, indications for anticoagulation therapy were not specific for VTE, allowing for atrial fibrillation or other indications to be included. (Skaistis & Tagami, 2015)

Intravenous andexanet alfa (Andexxa) is a new, first-in-class, universal antidote for reversal of the anticoagulant effects of factor Xa inhibitors. It is a recombinant modified factor Xa protein developed by Portola Pharmaceuticals and it received its first global approval on May 3, 2018 in the United States. It is indicated for patients treated with rivaroxaban or apixaban, when reversal is necessary in life-threatening or uncontrolled bleeding events. Andexanet alfa neutralizes the anticoagulant effects by acting as a decoy and binding to factor Xa inhibitors, therefore preventing the inhibitors for binding endogenous factor Xa. (Heo, 2018)

Heo (2018) compared the results of multiple completed and ongoing studies that analyzed andexanet alpha. A randomized, double-blind, placebo-controlled phase III trial (ANNEXA-R) studied the effects of andexanet alfa on 80 healthy volunteers aged 50–75 years. Results showed that andexanet alfa reversed $\geq 80\%$ of anti-factor Xa activity compared with placebo ($p < 0.001$).

In addition, administration of andexanet alpha significantly ($p < 0.001$) reduced unbound concentrations of rivaroxaban and increased thrombin generation, compared with the placebo. An ongoing, multinational, single-arm, open-label phase IIIb/IV study (ANNEXA-4) is reviewing the effects of andexanet alfa in patients who presented with acute major bleeding after taking factor Xa inhibitors. As of October 2017, the population of consisted of 227 patients, with 75 of those on rivaroxaban therapy. Atrial fibrillation was the most common indication for anticoagulation treatment (78%). ICH represented 61% of bleeding events, followed by gastrointestinal bleeding at 27%. On average, initiation of andexanet alfa was 4.7 hours after presentation. Andexanet-alfa reduced anti-factor Xa activity by 87% in those patients taking rivaroxaban; 12 hours after the infusion concluded, anti-factor Xa activity was reduced to 60%. 227 patients from the ANNEXA-4 trial were monitored for 30 days, after treatment with andexanet alfa, for safety analysis. Results revealed that andexanet alfa is generally well tolerated; infusion-related reactions occurring in about 3% of patients, and urinary tract infections and pneumonia occurring in about 5%. However, 11% had a thrombotic event within 30 days after treatment with andexanet alfa, but over half of those patients failed to restart anticoagulation treatment before the thrombotic event. Their current patent for the composition, manufacturing process, and therapeutic use is effective until 2030. (Heo, 2018)

Despite FDA approval of andexanet alfa, studies up to this point have had very small populations, which may not account for all patient differences. Post-therapy thrombotic events may be skewed due to patients not restarting any form of anticoagulant; this unaccounted for disparity may greatly skew the statistics because of the limited population size. Even with the dire need for a reversal agent, there are serious adverse effects that need to be considered.

Overall, this early assessment of andexanet alfa provides important information, but many trials are still ongoing. (Heo, 2018)

Theme Three: Comparison of food and drug interactions between warfarin and rivaroxaban

Nutescu, Chuatrisorn, and Hellenbart (2011) carried out a systematic review of clinical research to provide comprehensive lists of potential drug and dietary interactions for NOACs and warfarin. Each NOAC was examined individually and included dabigatran, rivaroxaban, apixaban, and edoxaban. Their intent for this review was to provide clinicians, who may be initiating any of these agents or reviewing changes to a patient's medication profile, an all-inclusive list of potential drug and dietary interactions. (Nutescu et al., 2011)

Warfarin contains a racemic mixture of S and R isomers, which are metabolized by different cytochrome P450 enzymes, increasing the amount of drug interactions. A recent review estimates 120 dietary and drug interactions with warfarin, but that list is expected to continuously grow as increasing numbers of new drugs are being released each year. Dietary interactions are typically associated the leafy green, vitamin K containing foods. On the other hand, rivaroxaban metabolism is mediated through CYP3A4/3A5, and to a lesser extent CYP2J2. In contrast to warfarin, no dietary interactions have been found to impact bioavailability or pharmacokinetic parameters of rivaroxaban. Also, there are far fewer drug interactions with rivaroxaban compared to warfarin. These lists are vast, so please see this reference or other appropriate literature for more information. (Nutescu et al., 2011)

Although few drug and dietary interactions have been reported with NOACs, they are relatively new agents, limiting time for discovery of interactions. Interaction lists for NOACs and warfarin continue to grow as new drugs are released and new interactions are discovered,

causing lists to become outdated. Also, rivaroxaban is associated with several theoretical interactions that must be considered, but further evaluation is needed. (Nutescu et al., 2011)

Theme Four: Comparison of patient adherence to treatment between warfarin and rivaroxaban

A retrospective cohort study by Chen et al. (2013) was conducted using claims from the Thomson Medstat's MarketScan Commercial and Medicare Supplemental Insurance Databases. The population consisted of adult patients with a VTE diagnosis and subsequent initiation of warfarin between January 1, 2006, and March 31, 2008. DVT accounted for the majority of initial VTE diagnoses (84.6%). In addition, the ACCP guidelines were used to identify high risk patients, which were absent of a reversible risk factor for VTE. Reversible risk factors include pregnancy, hormonal contraception, hormone replacement therapy, fracture, nonfracture trauma, pelvic or orthopedic surgery, any hospitalization, or cancer. After exclusions, the population consisted of 7,612 patients. Pharmacy claims were utilized to assess compliance for 12 months after the first warfarin prescription fill. Proportion of days covered (PDC) was calculated using the total number of days covered with warfarin supply, which was then divided by 365. Cox proportional hazards regressions were utilized to adjust for patient demographic and clinical characteristics. (Chen et al., 2013)

Chen et al. (2013) found that 51.7% of patients discontinued warfarin therapy within 12 months of initiating treatment. In total, 76.9 % of patients were considered noncompliant; patients were defined as having a PDC <0.8. Noncompliant patients were at a 2.6 times greater risk for recurrent VTE than compliant patients (HR 2.58, 95% CI 1.62–4.11). A 43% higher risk of recurrent VTE was observed in patients who discontinued warfarin (HR 1.43, 95% CI 1.06–1.92). (Chen et al., 2013)

This study consists of only a one-year assessment period, despite guidelines recommending indefinite anticoagulation for these patients. Using the first 12 months for compliance assessment provides statistics for that time, but it does not include the subsequent years that are likely to follow. Compliancy was measured using prescription fills, which is only part of the picture for patients on warfarin therapy and leads to a significant limitation of the data provided. Measuring refills does not account for patients taking the supplied medication or maintaining a therapeutic INR. Consequently, fluctuation above or below the recommended therapeutic range may result in adverse bleeding or recurrent VTE events. If therapeutic levels were included, many of the 23.1% of patients that were considered compliant might be subtherapeutic or supratherapeutic, increasing their risk for adverse events. (Chen et al., 2013)

A retrospective cohort study by Crivera et al. (2015) was conducted using claims from the Humana database to evaluate adherence of NOAC agents, as defined by the Pharmacy Quality Alliance. The population consisted of 21,175 adult patients in the U.S., regardless of the indication for therapy; 11,095 rivaroxaban, 6548 dabigatran, and 3532 apixaban users were identified. Inclusion required 2 or more dispenses in 2014 that were at least 180 days apart, with more than 60 days of supply, and had at least 180 days of continuous enrollment prior to the index date. Adherence was calculated by the percentage of patients who had a PDC $\geq$0.8 during their follow-up. Baseline variables were adjusted for using multivariate logistic regression analyses. (Crivera et al., 2015)

Based on a PDC $\geq$0.8, 72.7% of patients taking rivaroxaban were found to be adherent, compared to 67.2% dabigatran users ($p < 0.001$) and 69.5% of apixaban users ($p < 0.001$). Also, rivaroxaban users had a significantly higher probability being adherent compared to apixaban, before adjustment (OR 1.17, 95% CI 1.08–1.27, $p < 0.001$) and after adjustment (OR 1.20, 95%

CI 1.10–1.31, $p < 0.001$). Dabigatran users had a significantly lower probability being adherent compared to apixaban, before adjustment (OR 0.90, 95% CI 0.82–0.98, $p = 0.019$) and after adjustment (OR 0.85, 95% CI 0.77–0.93, $p < 0.001$). (Crivera et al., 2015)

Similar to the study from Chen et al. (2013), measuring refills does not account for patients taking the supplied medication, allowing missed doses and improper use to be unaccounted Also, a 1 year time frame may not accurately represent subsequent adherence. Despite the sizable population, individual indications for anticoagulation therapy were not distinguished, which may have distinctive adherence rates. (Crivera et al., 2015)

Discussion

Comparison of costs between warfarin and rivaroxaban

A retrospective analysis completed by Amin et al. (2015) concluded that rivaroxaban was associated with reduced rates of recurrent VTE and major bleeding events compared to warfarin. With the inclusion of healthcare costs associated with recurrent VTE and major bleeding events, the mean medical cost reduction for those treated with rivaroxaban was -$2979 US per patient year compared to warfarin. (Amin et al., 2015)

Seaman et al. (2013) found warfarin to have increased incidence of major bleeds and ICH compared to rivaroxaban. Regarding monthly medication costs, warfarin was more cost effective compared to rivaroxaban ($39 and $205, respectively). Rivaroxaban was associated with a mean medical cost reduction of -$2993 US compared to warfarin, which were similar results to the study by Amin et al. (2015). Thus confirming that the increased medication costs of warfarin are offset by the increased risk of complications that are associated with warfarin, making it a cost-effective alternative to warfarin. (Seaman et al., 2013)

Comparison of efficacy and safety between warfarin and rivaroxaban

Larsen et al. (2017) analyzed data from Danish health registries to compare the effectiveness of rivaroxaban and warfarin. Lower rates of recurrent VTE were seen with rivaroxaban compared to warfarin; however, rates of adverse bleeding and mortality were similar between both groups (Larsen et al., 2017).

A retrospective analysis by Coleman et al. (2018) used a similar format to the study conducted by Larsen et al. (2017), but instead data was acquired from the US MarketScan claims. Results also showed lower rates of recurrent VTE with rivaroxaban compared to warfarin. In contrast to Larsen et al. (2017), rivaroxaban was also associated with lower incidence of major bleeding, GIB, and ICH; the most significant was the reduction in rates of ICH. Reductions were present at all intervals; 3, 6, and 12 months. Despite the difference, it may be explained data acquisition methods by the databases used for the studies. Larsen et al. (2017) used billing codes to identify major bleeding. Recognizing the implication of such disparities, Coleman et al. (2018) used the Cunningham algorithm a validate diagnoses of major bleeding, reducing the significance of billing code mistakes. (Coleman et al., 2018)

Prins et al. (2013) used a different approach that the previous studies mentioned, by executing a prespecified analysis of the EINSTEIN-PE and EINSTEIN-DVT studies to prove noninferiority of rivaroxaban to standard anticoagulation therapy. As shown in Table 1, the rivaroxaban group demonstrated a minor risk reduction of recurrent VTE compared to warfarin, contrasting more significant reductions presented by the other included studies. However, as shown in Table 2, rivaroxaban was associated with more significant reductions in major bleeding when compared to the other studies. Rivaroxaban was also linked to a considerable net clinical

benefit. The study concluded that rivaroxaban is noninferior compared to standard therapy ($p < 0.001$), but superiority was not statistically demonstrated ($p = 0.41$). (Prins et al., 2013)

Meta-analyses and observational studies executed by Raschi et al. (2016) found rivaroxaban to have a risk reduction for recurrent VTE compared to warfarin, which was much more significant than the study by Prins et al. (2013). In contrast to the majority of other studies, rivaroxaban provided no statistically significant protective effect for ICH hemorrhage. However, NOACs as a collective group significantly reduced the risk of ICH across meta-analyses (RR 0.43) and observational studies (HR 0.08). The analysis uncovered a lack of consistency amongst the included studies, resulting in no statistical differences in risk of GIB, major bleeding, fatal bleeding, and clinically relevant bleeding. (Raschi et al., 2016)

A meta-analysis of 20 RCTs conducted by Skaistis and Tagami (2015) was conducted to compare rates of fatal bleeding associated with NOACs and VKA therapy. Rivaroxaban was associated with a 16% reduction of death due to ICH and a 55% reduction of death due to extracranial bleeding (Skaistis & Tagami, 2015).

Heo (2018) compared the results of multiple completed and ongoing studies that analyzed andexanet alpha, a new, first-in-class, universal antidote, for reversal of the anticoagulant effects of factor Xa inhibitors. Results showed that andexanet alfa reversed ≥ 80% of anti-factor Xa activity, reduced unbound concentrations of rivaroxaban, and increased thrombin generation, compared with placebo. However, there are some risks associated with the administration of andexanet alpha. Some side effects include infusion-related reactions, urinary tract infections, and pneumonia. In addition, 11% had a thrombotic event within 30 days after treatment with andexanet alfa, but significance is undetermined because over half of those did not restart anticoagulation treatment before the time of thrombotic event. (Heo, 2018)

Comparison of food/drug interactions between warfarin and rivaroxaban

A systematic review by Nutescu et al. (2011) was carried out to provide comprehensive lists of potential drug and dietary interactions, for warfarin and NOACs. Warfarin is a racemic mixture of S and R isomers, each of which are metabolized by different cytochrome P450 enzymes, leading to an extensive list of interactions. There are over 120 known dietary and drug interactions with warfarin, and that list is expected to continuously grow. Rivaroxaban is mediated by different and fewer CYP enzymes than warfarin, resulting in considerably reduced numbers of drug interactions. In contrast to warfarin, no dietary interactions have been found to impact bioavailability or pharmacokinetic parameters of rivaroxaban. (Nutescu et al., 2011)

Comparison of patient adherence to treatment between warfarin and rivaroxaban

Prins et al. (2013) executed a prespecified analysis of the EINSTEIN-PE and EINSTEIN-DVT studies, comparing rivaroxaban to standard anticoagulation therapy (warfarin). Included in their study was adherence rates of the 4151 rivaroxaban users and 4131 warfarin users. 80% adherence was seen in 93.5% of rivaroxaban users. In comparison, the mean percentage of time in a therapeutic INR (2.0-3.0) for warfarin users was only 61.7%. (Prins et al., 2013)

A retrospective cohort study by Chen et al. (2013) examined warfarin adherence rates of adult patients with a VTE diagnosis. Over a course of 12 months, 76.9 % of patients were considered noncompliant, with 51.7% of patients discontinuing warfarin therapy altogether. In addition, the risk of recurrent VTE was increased by 258% in noncompliant patients and increased by 43% in patients who discontinued warfarin. If therapeutic levels were included, many of the 23.1% of patients that were considered compliant may possibly be subtherapeutic or supratherapeutic, increasing their risk for adverse events. Also, this study involved measuring

refills, which does not account for patients not taking the supplied medication. (Chen et al., 2013)

Crivera et al. (2015) carried out a retrospective cohort study to evaluate adherence of NOAC agents. 72.7% of rivaroxaban users were found to be adherent, which was also higher than dabigatran and apixaban users (Crivera et al., 2015). Similar to the study from Chen et al. (2013), measuring refills does not account for patients taking the supplied medication.

Applicability to Clinical Practice

As previously mentioned, prophylactic anticoagulant use is a serious but crucial aspect in those with a previous VTE. Current guidelines recommend treatment with either VKAs or NOACs, depending on patient differences and/or preferences. However, without concrete recommendations, this can be a difficult and possible life threatening decision made collectively by the patient and provider. As stated earlier, rivaroxaban was chosen due to simplistic dosing, as it is the only NOAC that is available for once daily dosing. Warfarin also involves just once a day dosing. There are many considerations when choosing an agent, such as cost, efficacy, risks, interactions, and adherence; those of which were discussed in this review.

Cost is an initial concern for many, when considering the use of a NOAC. It is likely that rivaroxaban will not be available in generic forms until December 2020, or possibly as late as 2024 (“Orange book,” n.d.). According to the studies in this review, the initial cost of rivaroxaban will be more but will be offset by additional costs that are associated with warfarin therapy, such as regular INR checks, increased risk of recurrent VTE, and decreased safety. All reviewed studies presented rivaroxaban as more cost effective than warfarin, when all aspects were considered.

As for efficacy, rivaroxaban surfaced as a viable option for prevention of recurrent VTE. All reviewed studies found rivaroxaban to have a reduced risk of recurrent VTE compared to warfarin, with all but one having strong quality of evidence. Analysis of bleeding risk resulted in mixed results. Rivaroxaban was associated with reduced risk of bleeding, intracranial and extracranial, in about half of the studies. The others displayed no statistical difference in bleeding risk, between rivaroxaban and warfarin. Due to the mixed results, no definite conclusion can be made about bleeding risk. In addition, NOACs have always been limited by the lack of practical reversal agents. That aspect has recently changed with the release of an FDA approved agent, andexanet alpha. However, its efficacy and risks are still questioned due to limited data.

Drug and dietary interactions also differentiates these two classes of medications. Warfarin is infamous for the amount of drug and dietary interactions, which may be worrisome for many. On the other hand, rivaroxaban is associated with fewer drug interactions and has no known dietary interactions. These qualities may be significant for patients with multiple comorbidities and/or those who do not maintain regular dietary habits, possibly putting them at risk recurrent VTE or bleeding events.

Adherence is a crucial aspect of anticoagulant use. If these medications are not taken properly, the patient will not be adequately protected from recurrent VTE or even at risk for bleeding events. Rivaroxaban was shown to have a significantly higher rate of adherence compared to warfarin, although a missed dose renders them completely unprotected because of a shorter half-life.

With the information provided in the literature review, medical providers and hospital administration will be able to make an educated decision on prophylactic treatment for recurrent VTE, based on clinical evidence. Although concrete recommendations for the use of rivaroxaban

over warfarin are not available at this time, rivaroxaban has proven itself to be a viable option for VTE prophylaxis. Many aspects of rivaroxaban are statistically superior to those of warfarin; including overall cost, efficacy, interactions, and adherence. However, bleeding risks were inconclusive, but current data suggests that rivaroxaban is associated with a reduced or at least equal risk. NOACs have a potential drawback, which is the lack of a proven and affordable reversal agent. The recent release of andexanet alpha, a reversal agent for NOACs, appears promising, but more information is needed to prove its efficacy and safety.

Despite the evidence presented, the choice of agent is often still the patients' decision, but it is up to the medical professional to properly educate the patient. Costs, efficacy, bleeding risks, reversal agents, and interactions are likely major elements of a patients' decision, but they may be unaware of statistical comparisons and medical advances. Offering this information will provide the patient an opportunity to make an educated decision. However, it is undeniably easier to take the same dose every day, with no regular therapeutic monitoring.

Table 1

Comparison of Recurrent VTE Rates in Rivaroxaban and Warfarin Users

Study	HR	95% CI
Larsen et al. (2017)		
3 months	0.75	0.56 – 1.01
6 months	0.74	0.56 – 0.96
Coleman et al. (2018)		
3 months	0.61	0.54 – 0.68
6 months	0.60	0.54 – 0.67
12 months	0.53	0.47 – 0.61
Prins et al. (2013)	0.89	0.66 – 1.19
Raschi et al. (2016)		
Upper Limit	0.33	0.21 – 0.53
Lower Limit	0.91	0.54 – 1.54

Note. HR = hazard ratio, CI = confidence interval

Table 2

Comparison of Bleeding Rates in Rivaroxaban and Warfarin Users

Study	HR	95% CI
Larsen et al. (2017)		
3 months	0.99	0.47 – 2.07
6 months	1.19	0.66 – 2.13
Coleman et al. (2018), major bleeding		
3 months	0.77	0.60 – 0.98
6 months	0.80	0.66 – 0.98
12 months	0.71	0.56 – 0.89
Prins et al. (2013)		
Major bleeding	0.54	0.37 – 0.79
Nonmajor clinically relevant and major bleeding	0.93	0.81 – 1.06

Note. HR = hazard ratio, CI = confidence interval

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