How does the safety and efficacy of rivaroxaban compare to that of warfarin in the prevention of stroke in non-valvular atrial fibrillation patients?

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2016

Acknowledgements

I would like to acknowledge Dr. Linda Jo Dill for all of her time and help throughout the writing of this literature review.

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Definition of Terms

Non-valvular Atrial Fibrillation: Atrial fibrillation (AF) that is not related to rheumatic valvular disease or prosthetic heart valves (Breithardt et al., 2014).

$CHADS_2$: A risk assessment index used to estimate the risk of stroke in a non-valvular AF patient, based on the following criteria: A history of hypertension, a history of diabetes mellitus, a recent history of congestive heart failure, age ≥75 years, and a past history of stroke or TIA (Karthikeyan & Eikelboom, 2010).

Primary Prevention: To prevent disease before it occurs by removing its causes ("Primary Prevention," 2015).

Secondary Prevention: To detect disease while still asymptomatic and treatment can stop its progression ("Secondary Prevention", 2015).

International Normalized Ratio (INR): The ratio of the patient's clotting time to the clinical laboratory's mean reference value; normalized by raising it to the international sensitivity index (ISI) power to account for differences in thromboplastin reagents. INR = (Patient's prothrombin time/laboratory's mean normal prothrombin time)^{ISI} (Chisholm-Burns et al., 2010).

Double-Blind: of, relating to, or being an experimental procedure in which neither the subjects nor the experimenters know which subjects are in the test and control groups during the actual course of the experiments. ("Double-Blind," 2016)

Double-Dummy: A technique for retaining the blinding of a clinical trial, where the two treatments cannot be made identical. Supplies are prepared for Treatment A and for Treatment B; subjects then take two sets of treatment, either A (active) and B (placebo), or A (placebo) and B (active). ("double-dummy," 2011)

Harzard's Ratio: The likelihood that a group of people who are exposed to an event, toxin, or treatment will experience poor health, relative to a group of people who are not similarly exposed. ("Hazard ratio," 2009)

Non-inferiority Trial: A study to determine if a treatment is no worse than the current accepted therapy. ("Noninferiority trial," 2009)

Introduction

AF is the most common clinically significant arrhythmia among the population, occurring in 2.5 million people in the United States (Patel, 2010). Prevalence of AF varies by age and is seen largely in the older white populations (Ntaios et al., 2012). Atrial thrombi can develop as a complication of AF and has been associated with an increased risk of stroke (Wolf, Abbott, & Kannel, as cited in Becker et al., 2010). Anticoagulant drugs such as vitamin K antagonists are used to help prevent stroke in AF patients.

Warfarin is a vitamin K antagonist and has proven to be more effective than aspirin therapy in the prevention of stroke in AF patients (Hart, Pearce, & Aguilar, as cited in Becker et al., 2010). Patients taking warfarin must frequently monitor their INR in order to assure treatment is therapeutic (Ntaios et al., 2012). The therapeutic range of INR is between 2.0 and 3.0, which is challenging to achieve, as warfarin levels change constantly based on different environmental and genetic factors (Hirsh et al., as cited in Becker et al., 2010). According to Boulanger et al. (as cited in Becker et al., 2010), failure to achieve this therapeutic range results in a greatly increased risk of stroke or hemorrhage, and added that the INR falls within the therapeutic range less than 50% of the time in patients on warfarin therapy.

Rivaroxaban is an oral direct factor Xa inhibitor that has effects on the body that correlate with its plasma concentrations while failing to show any major variation among individuals based on body weight, age, or gender (Kubitza, Becka, Wensing, Voith, & Zuehlsdorf, as cited in Becker et al., 2010). The remainder of rivaroxaban's pharmacokinetic profile, including drug-drug and food-drug interactions has been determined to be safe, and suggests that frequent monitoring of anticoagulation is unnecessary in AF patients (Kubitza et al., as cited in Becker et al., 2010). Healthcare providers are now faced with the decision of which drug to use. This

literature review is aimed to allow healthcare providers to better decide which drug, rivaroxaban or warfarin, is safer and more efficacious in the prevention of stroke in atrial fibrillation patients.

Methodology

The search engines PubMed, Google Scholar, National Institute of Health (NIH), and the University of Toledo Mulford Library were used with the following search terms: Rivaroxaban, warfarin, atrial fibrillation, stroke, prevention, control, efficacy, safety.

Articles from double-blind studies, systematic reviews, and meta-analyses were included in the review. Research articles not published in English, secondary sources, studies involving the chronic use of non-steroidal anti-inflammatory drugs, and studies that included patients with significant valvular disease were excluded.

Literature Review

The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) was a phase III, randomized, double-blind, double-dummy, multicenter, event-driven study (Becker et al., 2010; Breithardt et al., 2014). The study consisted of 14,269 participants across 45 countries at 1,100 different sites. The primary objective of this trial was to compare the safety and efficacy of rivaroxaban with that of dose-adjusted warfarin in the prevention of thromboembolic events in nonvalvular AF patients. The primary efficacy endpoint for this study was number of non-central nervous system systemic embolism and stroke, which includes any emboli within the body and stroke. The primary safety endpoint was to compare the number of major and nonmajor bleeding events among patients. All patients that were recruited for this trial qualified as having moderate or high risk for thromboembolic events. Patients were excluded if they had hemodynamically significant mitral stenosis or valve prostheses. The study did not include any patients with end-stage renal disease (ESRD) (Chan, Edelman, Wenger, Thadhani, & Maddux, 2015). Two different drug regimens were given to participants: 20mg of rivaroxaban daily or warfarin titrated to a target of 2.5 INR. Patients had a follow up at 1, 2, and 4 weeks, then monthly until the study period of 42 months is over. This study was done with a noninferiority design because the efficacy of warfarin to prevent thromboembolic events in patients with AF has been well established. This will then allow medical professionals to choose which medication is right for their patient, knowing that rivaroxaban is equally as efficacious as warfarin among this patient population. Similar to the ROCKET AF trial, the J-ROCKET AF trial was a randomized, double-blind clinical trial comparing rivaroxaban and dose-adjusted warfarin using Japan-specific doses and guidelines (Tanahashi et al., 2013).

Efficacy

Rivaroxaban was found to be noninferior to warfarin in patients with nonvalvular AF in the prevention of stroke or systemic embolism (Halperin et al., 2014; Patel et al., 2011). The ROCKET AF trial was analyzed in comparing rivaroxaban with warfarin in patients less than 75 years old as well as greater than 75 years old. The primary efficacy endpoint of preventing stroke and systemic embolism showed no significant interaction of treatment efficacy and age (p=0.3131). Per 100 patient years, rivaroxaban showed a primary event rate of 2.29 in the older population, while warfarin showed a rate of 2.85 in that same population. Among the younger population, rivaroxaban and warfarin showed 2.00 and 2.10 primary event rates respectively.

Peripheral artery disease (PAD) and other vascular diseases are risk factors for stroke and systemic embolism in patients with AF (Rasmussen et al., 2011). Of the 14,269 patients that participated in the ROCKET AF trial, 839 had PAD (Jones et al., 2014). Rivaroxaban and warfarin had similar relative effects on the primary efficacy outcomes, whether the patients had PAD or not. Hazard Ratios (HR) were 1.19 and 0.86 among patients with and without PAD respectively.

Rivaroxaban was compared with warfarin in preventing stroke and systemic embolism among patients in the ROCKET AF trial with and without a previous stroke or transient ischemic attack (TIA) (Hankey et al., 2012). In the ROCKET AF trial, 7,468 participants had a previous stroke or TIA, and 6,796 participants had no prior history of stroke or TIA. Hankey and colleagues found that stroke rates were higher in patients who had previously had a stroke or TIA compared to those who had not. When treating patients in both of these groups, the authors found that rivaroxaban and warfarin were both consistent in decreasing the risk of stroke or TIA. There were no measures that showed a statistically significant difference between rivaroxaban and

warfarin among those patients. Disabling or fatal stroke (p=0.07) and fatal stroke (p=0.09) were the two closest measures to statistical significance. It should be noted that due to the low number of patient outcomes, statistical power was not met, increasing the possibility of false negative outcomes. These findings correlate closely with the J-ROCKET trial findings for secondary outcomes, demonstrating that rivaroxaban is noninferior to warfarin in secondary stroke prevention (Tanahashi et al., 2013)

According to the J-ROCKET trial, which included 1,278 patients and used a reduced dose of 15mg of rivaroxaban, the net clinical benefit from receiving rivaroxaban vs. warfarin nominally favored rivaroxaban (Tanahashi et al., 2013; Uchiyama, et al., 2014). While there was no significant difference between the two drugs, there was a positive net clinical benefit in patients with $CHADS_2$ (Congestive heart failure, Hypertension, Age≥75 year, Diabetes mellitus, prior Stroke or transient ischemic attack) having a score of 2 or more and moderate renal insufficiency patients. $CHADS_2$ scoring is a worldwide scoring system that grades stroke risk factors (Hori, et al., 2014). The primary efficacy endpoint of stroke or non-central nervous system (CNS) systemic embolism favored rivaroxaban at 1.26% per year vs. 2.61% among patients taking warfarin (p=0.050) (Hori, et al., 2012). The secondary endpoints of all-cause stroke and ischemic stroke both occurred at reduced rates among rivaroxaban patients compared to warfarin patients.

The J-ROCKET trial was broken down in relation to the $CHADS_2$ score and evaluated for the safety and efficacy of warfarin compared to rivaroxaban (Hori, et al., 2014).The mean $CHADS_2$ score among the 1,278 patients participating the J-ROCKET trial was 3.25 with scores of 0 and 1 being excluded from the trial. It was found that rivaroxaban decreased the primary efficacy end point rate of stroke or systemic embolism more so than warfarin numerically, but

without statistical significance. Rivaroxaban was found to be noninferior to warfarin in preventing stroke and thromboembolism in AF patients among this Japanese specific study (Tanahashi, et al., 2013). The J-ROCKET trial was analyzed for secondary prevention of stroke: This included patients with non-CNS systemic embolism, transient-ischemic attack, and a previous stroke. There was no significant difference found between rivaroxaban and warfarin among these patients in prevention of stroke. Both rivaroxaban and warfarin were found to be effective consistently among patients for both primary and secondary prevention of stroke.

In a recent meta-analysis, 21 articles were analyzed comparing anticoagulant medications with their use in preventing stroke in AF patients (Assiri et al., 2013). It was found that warfarin and the new anticoagulants, including rivaroxaban, decreased the risk of ischemic stroke by comparable degrees. When considering stroke or systemic embolism as a whole, rivaroxaban and the newer anticoagulants demonstrated increased protection over warfarin. None of the anticoagulants showed prevention of vascular death while both warfarin and rivaroxaban showed a comparable reduction in all-cause mortality. A Chinese randomized clinical trial has shown rivaroxaban producing significant results of lowered stroke and systemic embolism event rates compared to warfarin therapy (Mao, Li, Li, & Yuan, 2014). The results of this 353 patient trial included a 4% event rate of stroke or systemic embolism for warfarin and 2.8% for rivaroxaban with a p-value less than 0.05.

A meta-analysis comparing the efficacy of new oral anticoagulants and warfarin took into account three major trials, the RE-LY, ROCKET AF, and ARISTOTLE (Miller, Grandi, Shimony, Filion, & Eisenberg, 2012). As the data was collected for the new oral anticoagulant medications across the different studies, including rivaroxaban, it was shown that the new oral anticoagulants produced a 22% risk reduction (RR) for stroke and systemic embolism when

comparing them to warfarin. The risk of ischemic and unidentified stroke, hemorrhagic stroke, vascular mortality, and all-cause mortality was decreased with the new oral anticoagulant medications as well. Another meta-analysis also included ENGAGE AF-TIMI in the research which found that the new oral anticoagulants when compared to warfarin significantly decreased stroke and other systemic embolic events by 19% and all-cause mortality overall (Ruff, et al., 2014). While all stroke categories favored the new oral anticoagulants over warfarin, haemorrhagic stroke risk decreased the most.

Due to their increased risk of thromboembolism and bleeding, most healthcare providers choose not to prescribe patients with AF and renal dysfunction anticoagulant therapy (Fox, et al., 2011). Approximately two-thirds of rivaroxaban is metabolised by the liver with the remaining one-third being excreted as urine through the urinary tract (Kubitza, et al., as cited in Fox, et al., 2011). Patients with creatinine clearance (CrCl) rates of 30-49mL/min are considered to have moderate renal impairment. These patients achieve max serum concentrations 25-30% higher than patients without renal insufficiency (Kubitza D., et al., 2010). It was found that reducing the dose of rivaroxaban by 25% proved to be as effective as dose-adjusted warfarin. Rivaroxaban did not increase the rates of bleeding and had fewer number of total fatal bleeds.

Safety

The ROCKET AF trial produced results of major and non-major clinically relevant (NMCR) bleeding events among patients taking rivaroxaban vs. warfarin (Patel et al., 2011). Patel and colleagues added that 1,475 patients in the rivaroxaban group experienced a significant bleed compared to 1,449 patients in the warfarin group. The number of major bleeding events were non-significant in showing that rivaroxaban was better or worse than warfarin. The rate of

fatal bleeding was less significant in the rivaroxaban group, but produced more non-fatal episodes of gastrointestinal bleeding. Patients enrolled in the rivaroxaban group also a higher rate of hemoglobin dropping by 2 grams per deciliter or more, and required more blood transfusions than the warfarin population. Patients with a previous history of stroke or TIA who had a previous stroke or TIA, rivaroxaban continued to show these same safety outcomes when compared to warfarin (Hankey, et al., 2012). The Hankey international cohort study showed no difference in the case fatality from intracranial hemorrhage between the rivaroxaban and warfarin groups, but rivaroxaban showed a statistically significant lower risk of intracranial hemorrhage over warfarin.

When grouping patients into categories of less than 75 years old and 75 years old or greater in the ROCKET AF trial, the older population showed a greater risk of major bleeding than the younger population (4.63 per 100 patient-years and 2.74 per 100 person years respectively, $p<0.0001$) (Halperin et al., 2014). Regarding major bleeding events, when comparing rivaroxaban and warfarin between these two age groups, there was found to be no significant differences between them. Patients with PAD demonstrated a significantly higher risk of major or NMCR bleeding compared to those without PAD (HR 1.40 and 1.03 respectively, $p=0.037$) (Jones, et al., 2014). PAD patients on rivaroxaban therapy demonstrated a higher relative hazard of bleeding (major or NMCR) compared to the patients on dose-adjusted warfarin. This finding is inconsistent with the core trial results.

The average percentage of time that warfarin therapy fell within therapeutic range was 55% among the patients in the ROCKET AF trial (Patel, et al., 2011). This percentage is lower than other studies have suggested with patients taking warfarin therapy. For example, in the Veterans Affairs Study to Improve Anticoagulation, the average percentage of time spent within

therapeutic range was 58% (Rose, et al., 2011). It was found that after breaking the patient population of the ROCKET AF trial down into quartiles based on center time in therapeutic range (cTTR), the lowest quartile demonstrated a lower bleeding risk and the higher quartile demonstrated a higher bleeding risk for both rivaroxaban and warfarin (Piccini, et al., 2014). The reason for the lower bleeding risk among the lower cTTR can be attributed to the fact the deviation often occurs on the lower end of the therapeutic range rather than the higher end. When comparing rivaroxaban and warfarin among these patients it was found that cTTR does not have an impact on treatment effect. The event rate for major and NMCR bleeding was lower for rivaroxaban in the bottom two quartiles (11.30 and 11.72) compared to warfarin (14.12 and 12.21), but higher in the upper two quartiles (rivaroxaban: 15.10 and 20.61, warfarin: 14.88 and 16.72).

Adverse effects of temporary interruption (TI) of rivaroxaban therapy were compared with those of TI of warfarin therapy in The ROCKET AF trial (Sherwood et al., 2014). Sherwood and colleagues found that TI of either drug resulted in an increased risk of thromboembolism, with the at-risk period defined as the start of the TI to 30 days after restarting the medication. Of the 14,236 participants in the ROCKET AF, 4,692 required a TI. Of those patients, 2,130 patients required a TI because of a surgical or invasive procedure. When analyzing both the TI group as a whole and those that required a TI for an invasive procedure, there was found no difference in the risk of major bleeding or NMCR bleeding between patients given rivaroxaban and warfarin (Patel et al., 2013).

At the completion of the ROCKET AF trial, participating patients who were converting from their blind study drug to either warfarin or rivaroxaban were evaluated for stroke, non-CNS embolism, and aggregate thrombotic events. The number of stroke or systemic embolism events

was higher among the population making the transition from rivaroxaban to warfarin through the first month post-termination of the randomized treatment (rivaroxaban – 22, warfarin – 7, p=0.008) (Hankey et al., 2012). In a 32,886 participant retrospective cohort study, it was shown that rivaroxaban patients consistently had better persistence and lower discontinuation rates when compared to patients taking warfarin (Nelson et al., 2014).

Analysis of the ROCKET AF trial for the management and outcomes of major bleeding events found that patients taking rivaroxaban were less likely to need fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) (Piccini et al., 2014). The use of packed red blood cells (PRBCs) and the overall outcomes after bleeding events did not differ significantly between the rivaroxaban and warfarin treated groups. According to Siegal and Crowther (2013), there is expressed concern among physicians about no reversal agent being available for rivaroxaban as there is for warfarin. The authors added, however, that the clinical impact is not known for the use of reversal agents in the event of serious bleeding, as the overall outcomes did not differ significantly between the two drugs.

According to Hori et al. (2012), the J-ROCKET AF study demonstrated that rivaroxaban was non-inferior to warfarin when comparing the principle safety outcome of major or NMCR bleeding. The authors added that there were no significant differences between the two drugs in relation to bleeding rates, but pointed out that a higher incidence of gastrointestinal (GI) bleeding among the warfarin patient population was reported, compared to the rivaroxaban patient population. In addition, warfarin was associated with higher rates of intracranial hemorrhages and fatal bleeding events.

Hori et al. (2014) reported that there were no differences found between rivaroxaban and warfarin for major bleeding events, as patients with $CHADS_2$ scores of 2, 3, 4, and 5 produced

HR's of 0.57, 0.85, 0.77, and 1.01 respectively. The authors pointed out that major and NMCR bleeding rates were reported as 14.3%, 17.6%, 20.3%, and 22.8% per year for rivaroxaban patients and 13.7%, 14.5%, 25.6% and 15.9% per year for warfarin patients with $CHADS_2$ scores of 2, 3, 4, and 5 respectively (p=0.700).

According to Tanahashi et al. (2013), rivaroxaban demonstrated a 17.02% rate per year of principal safety outcome in the secondary prevention group of the J-ROCKET AF trial, with warfarin demonstrating a 18.26% rate per year. The authors pointed out that rivaroxaban produced a principle safety outcome rate in the primary prevention group of 19.76% per year, while warfarin produced a rate of 13.46% per year, and added that there was no significant interaction between the primary and secondary prevention groups for the principle safety outcome of major bleeding or NMCR bleeding. Hori et al. (2012) noted that these findings correlate well with those of patients with renal impairment, as there was no significant relative risk found for major bleeding or NMCR bleeding in patients with a baseline creatinine clearance (CrCl) of 30-49 ml/min, and added that patients with this renal function status received a reduced dose of 10mg of rivaroxaban in the J-ROCKET AF trial. Mao et al. (2014) reported that in a randomized controlled trial utilizing Chinese patients with AF, rivaroxaban produced a significantly higher number of major bleeding events from the GI site (4.5%) compared to warfarin (0.6%) (p=0.04), and added that no statistically significant differences were found in all other bleeding events in this trial between rivaroxaban and warfarin.

The mixed treatment comparison meta-analysis of 21 trials showed no statistically significant risk reduction of major bleeding events between warfarin and rivaroxaban (Assiri et al., 2013). There was no significant reduction between the two medications when comparing NMCR bleeding or rates of intracranial hemorrhage. The meta-analysis comparing the major

studies of new oral anticoagulants and warfarin found the results of major and GI bleeding risk was insignificant due to wide confidence intervals (Miller et al., 2012). Randomization to the new oral anticoagulants demonstrated a statistically significant risk reduction for intracranial bleeding (risk-reduction 0.49, 95% confidence interval 0.36 to 0.66).

Conclusions

AF is the most common clinically significant arrhythmia among the population due to its associated increased risk of atrial thrombi formation which increases a patient's risk of stroke. Warfarin therapy as long been used to prevent stroke in AF patients with much success. The new novel oral anticoagulant medication, rivaroxaban, has proven to be noninferior to warfarin in prophylaxis of stroke in nonvalvular AF while proving a safety profile which does not require regular blood level checks with dosing adjustments.

The ROCKET AF trial demonstrated that rivaroxaban and warfarin showed no statisticaly significan differences in preventing stroke and systemic embolism in those greater than 75 years old and those with PAD and other vascular diseases. Similar results suggesting no statistcally significant difference between rivaroxaban and warfarin were demonstrated when evaluating the ROCKET AF participants who previously had a TIA and preventing a future TIA. These results were further strengthened by the J-ROCKET trial which also demonstrated rivaroxaban being noninferior for secondary stroke prevention in comparison to warfarin. The new oral anticoagulants produced results of a 22% RR for stroke and systemic embolism in comparison to warfarin. Similarly, there was a 19% reduction in all cause mortality with the new anticoagulants compared to warfarin.

The ROCKET AF trial demonstrated that while rivaroxaban produced more events of gastrointestinal bleeds and more blood transfusion, it was associated with a lower rate of fatal bleeding compared to warfarin. Rivaroxaban also was proven to have a statistally significant lower risk of intracranial hemorrhage, compared to warfarin. It was found that rivaraoxaban and warfarin did not differ when TI's occurred among the population. While concern is high regarding the absence of a reversal agent for rivaroxaban, it was shown that the overall outcomes

after bleeding events did not differ significantly between the rivaroxaban and warfarin treatment groups.

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Abstract

Atrial fibrillation is the most common clinically significant arrhythmia among the population resulting in a large amount of our population being at an increased risk of stroke. Traditional vitamin-K anagonist therapy is now being challenged by the use of the novel anticoagulant medications such as rivaroxaban. The goal of this report is aid healthcare providers in making an educated decision on which medication start their AF patients on for the prevention of stroke. This report has been written after evaluating extensive search criteria in efforts to find any and all information related to warfarin's and rivaroxaban's efficacy and safety profiles in their relation to the prophylaxis of stroke in non-valvular AF. While there are clear risks and benefits to using either of these medications, each patient must be carefully evaluated before starting any form of treatment including the patients ability to follow up with warfarin clinics and INR monitoring. This report found that rivaroxaban was noninferior to warfarin the prevention of stroke in non-valvular AF patients. Rivaroxaban produced significantly more gastrointestinal bleeds while warfarin produced significantly more incidences of intracranial hemorrhages.