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Optimal Anti-Thrombotic Regimen in Watchman Therapy

John McCarty
Yale Physician Associate Program, john.mccarty@yale.edu

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Abstract

Nonvalvular atrial fibrillation is the most common sustained arrythmia and an independent risk factor for stroke. Today, 6 million Americans live with this disease. The current standard of care to prevent thrombus formation are anticoagulants such as warfarin. Left atrial appendage occlusion devices are a recently available alternative to long-term anticoagulation. However, it has been learned that thrombus may form on these devices in the early months after deployment, so short-term antithrombotic therapy is recommended for up to 6 months. To date, there have been no studies to determine the optimal antithrombotic therapy regimen post implant. The present study reviews what is known about antithrombotic therapy and proposes a randomized controlled trial to compare the potential utility of direct oral anticoagulant therapy to the presently recommended strategy using warfarin and dual-antiplatelet therapy. Determining the proper antithrombotic profile for post device-placement patients will reduce complications of atrial fibrillation.

Chapter 1

Background

Atrial fibrillation (AF) is the most common cardiac arrythmia in the United States.[1] The lifetime risk for developing AF is 1 in 4 for men and women 40 years of age or older who have congestive heart failure and 1 in 6 in those who don't.[2] It afflicts 10% of individuals 80 or older in the United States.[1] The prevalence of atrial fibrillation will likely increase in the coming years because its prevalence increases with age and the majority of our population is aging. It is estimated that by 2030, one in five Americans will be 65 or older.[3] Along with this, the average U.S. life expectancy has increased from 68 years in 1950, to 78.6 years in 2017.[4] Thus, by the year 2030, with no increase in the current incidence of AF, the prevalence of AF is expected to increase from 6 million to 9.3 million.[5]

AF is sub-classified into valvular and non-valvular AF forms because the threat of stroke is greater and the anticoagulant treatment strategy is more stringent in valvular AF. Non-valvular atrial fibrillation (NVAF) results from many potential physiologic and pathophysiologic mechanisms such as aging, hypertension, heart failure, cardiomyopathies, and coronary artery disease. In many people, it is idiopathic. There may be underlying genetic factors that predispose to its occurrence, but this knowledge is in its infancy. Complications of atrial fibrillation include stroke, heart failure, hospitalization, cognitive dysfunction, and lower exercise capacity.[6] The most disabling potential complication of NVAF is stroke; 15-25% of all strokes may be related to NVAF.[7]

Most strokes that occur as a result of NVAF are due to formation of a thrombus in the left atrial appendage. A portion of the thrombus may embolize to a distant vessel and prevent blood flow to its vascular territory, subsequently causing ischemia to the tissue that is perfused by the blood vessel. This process occurring in a cerebral vessel leads to embolic stroke that is often large and disabling. Warfarin was the first anticoagulant used to minimize the occurrence of left atrial thromboembolism. It has been shown to reduce the risk of stroke in AF patients by approximately 60%.[8] However, warfarin is not a perfect solution to this issue due to its many interactions with food and medications and the blood testing that is required to monitor the international normalized ratio (INR). INR monitoring is required to ensure therapeutic effect and minimize the risk of bleeding due to excessive anticoagulation. As many as 26 drugs and foods interact with warfarin, leading to both potentiation and inhibition of warfarin's pharmacological effects. Nafcillin, barbiturates, carbamazepine, cholestyramine, and foods high in vitamin K (such as spinach and other leafy greens) can reduce levels of warfarin in the blood, causing the INR to drop, and subsequently increase the risk of thromboembolism. The opposite effect is also possible with drugs such as amiodarone that can increase the levels of warfarin in the blood and subsequently cause the INR to increase.[9] An increase in INR can lead to increases in bleeding. Moreover, warfarin compliance is commonly poor, with one in five doses being taken incorrectly even in the setting of a dedicated anticoagulation clinic. An increase or decrease in INR can lead to excessive bleeding or a thrombotic state, respectively.[10]

In 2011, direct-acting oral anticoagulants (DOAC's) became available. Drugs such as dabigatran, a direct thrombin inhibitor, and the direct factor Xa inhibitors

rivaroxaban, apixaban, and edoxaban have expanded the field of antithrombotic therapy for stroke and systemic embolism prevention in NVAF.[11] Apixaban has been shown to be superior to warfarin in preventing stroke or systemic embolism, minimizing bleeding, and reducing mortality.[12] Rivaroxaban was shown to be noninferior to warfarin for the prevention of stroke or systemic embolism. There was also no significant difference in the risk of major bleeding and intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.[13] In a review of all four DOACs, apixaban, edoxaban, rivaroxaban, and dabigatran, these medications were shown to have a lower incidence of intra-cranial bleeding (0.6%) than warfarin (1.4% per year) with a relative risk reduction of 57% (95% confidence interval 31-73%).[14] The DOAC trials demonstrated that patients could safely take those agents instead of warfarin with equivalent therapeutic efficacy, no additional complications, reduced risk of intra-cranial bleeding, fewer drug and food interactions and no need for constant monitoring of INR. Although the DOAC's, have potential advantages over warfarin, they still present the problem of compliance. It is estimated that 50% of patients taking life-long/chronic oral medications either forget to take their medications regularly or do not adhere to the guidelines for taking the medication.[15] Even fairly brief suspension of DOAC therapy has been reported to result in thromboembolism.[13] Non-adherence is likely going to continue to be an issue and a major reason for concern with any antithrombotic drug prescribed for life-long anticoagulation.[16]

Given the potential limitations of oral anticoagulation therapy to reduce stroke risk in NVAF, and based upon observations in patients who undergo cardiac surgery, resection or occlusion of the left atrial appendage has been recommended as a therapy to

decrease the occurrence of stroke in patients with atrial fibrillation.[17] In a large retrospective cohort study, investigators observed that concurrent surgical left atrial appendage occlusion in patients undergoing coronary artery bypass graft and valve replacement was associated with a lower risk of subsequent stroke and all-cause mortality.[18] Complete surgical resection of the left atrial appendage may be technically challenging and hazardous in some patients and, therefore, is not suitable for all patients. For this reason, slightly less aggressive approaches to exclusion of the left atrial appendage through various techniques have been proposed. Unfortunately, they have proved to be disappointing. In the left atrial appendage occlusion study (LAAOS), transesophageal echocardiographic follow-up imaging demonstrated that only 45% of patients in whom the opening of the left atrial appendage had been sutured, and 72% in whom it had been stapled achieved complete occlusion.[19] Any residual flow that may accompany these incomplete occlusions increases the risk of patients developing a thrombus and subsequent embolic complications, leading investigators to search for new and safer alternatives.

Given the risk and potential limitations of surgical approaches to left atrial appendage exclusion, several approaches to less invasive, transcatheter left atrial appendage occlusion have been devised and tested. On March 13, 2015, one such device, the Watchman received FDA approval for use in the USA.[20] Watchman is a self-expanding nitinol frame left atrial appendage closure (LAAC) device that can be inserted into the left atrial appendage via a transvenous approach incorporating transseptal puncture to deliver the device from the right atrium to the left atrial appendage. Once in the left atrial appendage, the device is expanded and a polyester fabric cover prevents

clots from forming in the left atrial appendage. Over several months, the device then undergoes endothelialization in the left atrial appendage, with the hope that this will fully occlude the orifice of the left atrial appendage and prevent peri-device leakage.[21] The PROTECT AF trial showed that percutaneous placement of the Watchman LAAC device was non-inferior to warfarin in reducing the combined outcome of stroke, systemic embolism, and cardiovascular death and was superior to warfarin in reducing cardiovascular and all-cause mortality.[22] In the PREVAIL trial, WATCHMAN placement was noninferior to warfarin in reducing ischemic stroke and systemic embolism.[23] A recent study in high risk AF patients with CHA_2DS_2-VASc (CHF history, Hypertension history, Age, Diabetes history, Sex, Stroke/TIA/thromboembolism history, Vascular disease history) score of 5 of higher demonstrated that the Watchman device appeared to be safe with a residual annual ischemic stroke risk of 2.8%. In such a high-risk patient population, the estimated annual stroke risk is about 12% in patients not receiving oral anticoagulation and about 4% in those on warfarin anticoagulation.[24]

Statement of the Problem

The issue with Watchman is that the device itself may serve as the nidus for thrombus formation until it becomes fully endothelialized, a process that may take 3 to 6 months.[25] Thus, there is a continued need for antithrombotic therapy for at least several months after its placement. For this reason, in the three trials mentioned above, PROTECT AF, PREVAIL, and the recent WATCHMAN trials in high risk patients, all patients were started on oral anticoagulation after implantation of the device. This anticoagulation mostly consisted of warfarin and was continued for 45 days. At 45 days, patients were switched to clopidogrel and aspirin, a regimen that was continued for six

months post-procedure. This antithrombotic strategy was entirely empirical, no randomized studies have been conducted to determine the optimal antithrombotic therapy after placement of WATCHMAN. Current literature does suggest that there may be a better alternative to the strategy that was used in the trials above.

It was demonstrated in the RE-DUAL PCI trial that patients with atrial fibrillation who had undergone PCI with coronary stent placement, and thus had indication for both anticoagulant and antiplatelet medication, had equivalent protection from stent thrombosis but a lower risk of bleeding if they took dabigatran and a $P2Y_{12}$ inhibitor compared to warfarin, a $P2Y_{12}$ inhibitor, and aspirin.[26] Two further studies of anticoagulation in patients with AF who undergo coronary stenting reached similar conclusions: therapy with a DOAC and a $P2Y_{12}$ inhibitor (chiefly clopidogrel) proved to be superior to triple therapy with warfarin, aspirin, and clopidogrel.[27,28]

One small study that examined the potential use of DOAC medication instead of warfarin after Watchman placement in patients at the Cleveland Clinic gave promising results. The study monitored 37 patients who had received DOACs (either dabigatran, apixaban, or rivaroxaban) for any occurrence of bleeding or thromboembolic complications. In this study, all 37 patients completed 45 days of DOAC medication. There were 4 cases of bleeding: 2 minor gastrointestinal bleeds, 1 groin hematoma, and one arm hematoma. There were no reported device related thrombosis, stroke, or death in the group. Additionally, every patient on a DOAC medication demonstrated effective left atrial appendage occlusion on transesophageal echocardiogram at 45 days post implantation.[29] While this study was small, retrospective and had no control group, it

provides observational data supporting the use of DOAC medications after Watchman deployment.

These observations raise the question about what the proper antithrombotic therapy should be after PCI placement of the WATCHMAN device. Might therapy with DOAC plus clopidogrel be superior to use of warfarin, aspirin, and clopidogrel? The advantages of DOACs include lack of INR monitoring, less bleeding (especially intracranial bleeding), and possibly decreased thromboembolic events. No prospective trials of DOAC therapy after Watchman implant have been conducted. The present study will examine if a low dose DOAC and $P2Y_{12}$ inhibitor regimen after Watchman placement is more effective at preventing bleeding and thromboembolism compared to the antithrombotic therapy currently being used.

Goals and Objectives

This study aims to assess if there exists a more beneficial and less harmful antithrombotic profile for patients who undergo Watchman device implantation. Specifically, this study seeks to determine if substituting apixaban for warfarin and adding clopidogrel in the first 45 days of antithrombotic therapy will decrease the rate of device-related thrombus formation over 6 months of follow-up. Antithrombotic therapy after 45 days will continue as described by the current standard of care.

The objectives of this study are to: 1) randomize a sufficient number of patients who meet the inclusion criteria (and do not meet the exclusion criteria) into two separate groups: apixaban and clopidogrel post-procedure or warfarin and aspirin post procedure; 2) perform transesophageal echocardiograms at 45 days and 6 months post-procedure to evaluate for peri-device leakage and device related thrombus; and 3) determine over 6

months of follow-up whether patients in either group demonstrate lower rate of device-related thrombus formation.

Hypothesis

The chief hypothesis of the study is that patients who receive the Watchman device and direct oral anticoagulant (apixaban) and $P2Y_{12}$ inhibitor (clopidogrel) therapy transitioning into daily aspirin therapy will experience device associated thrombosis, over 6 months of post-implant follow-up at a rate equal to or less than those who receive warfarin, transitioning to clopidogrel and aspirin, the current standard of care.

Definitions

Watchman- The left atrial appendage occlusion device under study (and the only device that has to date received FDA approval for clinical use in the USA).

"Current standard of care"- warfarin, with target INR of 2-3, plus aspirin 81 mg daily for 45 days post-implant of Watchman, then, if there are no signs of device-related thrombus or peri-device leakage, clopidogrel 75 mg daily and aspirin 81 mg daily until 6 months have elapsed post-device implant. After this, aspirin is continued at 81 to 324 mg daily indefinitely.

Apixaban dosing- 5 mg twice daily [reduced to 2.5 mg twice daily if patient has 2 of 3 of the following characteristics: age of 80 or older, serum creatinine > 1.5 mg/dL or weight < 60 kg].

Clopidogrel dosing- 75 mg daily

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Chapter 2

Introduction

A thorough literature search was conducted between July 2019 and April 2020 using PubMed and Ovid. Keywords used initially to identify relevant articles included combinations of “Watchman”, “Warfarin”, “Atrial Fibrillation”, “DOAC”. All clinical trials, controlled studies, meta-analyses and systematic reviews that were considered pertinent to the topic were retained for review. After this initial search, the abstract of each of these articles was screened for relevance. Relevant articles were completely and critically reviewed. Relevant source material found within the bibliography of these sources was also reviewed. The entire process included 22 articles critically read and annotated.

Review of Empirical Studies About the Relationship Being Studied

History of Anticoagulation

The need for anticoagulation in AF is an undisputed fact today in medicine. The decreased movement of blood in the left atrium creates an environment suitable to forming a thrombus. In a meta-analysis analyzing six separate trials and 2900 participants, it was found that patients who achieved a mean International Normalized Ratio (INR) from 2.0-2.6 on dose-adjusted warfarin had an average stroke rate of 4.5% per year, far less than patients who received no anticoagulation and had a stroke rate of 12% per year.[1] In this same study, patients treated with warfarin experienced a 64% (95% Confidence Interval, 49% to 74%) reduction in all strokes, with the reduction in disabling and nondisabling stroke similar. When only ischemic strokes are taken into consideration,

the warfarin treated patients demonstrated a 67% (Confidence interval, 54% to 77%) relative risk reduction.[1] It is apparent that anticoagulation in AF is a necessity, but the authors did acknowledge that warfarin therapy posed difficulties due to the INR blood testing required for its safe and effective administration and its many interactions with food and medications that can alter the INR.[2] An alteration of the INR can cause patients to be hypo/hypercoagulable depending on which way the INR moves, which can lead to complications. The hypercoagulable state and associated complications were examined in a 1996 study. Patients with a mean sub-therapeutic INR level (< 2.0) were found to have a higher risk of stroke compared to those with therapeutic INR levels (2.0-3.0) (INR = 1.7 hazard ratio 2.0, 95% Confidence interval 1.6-2.4, INR = 1.5 hazard ratio 3.3, 95% Confidence interval 2.4-4.6, INR = 1.3 hazard ratio 6.0, 95% Confidence interval 4.4-24.5).[3] Even with these known complications, dose-adjusted warfarin was the standard of care for AF anticoagulation for the last two to three decades of the 20th century due to its effectiveness in reducing stroke and mortality while patients maintained a therapeutic INR.

Advancement of Anticoagulation for Atrial Fibrillation

Due to the difficulties associated with warfarin dosing and maintenance, direct oral anticoagulant (DOAC) medications were created. These medications work through non-vitamin K antagonistic mechanisms and are collectively referred to as direct acting oral anticoagulants (DOACs). The four medications in this class of drugs that are presently available for clinical use are dabigatran, edoxaban, rivaroxaban, and apixaban.

The first DOAC that was studied and approved for us by the FDA in 2010 for the use in patients with non-valvular AF was dabigatran. This drug works through direct

thrombin inhibition. Contrary to warfarin, dabigatran does not need to be monitored through routine blood testing and has many fewer drug and food interactions. In the Dabigatran versus Warfarin in Patients with Atrial Fibrillation trials (RE-LY trial), dabigatran was investigated as being an alternative to warfarin for reducing stroke in patients with AF. The RE-LY trial was a randomized control trial that sought noninferiority for dabigatran. A total of 18,113 patients was enrolled and the median duration of the follow-up period was 2 years, with complete follow up achieved in over 99% of participants. The primary outcome of stroke or systemic embolism was 1.53% per year in patients receiving 110 mg of dabigatran twice daily, 1.11% per year in patients receiving 150 mg of dabigatran twice daily, and 1.69% per year in patients receiving warfarin; both doses of dabigatran were statistically noninferior to warfarin therapy in preventing stroke or systemic embolism ($p < 0.001$). The 150 mg dose of dabigatran also achieved superiority to warfarin for this outcome with a relative risk of 0.66 (95% Confidence interval 0.53-0.82, $p < 0.001$).[4] The rates of hemorrhagic strokes were also lower in both dabigatran groups compared to warfarin with a relative risk of 0.31 (95% Confidence interval 0.17-0.56, $p < 0.001$) for the 110 mg group and a relative risk of 0.26 (95% Confidence interval 0.14-0.49, $p < 0.001$) in the 150 mg group.[4] Another concern with anticoagulation is an increase in bleeding. In the RE-LY trial, the relative risk in the 110 mg group was 0.80 compared to warfarin (95% Confidence interval 0.69-0.93, $p = 0.003$). However, the 150 mg group did not achieve significance in reduction of major bleeding compared to warfarin (relative risk 0.93, 95% Confidence interval 0.81-1.07, $p = 0.31$).[4] The RE-LY trial demonstrated that dabigatran was not only noninferior to warfarin but superior when assessing stroke, systemic embolism, and hemorrhagic stroke,

all while being an easier medication for patients to take and reducing the need for routine INR monitoring. In another trial, REDUAL PCI, the use of dabigatran and clopidgrel was compared to warfarin, clopidogrel, and aspirin for patients with AF that who had undergone percutaneous coronary intervention with coronary stents that required antiplatelet therapy to prevent stent thrombosis. This study achieved noninferiority for the high-dose dabigatran group and noninferiority and superiority for the low-dose dabigatran group compared to warfarin, clopidogrel, and aspirin therapy when considering a primary end point of first major or clinically relevant nonmajor bleeding events (low-dose hazard ratio 0.52, 95% Confidence interval 0.42-0.63, $p < 0.001$ for noninferiority, $p < 0.001$ for superiority; high dose hazard ratio 0.72, 95% Confidence interval 0.58-0.88, $p < 0.001$ for noninferiority).[5] This is another trial that demonstrates that dabigatran is an effective alternative to warfarin for anticoagulation in AF patients.

In a more recent systematic search, including observational studies comparing dabigatran with warfarin, dabigatran was found to be comparable (noninferior) to warfarin in preventing ischemic stroke among patients with AF. Patients who received dabigatran 150 mg twice daily had a hazard ratio of 0.92 (95% Confidence interval 0.84-1.01, $p = 0.066$) when compared to warfarin.[6] Dabigatran, given in a dose of 150 mg twice daily was also found to have a significantly greater hazard of gastrointestinal bleeding compared to warfarin in patients over 75 years old (hazard ratio 1.23, 95% Confidence interval 1.01-1.50, $p = 0.041$) which was not observed in the RE-LY trial.[6] This is most likely due to the fact that the RE-LY trial had a mean age of 69.[4] The risk of gastrointestinal bleeding with dabigatran is significant, in great part due to the fact that the drug requires an acidic gastric milieu for optimal absorption, so it is compounded

with tartaric acid in the capsule. Its use necessitates careful patient selection and patient-provider shared decision making when choosing between dabigatran and warfarin. It should also be noted that dabigatran, even in its highest dose, demonstrated a lower risk of intracranial bleeding compared with warfarin (hazard ratio 0.44, 95% Confidence interval 0.34-0.59, $p < 0.001$). In summary, studies with dabigatran demonstrate that it is at least non inferior to warfarin in preventing left atrial thromboembolism in patients with AF, is associated with lower risk of intra-cranial bleeding and provides greater convenience and freedom from potentially harmful interactions with food, drink, and medications than warfarin. Its greater tendency to cause gastro-esophageal irritation and bleeding represents its one potentially serious drawback compared to warfarin.

The second DOAC that received FDA approval for clinical use, in November 2011, is the factor Xa inhibitor rivaroxaban. Rivaroxaban was also studied against warfarin in the prevention of stroke and systemic embolism in patients with AF in the rivaroxaban versus warfarin in nonvalvular atrial fibrillation trial (ROCKET-AF trial). This was a double blinded randomized control trial that enrolled over 14,000 patients with AF. In the primary endpoint, a composite of stroke and systemic embolism, rivaroxaban was found to be noninferior to warfarin with a hazard ratio of 0.79 (95% Confidence interval 0.66-0.96, $p < 0.001$).[7] Major and nonmajor bleeding were also evaluated in the trial, with rivaroxaban having a hazard ratio of 1.03 (95% Confidence interval 0.96-1.11, $p = 0.44$).[7] Lastly, the study examined intracranial hemorrhage and gastrointestinal bleeding between rivaroxaban and warfarin. Rivaroxaban had significantly less rates of intracranial hemorrhage (hazard ratio 0.67 95% Confidence interval 0.47-0.93) when compared to warfarin. However, rivaroxaban did have

significantly more gastrointestinal bleeding during the study with 224 events (3.2%) compared to warfarin with 154 events (2.2%) ($p < 0.001$).[7] This study demonstrated that rivaroxaban was clinically a more useful drug than warfarin due to the lack of monitoring that is needed, noninferior nature of preventing stroke and systemic embolism, and superior nature of preventing intracranial hemorrhage. However, the study did highlight the excessive gastrointestinal bleeding events seen with rivaroxaban compared to warfarin. Another study examined the use of rivaroxaban over warfarin in patients with both AF and stage IV-V chronic kidney disease. In this study, rivaroxaban was found to have a hazard ratio of 0.93 (95% Confidence interval 0.46-1.90, $p = 0.85$) compared to warfarin for the risk of stroke and systemic embolism. Rivaroxaban also had a hazard ratio of 0.91 (95% Confidence interval 0.65-1.28, $p = 0.60$) compared to warfarin for major bleeding.[8] These data did not show superiority or noninferiority, but did demonstrate equivalence between the two drugs. Rivaroxaban, like the other DOACs, has many fewer drug or food interactions than warfarin and it does not require routine INR monitoring.

The third DOAC medication available on the market is apixaban, which received FDA approval in December 2012. Apixaban is another factor Xa inhibitor. In the apixaban versus warfarin in patients with atrial fibrillation trial (ARISTOTLE), it was found that apixaban was both noninferior and superior to warfarin for stroke and systemic embolism prevention (hazard ratio 0.79 95% Confidence interval 0.66-0.95, $p < 0.001$ for noninferiority and $p = 0.01$ for superiority).[9] The apixaban group also demonstrated significantly lower rates per year of major bleeding compared to the warfarin group (hazard ratio 0.69 95% Confidence interval 0.60-0.80, $p < 0.001$).[9] The rate of

hemorrhagic stroke per year was also significantly lower in the apixaban group compared to the warfarin group (hazard ratio 0.51, 95% Confidence interval 0.35-0.75, $p < 0.001$).[9] Finally, this study showed that apixaban had a lower rate of death per year compared to warfarin over the duration of the study (hazard ratio 0.89, 95% Confidence interval 0.80-0.99, $p = 0.047$).[9] All of these findings demonstrated that apixaban, compared to warfarin, prevented more strokes and systemic embolism, was responsible for fewer events of major bleeding, reduced the rate of hemorrhagic stroke, and had a lower mortality rate compared to warfarin. This study cemented apixaban as one of the most beneficial anticoagulants in treating patients with AF.

The fourth DOAC medication that has been compared to warfarin in the setting of AF is edoxaban. Edoxaban is another direct oral factor Xa inhibitor. It was approved for use by the FDA in January 2015. In the edoxaban versus warfarin in patient with atrial fibrillation trial, (ENGAGE AF-TIMI48) high dose edoxaban (60 mg daily) was found to be noninferior and superior to warfarin for stroke and systemic embolism prevention with a hazard ratio of 0.79 (95% Confidence interval 0.63-0.99, $p < 0.001$ for noninferiority, $p = 0.02$ for superiority). The low dose edoxaban group (30 mg daily) was found to be noninferior to warfarin for stroke and systemic embolism with a hazard ratio of 1.07 (95% Confidence interval 0.87-1.31, $p = 0.005$ for noninferiority and $p = 0.44$ for superiority).[10] The hazard ratio for major bleeding events for high dose edoxaban compared to warfarin was 0.80 (95% Confidence interval 0.71-0.91, $p < 0.001$) and low dose edoxaban compared to warfarin was 0.47 (95% Confidence interval 0.41-055, $p < 0.001$).[10] Thus, both doses proved more beneficial than warfarin for treatment of AF due to the reduced side effect profile and similar, if not superior, outcomes seen in the

ENGAGE AF-TIMI48 trial. Another trial that examined the use of edoxaban was the ENSURE-AF trial. This trial compared the efficacy and safety of edoxaban to a combination of warfarin and enoxaparin. When considering the primary outcome of the study, a composite of stroke, systemic embolism, and myocardial infarction, edoxaban was found to have fewer events when compared to warfarin-enoxaparin therapy in both patients who had previously received warfarin or were warfarin naïve (0.5% vs 0.9% in non-naïve [odds ratio 2.09, 95% Confidence interval 0.72-6.81] and 0.3% vs 1.4% in naïve patients [odds ratio 0.77, 95% Confidence interval 0.15-3.60]).[11] This study demonstrated no difference between the edoxaban and warfarin-enoxaparin patient groups. There was, however, one potential clinical problem with the use of edoxaban – its effectiveness was found to be uniquely sensitive to renal function. A 2016 study showed that in patients with very normal estimated creatine clearance (> 95mL/min) even high dose edoxaban (60 mg daily) was less effective than warfarin for prevention of stroke and systemic embolism.[12] At estimated creatinine clearance < 30 mL/min, the dose should be decreased and at estimated creatinine clearance < 15 mL/min, the drug is contraindicated due to anticipated poor clearance. The need for such careful dose adjustment in relation to renal function diminishes the potential population of patients to which this drug may be safely prescribed.

Selecting a DOAC

The literature provides little guidance by which to select one DOAC over another for few studies have provided head-to-head comparisons of the four available agents. However, some analyses have emerged. In a 2020 retrospective cohort study of over 99,000 patients who either took apixaban or rivaroxaban from December 2012 to January

2019, patients taking apixaban experienced ischemic stroke or systemic embolism at a rate of 6.6 per 1,000 person-years whereas patients taking rivaroxaban had an incidence of ischemic stroke or systemic embolism of 8.0 per 1,000 person-years (hazard ratio 0.82, 95% Confidence interval 0.68-0.98).[13] The authors also related that patients taking apixaban had a lower rate of gastrointestinal bleeding and hemorrhagic stroke at 12.9 per 1,000 person-years, compared to patients taking rivaroxaban at 21.9 per 1,000 person-years (hazard ratio 0.58, 95% Confidence interval 0.52-0.66).[13] Although this study suggests that apixaban may be more effective and less harmful than rivaroxaban for reducing incidence of ischemic stroke, systemic embolism, gastrointestinal bleeding and hemorrhagic stroke, the authors do outline many limitations of their analysis. Because the study was retrospective and observational, the authors were unable to control for unmeasured confounding variables (such as aspirin use, renal function, and body mass index between the two groups). Despite these limitations, this study does echo findings from prior retrospective studies in which apixaban and rivaroxaban were compared. In a 2019 retrospective population-based cohort study, over 15,000 patients either taking apixaban or rivaroxaban were examined for risk of recurrent thromboembolism and major bleeding events. Patients taking apixaban were noted to have an incidence of recurrent thromboembolism of 3 per 100 person-years compared to the rivaroxaban group who experienced an incidence of 7 per 100 person-years (hazard ratio 0.37, 95% Confidence interval 0.24-0.55, $p < 0.0001$).[14] Those taking apixaban also experienced less major bleeding (3 per 100 person-years compared to 6 per 100 person-years in the rivaroxaban group [hazard ratio 0.54, 95% Confidence interval 0.37-0.82, $p = 0.0031$]).[14]

The findings of these two large retrospective studies suggest that apixaban may be a better option than rivaroxaban.

A recent meta-analysis examined results from DOAC versus warfarin trials and highlighted a difference between apixaban and dabigatran. The meta-analysis found dabigatran was associated with a higher risk of major bleeding compared to apixaban (hazard ratio 1.37, 95% Confidence interval 1.14-1.67).[15] While this meta-analysis does pull data from multiple trials that were not controlled in the same way, it does highlight a potential shortcoming of dabigatran when compared to apixaban. The nature of this relationship not being explored in a head-to-head study should be emphasized. However, it is unlikely that dabigatran, or any DOAC, will be directly compared to apixaban.

Given its tendency for less major bleeding compared to rivaroxaban and dabigatran, lower chance of recurrent thromboembolism compared to rivaroxaban, and absence of need for renal function monitoring, apixaban has been chosen as the DOAC that will be used in our study.

Review for Confounding Variables

Major Studies

There have been three main studies examining the use of Watchman in AF patients. These are the PROTECT AF, PREVAIL, and EWOLUTION trials. The PROTECT AF and PREVAIL trials were unblinded randomized control trials in which Watchman therapy was compared to warfarin therapy. The EWOLULTION study was a multicenter, prospective, nonrandomized cohort study aimed at assessing the safety and efficacy of the Watchman device.

Operator Experience

In the PROTECT AF trial, the first study of the Watchman device, operators with more experience deploying Watchman had a lower peri-procedural complication rate of peri-device leakage and device embolization.[16] In the subsequent PREVAIL trial, no such impact of the procedural learning curve was observed: implantation success was achieved by 96.3% of experienced operators and 93.2% of new operators ($p = 0.256$).[17] This may have reflected improvement in the ability of the company proctors who attended the procedures becoming better teachers of new implanters. In the third Watchman study, the EWOLUTION trial, 75% of Watchman cases were performed by operators with less than 2 years of Watchman experience. Periprocedural adverse events occurred at a very respectable low rate of 1.5% with only one case of device embolization requiring surgery.[18] Another prospective study examined the effect of operator experience on the incidence of major adverse cardiac events, including mortality, stroke, bleeding, and vascular complications. This study showed that across three separate operator groups with differing levels of experience, major adverse cardiac event outcomes were similar (odds ratio 0.59, 95% Confidence interval 0.15-2.29, $p = 0.45$).[19] While it is impossible to completely rule out operator experience as a confounding variable, the literature does suggest that it may not play a significant role in influencing the results of our study. Moreover, physicians in the Yale New Haven Health System, as of April 1, 2020, have performed more than 150 Watchman procedures (personal communication: Dr. Craig McPherson, Director, Cardiac EP Service at Bridgeport Hospital), so operator experience is not expected to have any significant impact on our study.

Review of Methodology

Selection of Patients

In the PROTECT AF trial, patients were screened for the type of AF that they had and their CHADS score (with the more current scale being the CHA_2DS_2VASc score). A patient with a CHADS score of one or greater would be estimated to have a greater than 2% annual risk of stroke. Patients in the PROTECT AF trial were required to have a score of one or greater.[16] Patients in the PREVAIL trial were required to have a score of two or greater.[17] Patients in the EWOLUTION study did not have a required CHADS score.[18] CHADS/ CHA_2DS_2VASc scores will not be used as a selection criterion for the present study due to the clinical benefit that has already been demonstrated by Watchman for AF patients. This study aims to focus on the difference in anticoagulation regimens for the already FDA approved Watchman. Although CHA_2DS_2VASc scores may be used to characterize patients in outcome analysis they will not be part of the inclusion criteria. The patients included in this study will be those who have already been selected for Watchman implantation by their managing physicians in consultation with the members of the Electrophysiology Service staff.

Monitoring for Thrombus Formation

The occurrence of thrombus formation on the Watchman device is the primary outcome of the proposed study. The imaging modality used in the PROTECT AF, PREVAIL, and EWOLUTION trials was transesophageal echocardiography.[16-18] A recent meta-analysis examined whether another modality of imaging, intracardiac echocardiography, was feasible and useful in this population. The authors reviewed 42 studies and determined that transesophageal echocardiography and intracardiac

echocardiography gave similar results when comparing procedural success, (relative risk 1.00, 95% Confidence interval 0.97-1.03, p = 0.98) complications, (relative risk 0.77, 95% Confidence interval 0.52-1.15, p = 0.20) and procedural time (mean difference -8.02, 95% Confidence interval -22.81-6.76, p = 0.29).[20] Given that intracardiac echocardiography is an invasive study, requiring cannulation of a femoral vein, transesophageal is a somewhat less invasive procedure that lends itself well to performing post-implant follow-up in patients. It is the clinical gold standard imaging modality for detecting thrombus formation in the left atrium and on implanted left atrial appendage occlusion devices and, therefore, will be the imaging modality used in the present study.

It is imperative to monitor the device for thrombus formation due to the observed increased risk of embolic stroke. A 2018 study that analyzed the incidence of device-related thrombus after left atrial appendage occlusion found an incidence of device-related thrombus to be 7.2%. The study also demonstrated an increased risk of ischemic strokes and transient ischemic attacks in patients with a device-related thrombus (hazard rate 4.39, 95% Confidence interval 1.05-18.43, p = 0.04).[21] Another 2018 study analyzed device-related thrombus after Watchman implantation and came to similar conclusions. The incidence of device-related thrombus was lower in this study at 3.7%, however patients with a device-related thrombus were more likely to develop stroke or systemic embolism compared to those who did not develop device-related thrombi (adjusted rate ratio 3.55, 95% Confidence interval 2.18-5.79, p < 0.001).[22] These two studies highlight the importance of adequate anticoagulation after left atrial appendage occlusion and demonstrate the adverse events that are possible if a thrombus forms on the device.

The time period of monitoring for thrombus formation is also important to consider. In the PROTECT AF and PREVAIL trials, transesophageal echocardiography was completed at 45 days, 6 months, and 12 months after implantation of the Watchman.[16,17] A length of 45 days was deemed long enough in these trials for endothelialization of the device to occur. Once this has occurred, there should no longer be a substantial risk of forming a thrombus on the device. At 45 days, patients with no thrombus formation were transitioned off anticoagulant therapy and placed on dual antiplatelet therapy. Another transesophageal echocardiogram was performed at 6 months after device implantation. This was to ensure that patients were not developing thrombus formation while off anticoagulation therapy. The transesophageal echocardiogram performed 12 months post-implant was a precautionary measure to ensure that no thrombus formation had occurred after patients were transitioned to aspirin monotherapy. Neither study found a significant number of patients with device thrombus formation at the 12 months period.[16,17] These studies support our use of transesophageal echocardiography for thrombus formation surveillance and our proposed timeline of post-implant imaging, which follows current clinical practice.

Therapy Transitioning Timing

The decision on when to transition therapy from systemic anticoagulantion to dual antiplatelet therapy to eventual antiplatelet monotherapy is also described in the literature. In the PROTECT AF and PREVAIL trials, warfarin therapy was administered during the first 45 days after implantation in order to prevent thrombus formation while device endothelialization occurred. Low dose aspirin was also part of the antithrombotic therapy during this 45-day period. As described above, if there was an absence of

thrombus formation and an absence of peri-device leakage by transesophageal echocardiography at 45 days, patients were transitioned from warfarin and aspirin to dual antiplatelet therapy consisting of clopidogrel and high dose aspirin. At 6 months if there were no complications or evidence of device thrombus formation, then patients would discontinue clopidogrel therapy and continue with lifelong high dose aspirin therapy.[16,17] Again, this logic is sound due to the nature of the Watchman device. Once the device has endothelialized, the risk of thrombus formation decreases due to the body no longer reacting to the device as being a foreign object. At the 6-month period if patients have had no thrombus formation on dual antiplatelet therapy, then it is acceptable to switch patients to antiplatelet monotherapy for life-long treatment. These antithrombotic methods were also used in a recent retrospective cohort study examining the use of Watchman in patients at increased risk of intracranial hemorrhage with comorbid atrial fibrillation and a prospective study examining the use of concomitant Watchman deployment immediately after epicardial ablative therapy. The patients receiving Watchman also followed the same antithrombotic regimen stated above.[23,24] Our study will continue with the antithrombotic schedule described due to its proven effectiveness and acceptance. The goal of the present study is to determine if substitution of apixaban for warfarin represents an equivalent, or possibly superior, therapeutic strategy.

Conclusion

A thorough review of the literature examining AF and its many treatment options makes a few points extremely clear. It has been proven in multiple trials, including the RE-LY, ENGAGE AF-TIMI48, ROCKET AF, and ARISTOTLE, that DOAC medications are noninferior, and in some cases superior to warfarin in preventing left

atrial thromboembolic events in patients with AF. Specifically, DOAC medications are beneficial in preventing complications of AF such as: ischemic stroke, systemic embolism, hemorrhagic stroke, intracranial bleeding, and mortality. In cases where DOAC medications are simply noninferior to warfarin, it must be remembered that warfarin has many drug and food interactions that can create hypo/hypercoagulable states. DOAC medications have far fewer such interactions and are more convenient for patients, which may improve compliance with therapy.

Among the DOAC medications, it has been noted in multiple studies that apixaban appears to be the medication with the least amount of adverse events while providing the most benefit. That is why it has been chosen for use in the present study.

In 2015, as a result of two randomized trials, the Watchman left atrial appendage occlusion device was approved by the FDA for the prevention of left atrial thromboembolism in patients with nonvalvular AF.

The current standard of care for antithrombotic therapy after Watchman implantation consists of warfarin and aspirin, transitioning to dual antiplatelet therapy with clopidogrel and aspirin, and finally to aspirin monotherapy. This antithrombotic regimen was empirically developed and has not been tested in a randomized control trial. Current literature suggests that DOAC therapy may be a better antithrombotic regimen than warfarin for preventing device-associated thrombus formation in the first three to six months after Watchman implantation.

The currently proposed study aims to assess whether substituting the DOAC apixaban for warfarin during the first 45 days post-implantation of Watchman will be

noninferior to the current warfarin-based standard of care. Due to the nature of apixaban carrying a less burdensome side effect profile, no need for routine monitoring, and fewer drug and food interactions, this medication could be more beneficial than warfarin for patients undergoing Watchman implantation for AF.

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Chapter 3

Study Design

The proposed study will be a prospective, single (specific clinician) blinded, single health system, randomized controlled trial. The trial will take place in the Yale New Haven Health system at the New Haven, St. Raphael, and Bridgeport campuses.

Study Population and Sampling

The population will consist of men and women with nonvalvular atrial fibrillation who are referred for Watchman device therapy. Individuals who meet inclusion criteria and do not meet exclusion criteria will be enrolled on a consecutive basis as they are referred and will be randomized as they are accepted to the study (inclusion and exclusion criteria found in Table 1). The study will aim to enroll 340 patients to the study, 170 in the control group and 170 in the intervention group in order to establish a noninferiority outcome.

Inclusion Criteria	Exclusion Criteria
Age > 18	Reasons for long term anticoagulation other than atrial fibrillation
Nonvalvular Atrial fibrillation	Contraindication to warfarin or aspirin
Eligible for long term warfarin therapy	Prior stroke or transient ischemic attack within the last 90 days
Eligible to come off warfarin therapy	Symptomatic carotid disease
	Atrial septal defect requiring treatment

Table 1: Inclusion and Exclusion Criteria

Subject Protection and Confidentiality

Study participation will remain confidential to all personnel not directly involved with the study. Participants will be monitored throughout for adverse events, including stroke, systemic embolism, gastrointestinal bleeding, intracranial hemorrhage, and mortality. If a safety threshold is met, the study will be discontinued and all remaining patients will be moved to the group not experiencing the adverse events. The safety

threshold and number/severity of adverse events required to meet the threshold will be established by an outside ethics board.

Recruitment

The Bridgeport and New Haven campuses of the Yale New Haven Health system are currently eligible to proceed with the Watchman implantation procedure. These two campuses will be asked to refer patients that are sent for Watchman therapy to our study. The study will be described to the clinicians and with their permission the patients will be invited to participate. Patients will be informed of the benefits and risks associated with the study. With the patient's consent, they will be added to our sample list and randomized into either the control or intervention arm of the study. Patients will be randomized before their procedure date.

Study Methods

Participants will be instructed to discontinue oral anticoagulation 24 hours pre-procedure. Participants will be placed under general anesthesia and the Watchman device will be placed in the standard manner, percutaneously via a trans-septal approach under transesophageal echocardiographic and fluoroscopic imaging guidance. Clinicians will be able to choose from devices ranging in size between 21 and 33 millimeters. The choice of device size will be determined, as per current standard of practice, by the clinician based upon pre-implant echocardiographic imaging of the left atrial appendage.

After the device has been implanted, patients in the intervention group will be anticoagulated with 5 mg apixaban twice daily and 75 mg clopidogrel while patients in the control group will be anticoagulated with warfarin, dosed to achieve INR between 2.0-3.5, along with 81 mg aspirin.

As per standard clinical practice, patients will undergo transesophageal echocardiograms 45 days and 6 months after device implantation. Evidence of device endothelialization, flow < 5 mm in width, and absence of device related thrombus on transesophageal echocardiogram at 45 days will permit transition of antithrombotic therapy from apixaban/warfarin to dual antiplatelet therapy. Dual antiplatelet therapy will consist of 75 mg clopidogrel and 324 mg aspirin daily for both the intervention group and control group. Participants who do not show evidence of device endothelialization or who show evidence of device related thrombus will be continued on their respective anticoagulation medication for another 7 days. After 7 days, the participant will be reassessed under transesophageal echocardiography. This is a decision made by the research team and has not been used as standard practice. This process will continue until the participant shows evidence of device endothelialization and there is no evidence of device related thrombus.

At 6 months post-procedure, patients will be reassessed with transesophageal echocardiography for presence of device related thrombus. If the participant shows evidence of device related thrombus, they will be restarted on their respective oral anticoagulation. If the patient shows no signs of device related thrombus, clopidogrel will be discontinued and the patient will continue with 324 mg of aspirin daily.

Study Variables and Measures

Dependent variable: the dependent variable measured in this study will be presence of device thrombus. This is due to the correlation between existence of a thrombus and development of ischemic stroke and systemic embolism. Thrombus formation will be assessed at the transesophageal echocardiograms at 45 days and 6 months.

Independent variable: the independent variable is the choice of anticoagulant, between apixaban and warfarin.

Control variables: the control variables include: 1) the transition to dual antiplatelet therapy will be the same in both groups, at day 45 post-implant if there is no evidence of device related thrombus or peri-device leakage; 2) the agents for dual antiplatelet therapy will be the same as previously stated in the literature, 75 mg clopidogrel and 324 mg aspirin; 3) at 6 months post procedure, both groups will be transitioned from dual antiplatelet therapy to aspirin monotherapy at 324 mg per day.

Methodology Considerations

This study relies on patients adhering to their scheduled medication regimens, whether that is taking the proper dose of warfarin each day or remembering to take their apixaban. This part of the study will not be influenced by any extra outside forces in order to maintain generalizability of the study. The advantages and limitations of this decision will be discussed in chapter 4.

The decision to only blind the clinician responsible for echocardiographic interpretation was made to increase the ease of the study. More information can be found under the following section.

The decision to monitor patients for a total of 6 months is due to this being the time period where they are most likely to form a thrombus and is the current standard of clinical practice. Any thromboembolism risk outside of this time period has been shown to be minimal due to the effectiveness of the Watchman device coupled with proper daily aspirin use.

Blinding of Intervention

This is a single blinded study in which the only individuals who need to be blinded are the clinicians that read the echocardiographic images, who will be blinded to the antithrombotic regimen that each study subject is receiving. The patients do not need to be blinded because their knowing which drug they are taking cannot reasonably influence the incidence of thrombus formation on the device. The clinicians providing care to the patients do not need to be blinded because their knowledge of the patient's care is also not likely to affect the occurrence of device-related thrombus formation. This will also reduce the difficulty of the study for both patients and providing clinicians. Control group patients will be able to have their INR monitored regularly and their warfarin dose adjusted as needed. Intervention group patients will have no need to undergo routine blood testing and will be monitored by their clinicians according to the protocols for apixaban.

Blinding of Outcome

As stated above, the clinicians interpreting the transesophageal echocardiographic images are the only individuals involved with the study subjects who will be blinded to the antithrombotic therapy that each subject is receiving. Patients and other providing clinicians are able to know the results of the transesophageal echocardiographic images without influencing the results of the study.

Assignment of Intervention

The assignment of intervention will take place immediately following referral of patients to our study and before the patient undergoes Watchman implantation. A random number generator will be used with numbers between 1-340. Patients who receive an odd

number will be placed into the control group while patients who receive an even number will be placed in the intervention group. Once a number is selected from the random number generator, it will be removed from the sequence, meaning that there can be only one patient that is assigned to each study number. This will ensure an equal number of patients in each group and as we attempt to reach our target sample size of 340 patients. Randomization of the patients can be done by the investigators due to the fact that they will not be blinded to group assignment of the patients.

Adherence

Adherence to anticoagulation in the first 45 days and continued dual antiplatelet therapy up to 6 months will not be directly monitored in this study. The control group will have minor indirect monitoring of their anticoagulation compliance due to the INR checks that are required for patients taking warfarin. There are no other parts of the study that require adherence monitoring due to the nature of an implantable device. The implications and limitations of not monitoring adherence will be discussed in chapter 4.

Monitoring of adverse events

Adverse events will be monitored through routine clinician visits. Patients in the control group will already be attending periodic visits for INR checks. In these visits, the clinician will also ask if the patient has experienced any abnormal bleeding or other side effects. The intervention group will not be brought in for frequent clinical visits, but these patients will be called by a nurse on a weekly basis in order to monitor for adverse events including any bleeding, signs of peripheral embolization, symptoms of splenic or renal infarction (abdominal or flank pain, darkening of urine) or any new neurological symptoms. Patients will be encouraged to take all of their medications as prescribed and

to report any new symptoms, alterations of medications by their physicians (especially any interruption of their prescribed antithrombotic therapy), any visits to an urgent care or emergency department and any hospital admissions that they undergo during the year following device implantation.

Data Collection

Data collection will be completed within 2 years of the study start date, including up to 18 months of recruitment/enrollment and 6 months of follow up. Each patient will begin follow-up after their procedure, meaning that statistical analysis will have to wait until all 340 patients have completed 6 months of follow-up. Baseline patient data will be gathered through medical record review and interview when the patient enrolls in the study. CHA_2DS_2-VASc and HAS-BLED scores will be calculated when participants are enrolled in the study. The event rate of device thrombus formation will be assessed at 45 days and 6 months by transesophageal echocardiographic interpretations performed by blinded clinicians.

Sample Size Calculation

This trial seeks to demonstrate that apixaban is noninferior to standard warfarin therapy post-Watchman implant. The anticipated outcome of the primary event (device-related thrombus detected by transesophageal echocardiogram) was estimated using data from the PREVAIL trial, in which such thrombus occurred in 6.4% of patients. Although our trial is not specifically examining ischemic stroke, systemic embolism, or mortality as study endpoints (because their anticipated occurrence is low), these events will be catalogued to characterize patient outcomes. Transesophageal echocardiography is the imaging modality of choice when assessing for left atrium thrombus and will be used in

our study to track the efficacy of anticoagulation. The anticipated outcome in our intervention group was estimated from the results of the ARISTOTLE trial comparing apixaban and warfarin. In that study, patients treated with apixaban experienced 20% fewer episodes of stroke and systemic embolism when compared to warfarin. Using this information, we estimated a 20% reduction in primary event outcome for our intervention arm, giving a value of 0.051. The alpha was set to 0.05 and the power was set to 0.80. Due to this study being noninferiority in nature, the statistical difference between the control and treatment arms will be judged by a one tail test. Our calculation also relies on the event rate in the intervention arm being as low as the event rate in the control arm due to our outcome event being a poor outcome (instead of a positive one such as increased vision). The acceptable difference for this calculation was set to 0.05, reflecting the standard noted in previous literature. This calculation produced a sample size of 170 individuals for each arm of the trial, bringing our sample population to 340 individuals.

Analysis

Baseline participant characteristics, CHA_2DS_2-VASc scores, and HAS-BLED scores will be compared between intervention and control groups with χ^2 tests. Due to our study assessing a dichotomous outcome variable at specific points in time, 45 days and 6 months, we will use simple logistic regression. This value will then be compared between the two groups using person-time (days).

Timeline and Resources

Timeline: pending IRB approval, enrollment for the study will begin on January 1, 2021. Enrollment will continue until June 25, 2022 to ensure that those that are enrolled, even up to the deadline, will have adequate time to undergo the procedure and

follow-up for 6 months. The primary outcome data will be collected at 45 days and 6 months of follow-up. Data analysis will commence on January 1, 2023.

Personnel: Due to the single blinded nature of this study, in which clinicians interpreting the echocardiograms are the only ones being blinded, minimal personnel will be required. A study-specific assistant will be needed to coordinate patient enrollment, treatment randomization, and entry of information and data into the study database. Investigators will be unblinded, and therefore will be able to receive information on patient echocardiogram results. An independent team will monitor the study for number and severity of adverse events and be in charge of deciding whether or not the study needs to be discontinued early due to ethical reasons.

Location: This trial will take place in the Yale New Haven Health System at the Yale New Haven, St. Raphael, and Bridgeport Hospital campuses. The Watchman device is currently being implanted at all of these venues.

Chapter 4

Advantages

There are numerous potential advantages in the present clinical care of patients undergoing Watchman implant that may result from this study. Apixaban, if found to be at least not inferior to warfarin therapy may simplify the care of patients undergoing Watchman implant. Frequent blood testing to monitor INR will not be required. Potential interactions with other medications will be of lesser concern. Patients may realize fewer dietary restrictions, since alcohol and certain foods do not interact with apixaban as they do with warfarin. This may also result in fewer instances of device-related thrombosis or severe bleeding since the level of anticoagulation on apixaban may not vary erratically as it sometimes does in patients taking warfarin. Moreover, apixaban has demonstrated lower risk of intra-cranial bleeding than warfarin. Finally, apixaban may prove to be superior to warfarin in preventing Watchman-related thrombosis (and subsequent stroke from cerebral embolism) as it proved to be in the ARIATOTLE study. The study design may prove to be advantageous as it allows this study to be a single blind, which simplifies study conduct. Finally, study design may permit its expeditious completion. Enrollment is simplified, the drugs employed are non-experimental, clinically available agents that are in wide use, the study protocol follows the protocol for Watchman implant and follow-up that is in present use and enrolled subjects are not asked to undergo any experimental or extraneous procedures. All of these features may facilitate patient enrollment and study completion.

Limitations

Our study does present some limitations in its design. Drug compliance will not be monitored by pill counting. This is not felt to be necessary. Warfarin therapy will be monitored by INR testing as per routine clinical practice. Patients will be periodically contacted to assess for any symptoms and remind them of the importance of medication compliance. It is anticipated that such procedures will be sufficient to insure medication compliance. Another potential limitation is that the compliance of warfarin patients following the restrictive diet required will not be scrupulously monitored. Many foods interact with warfarin, either increasing or decreasing its anticoagulant level. This mirrors usual clinical practice and may make the results of the study more generalizable to usual clinical practice.

Clinical and Public Health Significance

Our study aims to improve the management and treatment of patients with atrial fibrillation. As our population continues to age, atrial fibrillation will become an even more prevalent issue. The current Watchman antithrombotic profile has not been rigorously studied, leaving questions about its safety and efficacy unanswered. As left atrial appendage occlusion devices, such as the Watchman, become more frequently used, it is imperative that the literature provides clinicians with evidence based trials for which to use to guide antithrombotic therapy after device implantation. Our proposed study will assess the use of apixaban for anticoagulation after Watchman implantation compared to warfarin. If our study is successful, this will prevent patients from having to adhere to the stringent protocols surrounding warfarin therapy, such as modified diets and continuous

monitoring of INR. Our study will hopefully pave the way to an easier antithrombotic profile for patients receiving Watchman.

Appendices

IRB consent forms

Yale NewHaven Health Bridgeport Hospital

PROPOSAL FOR RESEARCH INVOLVING HUMAN SUBJECTS

Title: Optimal Anti-Thrombotic Regimen in Watchman Therapy

Principal Investigator: John McCarty

☐ BH Employee ☐ BH/NEMG Physician ☐ BH Resident/Fellow ☒ Other PA Student

Work Phone: (248) 346-1589 Cell: (248) 346-1589 Fax: N/A

Email: John.mccarty@yale.edu

Business Address: 267 Grant St
Bridgeport, CT 06610

Supervising Investigator: (Required for students, residents, fellows or other trainees)

Dr. Craig McPherson

Supervising Investigator Department: Cardiology Work Phone: (203) 887-9925

Associate Investigators: N/A

PROJECT CLASSIFICATION (check all that apply):

☐ Investigator initiated ☒ Student thesis/project ☐ Multicenter trial

Name/address of Project Coordinator of Multicenter Trial:

☒ Involves randomization of subjects into different treatment/study groups
☐ Involves new or unapproved testing procedure(s)
☒ Involves personal/phone contact of subjects by research personnel
☐ Involves medical record review to identify potential study subjects
☐ Involves blood or diagnostic testing beyond that of routine care
☐ Involves unapproved use of presently FDA-approved drug(s) or device(s)
☐ Involves investigational drug or device: ☐ Phase I ☐ Phase II ☐ Phase III

Name: IND No:

Location where will study be conducted: Yale New Haven, St. Raphael, and Bridgeport Hospital

Involves Department(s) of: Cardiology and Electrophysiology

Will the following services be required? (If so, departmental approval required):

☒ Laboratory: Manager (Designee) Approval:
☒ Pharmacy: Manager (Designee) Approval:
☒ Radiology: Manger (Designee) Approval:
☐ Other:

Is this study registered in a public database ☐ Yes ☒ No

If so, where is it registered?

STUDY SUBJECTS (check all that apply):

Enrollment goal: 100 subjects at Bridgeport Hospital, 340 total subjects.

Enrollment will include (check all that apply):

☐ Fetuses ☐ Children ☐ Emancipated minors ☐ Non-English Speaking

☐ Women of childbearing potential ☐ Patients with dementia, psychosis or altered mental state

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Will study involve **advertisement for subject recruitment?** ☐ Yes ☒ No (if yes, attach copy of advertisement)

Will Enrolled subjects receive compensation? ☐ Yes ☒ No Amount _____

FUNDING SOURCE:

☐ None ☐ Local funds ☒ Yale Funds ☐ Other _____

Principal Investigator (PI) Agreement:

As the PI of this research project, I certify that the information is complete and accurate. I will assume full responsibility for the protection of human subjects and the proper conduct of the research, making every effort to protect subject's rights and welfare. I agree to conduct this research according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations regarding the protection of human subjects.

Signature of the PI _____ 4/9/2020 Date

Supervising Investigator Agreement (If applicable):

As the Supervising Investigator of this research project, I certify that the information provided in this application is complete and accurate; that this project has scientific value and merit and that the student or resident/fellow has the necessary resources to complete the project and achieve the aims. I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research. The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations regarding the protection of human subjects.

_____ 4/9/2020

Signature of the Supervising Investigator Date

Approval by Chair(s) of Involved Department(s):

The Principal Investigator of this study and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research and have the support of the department for this project.

_____ _____

Signature of the Departmental Chair Signature of the Departmental Chair

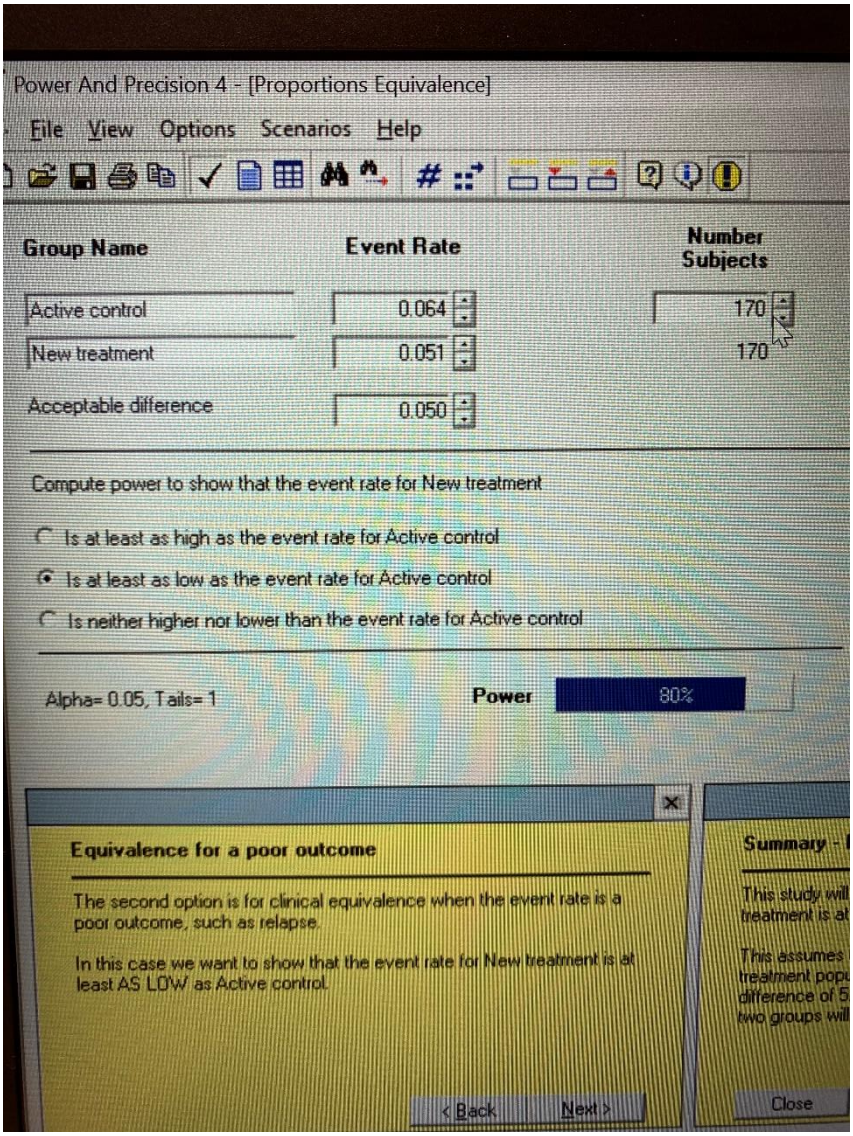
Department of _____ Department of _____

Date:_____ Date:_____

Recruitment flyers

Recruitment flyers will not be necessary for this study. Patients will be referred to our study by their electrophysiology physicians; none will be recruited from the general public or local cardiologists. The research assistant will be responsible for reviewing the EP Lab and OR schedules and identifying potential patients for the study. When a potential patient is identified, the research assistant will ask the electrophysiologist for permission to recruit the patient for the study.

Sample size calculation



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