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Stroke Prevention in Patients with Non-valvular Atrial Fibrillation: The Watchman Device versus Warfarin

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Table of Contents

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Abstract

Background: Atrial fibrillation is a common heart arrhythmia that leads to an increased risk of stroke. Warfarin was the original anticoagulant that would be used as the treatment for atrial fibrillation. However, there are people who have contraindications to anticoagulation or are a high fall risk and shouldn't be on Warfarin. The Watchman Device was originally designed in 2005 as a way to close the left atrial appendage where clots are usually present with atrial fibrillation. The watchman may be a superior way to help reduce the risk of stroke compared to the traditional use of Warfarin. **Purpose:** Literature review of studies to examine if in patients with nonvalvular persistent atrial fibrillation, is the Watchman Device superior to Warfarin anticoagulation therapy for the reduction of stroke risk **Methods:** A comprehensive literature review was conducted using <PubMed> using the search terms <(non-valvular atrial fibrillation) AND (Watchman)) AND (warfarin)) AND (stroke)>. Inclusion criteria were studies that were published from 2015 and newer. Exclusion criteria were studies that were not in English language and did not use human subjects **Conclusions:** The Watchman device is a great option for treating atrial fibrillation if there are contraindications to oral anticoagulants, history of intracranial hemorrhage or severe bleeding. It was not proven yet to be superior to warfarin in the reduction of stroke but the long term risks seem to be safer compared to warfarin.

Key Words: "non-valvular atrial fibrillation", "Stroke", "watchman", "Warfarin"

Stroke Prevention in Patients with Non-valvular Atrial Fibrillation: The Watchman Device versus Warfarin

Introduction

In the United States (US) and European countries, one in every four middle-aged adults will develop atrial fibrillation (AF).[1] A fibrillating atrium may cause stasis of blood and activation of coagulation, which may elevate the risk of thromboembolism; this leads to an overall risk of stroke by 5% every year.[2] Atrial Fibrillation is associated with a five-fold greater risk of stroke, increased risk of death and development of heart failure, and a greater risk of hospital admission, with 10-40% of AF patients hospitalized annually.[1] Atrial fibrillation (AF) causes 15% to 20% of ischemic strokes, and the overall risk of stroke in patients with nonvalvular AF is as high as 5% per year.[3] Embolic events in a majority of patients with AF result from thrombus formation in the left atrial appendage (LAA).[4]

This literature review will examine studies that discuss patients with non-valvular atrial fibrillation and the superiority of the Watchman device versus warfarin (Coumadin) anticoagulation therapy for the prevention of stroke. Nonvalvular atrial fibrillation, which occurs in the absence of rheumatic valve disease, a mechanical or bioprosthetic valve, or mitral valve abnormalities, is the most common form of atrial fibrillation.[6] The Congestive heart failure, Hypertension , Age (> 65 = 1 point, > 75 = 2 points), Diabetes, previous Stroke/transient ischemic attack (2 points) ($CHADS_2$) and the congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female) (CHA_2DS_2-VASc) scoring systems assess the risk of stroke, with a score of 2 or greater indicating a need for anticoagulation.[6] It is a patient-doctor decision on how to anticoagulate based on things like patient age, contraindications for anticoagulation, fall risk, unable to do regular monitoring for Warfarin and other previous co-morbidities that would make

anticoagulation unsafe. Historically, warfarin was the main option for anticoagulation, but recently novel oral anticoagulants (NOAC) have become a more favorable option with less monitoring and side effects. Despite their effectiveness (NOACs), patients with perceived or absolute contraindication to oral anticoagulants due to the risk of bleeding cannot benefit from this therapy. For these patients, left atrial appendage occlusion has emerged as a nonpharmacological alternative for the prevention of stroke.[6] Warfarin lowers the risk of thromboembolic events, but it has a narrow therapeutic range, multiple drug and food interactions, and requires frequent blood monitoring of the international normalized ratio.[6]

Because thrombi typically occur in the left atrial appendage in nonvalvular AF, mechanical left atrial appendage closure (LAAC) has emerged as an alternative to OAC in selected patients.[5] The critical role of the LAA in stroke pathogenesis was recently demonstrated by the use of the Watchman LAA closure device (Atritech, Plymouth, Minnesota) in the PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) study[3]. The PROTECT AF study will be discussed later on in the paper as it lays the foundation for this literature review.

The Watchman device can become a mainstay of treatment for AF with benefits of not having regular INR labs, no dietary restrictions, cost effectiveness as you do not have to pay for OAC and a lower risk of bleeding not being on an anticoagulant. The favored therapy for valvular Afib is vitamin K antagonism, but trials have demonstrated an essential role for percutaneous LAA occlusion (LAAO) in non-valvular Afib[6]. All types of OAC treatments, however, confer a risk of bleeding in the long term. This was an important issue that has been addressed by the most advanced treatment approach of LAAO through endocardial and epicardial devices, which have shown to reduce the rate of bleeding in the long run.[6]

This literature review will be comparing and contrasting the benefits of Watchman Device versus warfarin therapy for the prevention of stroke. Efficacy and safety, complications of both and long term outcomes will all be considered. The data for the Watchman device and other LAAC devices are still new and many large studies have the opportunity to be conducted and lead to advancements in atrial fibrillation treatment that doesn't require patient's to be on anticoagulation.

Methods

A comprehensive literature review was conducted using PubMed using the search terms (non-valvular atrial fibrillation) AND (Left Atrial Appendage) OR (Watchman) AND (warfarin) AND (stroke). Inclusion criteria were studies that were published from 2015 to present, with full free text available, studies that took place in America or European countries and patients who had contraindications to oral anticoagulation therapies. Exclusion criteria were studies that were not in English language and did not use human subjects. Systemic reviews were also excluded. One article from 2014 was used in the review of literature, the PROTECT AF trial which was the original trial for the Watchman Device.

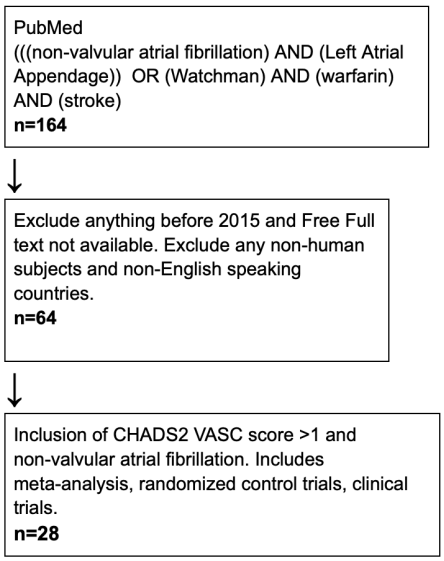

Figure 1

Review of the Literature

The first trial using the Watchman device was conducted in February of 2005, in the famous trial known as PROTECT-AF. This was a randomized clinical trial with 800 participants. Participants included patients with paroxysmal, persistent or permanent non-valvular atrial fibrillation (AF), eligible for long term warfarin and a CHADS score >= 1 [congestive heart failure (CHF), history of high blood pressure, 75 years of age or older, diabetes, prior stroke or transient ischemic attack (TIA)][7]. The experimental arm of the trial was the Watchman device being implanted into the left atrial appendage. The active comparator subjects are treated with current standard of care oral anticoagulation therapy with Warfarin[7]. The two primary outcomes they were recording were a composite of stroke, systemic embolism and cardiovascular or unexplained death and the occurrence of life-threatening events, including device embolization or serious bleeding events [Time Frame: 5 years][7]. As a secondary outcome they were measuring the success rate of the procedure and implanting the device which was defined as the delivery and release of a WATCHMAN Device into the LAA[7]. Of the 463 patients who were selected for the Watchman group 299 completed the trial, and for the Warfarin group there were 244 that started and 133 that completed.

The results for their first primary outcome measure (composite of stroke, systemic embolism and cardiovascular or unexplained death) was based on a 95% confidence interval. Of the 463 individuals analyzed, using the unit as a measure of events per 100 patient years got the average of 2.2 events for the watchman device[7]. For warfarin using the same units of measurement but with the starting patient number at 244 calculated an average of 3.7 events[7]. They then took this data and ran it through a Non-Inferiority or Equivalence statistical analysis which showed that the posterior probability of non-inferiority is defined as the probability that the event rate for the Device group is less than twice that for the Control group[7]. This probability

was required to be greater than 0.975 for a finding of non-inferiority. The criterion for non-inferiority was consistently met at each analysis time point demonstrating the Device group is non-inferior to the Control group[7].

The second primary outcome they were measuring (occurrence of life-threatening events, including device embolization or serious bleeding events [Time Frame: 5 years]) calculated the same as the first primary outcome. The results were Watchman device 3.5 events to the Warfarin group 3.2 events[7]. They did not calculate a statistical analysis for this outcome. Adverse events were followed for a five year time frame via electronic case report form (e-CRF) completion by sites, followed by independent Clinical Events Committee (CEC) adjudication[7]. Of the serious adverse events reported the Watchman device 30.89% where Warfarin had a 28.69% risk[7]. One of the adverse events was death though it was not traced back to either Warfarin or Watchman device use which may have skewed their results but needed to be included. Gastrointestinal bleeding (32) and ischemic stroke (26) were the two highest reported adverse events with the Watchman device[7]. Gastrointestinal bleeding (27) and ischemic stroke (11) were the two highest reported adverse events with Warfarin[7].

Overall the PROTECT-AF trial showed a non-inferiority of the Watchman device compared to Warfarin[7]. I believe the limitations of this study is the lack of long term follow up and also it needs to be considered that there is a slightly high risk with the Watchman device because it is a surgery. One problem with this study is the large drop in participants whether they were lost to follow up, the physician decided it was best not to continue or the device was just never planted. This trial lacks in depth analysis and pros/cons to boths arms of treatment. This literature review will be building off this initial PROTECT-AF trial to compare and contrast risks, benefits and long term outcomes of the Watchman device versus Warfarin.

The Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) trial follows up on the PROTECT-AF trial. The goal of this study was to assess the safety and efficacy of LAA occlusion for stroke prevention in patients with NVAF compared with long-term warfarin therapy[8]. This randomized trial further assessed the efficacy and safety of the Watchman device[8]. With PROTECT-AF several concerns were raised by the U.S. Food and Drug Administration regarding patient selection criteria (e.g., inclusion of patients with $CHADS_2$ [congestive heart failure, hypertension, age >75 years, diabetes mellitus, and previous stroke/transient ischemic attack] scores of 1) and acute safety events, particularly in the early portion of the trial, and a second trial was recommended[8]. Inclusion criteria were patients with a $CHADS_2$ score of 1 if they also had any of the following higher-risk characteristics: female age ≥75 years, baseline ejection fraction ≥30% but <35%, age 65 to 74 years and either diabetes or coronary disease, and age ≥65 years with congestive heart failure[8]. These inclusion criteria were meant to include a higher risk group than had been evaluated in PROTECT AF[8]. Exclusion criteria included requirement for long-term anticoagulation therapy for reasons other than AF, contraindication to warfarin or aspirin, previous stroke/transient ischemic attack within 90 days of enrollment, symptomatic carotid disease, or a patent foramen ovale or atrial septal defect requiring treatment[8].

The PREVAIL trial was measuring three specific outcomes; the first was the primary efficacy, a composite of hemorrhagic or ischemic stroke, SE, and cardiovascular/unexplained death[8]. The second was late-ischemic efficacy, a composite of ischemic stroke or SE, excluding the first seven days after randomization[8]. The third coprimary endpoint was early safety, a composite of all-cause death, ischemic stroke, SE, or device-/procedure-related events requiring

open cardiovascular surgery or major endovascular intervention such as surgical treatment of a pseudoaneurysm between randomization and within 7 days of the procedure or during the index hospitalization.

PREVAIL enrolled 407 patients; 269 were randomized to the device group and 138 to the control group[8]. The device was successfully implanted in 95.1% of the patients in whom it was attempted (252 of 265)[8], which is a much higher completion rate compared to the PROTECT-AF trial. Transesophageal Echocardiogram (TEE) was performed at 45 days', 6 months', and 12 months' follow-up to assess device stability, document optimal ostial position, and evaluate the presence and degree of residual peridevice flow[8]. If the 45-day TEE documented either complete closure of the LAA, or if residual peridevice flow was <5 mm in width and there was no definite visible large thrombus on the device, warfarin was discontinued[8]. Patients were then on clopidogrel 75 mg and aspirin 81 to 325 mg were prescribed until the 6-month follow-up visit where it was then discontinued.

Procedural success, defined as device deployment and release, increased from 90.9% in PROTECT AF to 95.1% in PREVAIL ($p = 0.04$)[8]. Procedural and device-related strokes decreased, from 1.1% in PROTECT AF to 0.4% in PREVAIL ($p = 0.007$)[8]. The major findings of the trial were: 1) LAA occlusion with the Watchman device was not noninferior to warfarin for the primary efficacy composite endpoint of all-cause stroke, cardiovascular or unexplained death, and SE, although the event rates with warfarin were significantly lower than expected, affecting the ability of the study to establish noninferiority[8]. The PREVAIL trial also found the Watchman device was noninferior to warfarin for the occurrence of late ischemic events, such as ischemic stroke or SE occurring after the first 7 days following randomization to isolate the effect of early periprocedural events from a longer term mechanism of action[8]. At 45 months of follow-up,

LAA occlusion was superior to warfarin for the primary composite efficacy endpoint[8]. At 45 months, the primary safety endpoint was noninferior for the device group because of the continued increase in adverse safety events with warfarin, emphasizing the long-term hazard of anticoagulants that could be avoided with mechanical intervention. The PREVAIL trial shows that there are risks to both the device and anticoagulation but potentially more long term adverse effects with Warfarin due to the constant bleeding risk.

As discussed above, the PROTECT AF and PREVAIL trial were the first two trials to study the Watchman device. Reddy et al conducted a Meta-analysis comparing and contrasting the five-year follow up results between the PROTECT-AF and PREVAIL trails. At 5 years, LAAC with Watchman was associated with a statistically significant 41% decrease in cardiovascular mortality and a 27% decrease in all-cause mortality.[5] The bleeding risk score, HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly), was not prospectively captured in these trials[5]. Reddy et al determined a modified HAS-BLED score for these trials to better compare the patient's risk for major adverse reactions.

To go about performing a meta-analysis of the PROTECT-AF and PREVAIL trail, the datasets were combined with all available follow-up and analyzed to provide a more robust exploration of the role of covariates[5]. The risk profile of the PROTECT AF cohort was somewhat lower than that of PREVAIL cohort[5]. The modified HAS-BLED scores were elevated in both the PROTECT AF and PREVAIL trials, with only 6.4% and 1.7%, respectively, considered at low risk (HAS-BLED score = 0); 73.7% and 68.6%, respectively, at moderate risk (HAS-BLED score = 1 to 2); and 19.9% and 29.7%, respectively, at high risk (HAS-BLED score

≥3)[5]. These percentages show that the PREVAIL trial had more patients who were high risk based on their HAS-BLED score but still showed improving outcomes from the PROTECT-AF.

In Reddy et al a patient-level meta-analysis was conducted of all patients enrolled in the PROTECT AF and PREVAIL trials. The composite of stroke, systemic embolism, or cardiovascular/unexplained death occurred with similar frequency in the LAAC and warfarin groups[5]. The rate of all-stroke or systemic embolism was also similar between groups, however, there were directional variations in the individual components of this endpoint: the rate of ischemic stroke or systemic embolism was numerically higher with LAAC[5]. If procedure-related strokes were excluded, the difference in ischemic stroke or systemic embolism remained nonsignificant[5]. LAAC was also associated with statistically-significantly lower rates of cardiovascular or unexplained death[5]. In a patient-level meta-analysis combining the 5-year outcomes of the PREVAIL and PROTECT AF trials, compared with warfarin, LAAC provided equivalent rates of all-cause stroke, with reductions in hemorrhagic stroke and disabling/fatal stroke[5]. This means after comparing data between the two trials LAAC was not shown to cause significantly worse outcomes compared to Warfarin. This meta-analysis did show that LAAC didn't cause a reduction in ischemic stroke but did however reduce significant cardiovascular outcomes and death overall.

Even with promising results, any treatment or procedure needs to be reasonably safe for patients to endure. Philips et al conducted a multicenter study quantifying the feasibility of implant, safety during the implant and followed up 30 days post-implantation of the Watchman device. With anticoagulation therapy you have the risk of bleeding, so patients who are high falls risk or high bleeding risk should look into options like the Watchman device. Another treatment

option the multicenter study looks at is cardiac ablation where a surgeon tries to "zap" the places in your heart that are randomly producing signals and therefore causing AF.

Data were pooled from two prospective, real-world Watchman LAAC registries running in parallel in Europe/Middle-East/Russia (EWOLUTION) and Asia/Australia (WASP) between 2013 and 2015. Of the 1140 patients, 139 subjects at 10 centers underwent a concomitant AF ablation and LAAC procedure.[9] Long-term results from catheter ablation therapy for atrial fibrillation (AF) remain uncertain with significant rates of arrhythmia recurrence over time, especially in the persistent AF population.[9] The CHA_2DS_2-VASc risk score has been demonstrated to correlate with both risk of AF recurrence and risk of thromboembolic events post-ablation, suggesting a need for on-going stroke protection in high risk patients.[9] As a result, clinical practice guidelines recommend continuation of long-term oral anticoagulation in these patients following catheter ablation therapy.[9] With the Watchman device after you titrate off your anticoagulant and post-op echocardiograms look good, you no longer need any form of anticoagulant.

In Philips et al their multicenter study showed complete occlusion was achieved in 97.1% of the implants, while 2.9% of patients had a residual leak ≤5 mm. The seven day device and/or procedure related significant adverse events (SAE) rate was 0.7% (0.1%, 3.6%). The overall 30-day SAE rate was 8.7% (4.7%, 14.1%) with 14 events in 12 patients, while the device and/or procedure-related SAE rate was 1.4% (0.3%, 4.7%).[9] There were no strokes, TIAs, device embolization or deaths over the initial follow-up for this cohort.[9] A first follow-up TOE was performed at least 28 days post-procedure in 105/139 patients and demonstrated proper seal (residual leak ≤5 mm) in almost all of the patients studied (98.1%).[9] The results support the EHRA/EAPCI expert consensus statement on catheter based LAA Occlusion that proposed the

combination procedure 'seems to be a valuable and practical approach: patients with a significant risk of thrombo-embolic events (CHA_2DS_2-VASc score of >2) undergoing an ablation procedure to treat symptomatic AF, who, in addition, have a strict or relative contraindication to (N)OACs.[9]

The Philips et al multicenter study showed high efficacy and safety of the Watchman device. It is important to look at the implications and complications if the Watchman Device implantation does go wrong. Price et al conducted a randomized control trial to compare the relative risk of major bleeding with left atrial appendage (LAA) closure compared with long-term warfarin therapy. A total of 1,114 patients were included, with a median follow-up of 3.1 years.[10] The overall rate of major bleeding from randomization to the end of follow-up was similar between treatment groups (3.5 events vs. 3.6 events per 100 patient-years.[10] LAA closure significantly reduced bleeding >7 days post-randomization, with the difference emerging six months after randomization when patients assigned to LAA closure were able to discontinue adjunctive oral anticoagulation and antiplatelet therapy.[10] LAA closure significantly reduced bleeding beyond the procedural period, particularly once adjunctive pharmacotherapy was discontinued.

Major bleeding was defined as an adverse event that was assigned one of several bleeding codes and was adjudicated by the clinical events committee as significant (life-threatening or resulting in hospitalization, prolongation of hospitalization, substantial disability, or death).[10] Approximately one-half of the bleeding events in the device group (48%) occurred within the first seven days after randomization, that is, during the periprocedural period.[10] The decrease in bleeding with LAA closure was driven by reductions in both gastrointestinal bleeding and hemorrhagic stroke.[10] The significant adverse events or major bleeding experiences that occurred with LAAO were as follows: 10 patients had gastrointestinal bleeding, one had epistaxis, two

had hemorrhagic stroke, three had a cranial bleed, two had anemia requiring transfusion and one had major bleeding requiring transfusion.[10] Landmark analyses across several intervals suggest that the reduction in bleeding with LAA closure began 6 months after randomization, consistent with when patients in the device group could discontinue adjunctive pharmacotherapy (warfarin and aspirin followed by dual antiplatelet therapy).[10]

Although the clinical efficacy of OAC is well established, concerns about long-term bleeding are a major driver of OAC prescribing patterns as well as treatment discontinuation in patients who have already initiated therapy.[10] The current analysis demonstrates that, although the overall rate of bleeding was similar between groups at a median follow-up duration of three years beyond the immediate procedural period, the risk of bleeding was substantially lower after LAA closure than with long-term warfarin therapy.[10] The reduction in bleeding with LAA closure compared with chronic warfarin was directionally consistent among all patient subgroups examined.[10] These observations suggest that the long-term safety benefit of LAA closure over warfarin applies across the spectrum of bleeding risk.[10]

Uberham et al conducted a meta-analysis on the various pharmacologic and nonpharmacologic treatments for atrial fibrillation. Warfarin, a non-vitamin K antagonist has been around much longer than the Watchman device and has been the first line treatment for afib until the invention of non-vitamin K anticoagulants (NOACs). Vitamin K Antagonists (VKAs) have been proven to be effective and safe in the prevention of AF-related thromboembolic complications, and large randomized controlled trials (RCT) on VKA therapy reported a two-third risk reduction in strokes compared to placebo.[11] However, it is important to note that the efficacy and safety of VKAs are highly dependent on the patient's Warfarin management. Regular monitoring of the INR, a measure of VKA anticoagulation intensity, is mandatory

because of the narrow therapeutic window of VKAs.[11] This means patients are required to go in weekly or biweekly to get an INR drawn which can be time consuming and an inconvenience. Warfarin are also food interactions like leafy green vegetables and many other drug interactions.

With NOAC's now on the market they may have more of a role than VKA's due to less monitoring and drug interactions. There is still a large pool of patients ineligible for OACs, (both VKA and NOACs) where surgical or interventional stroke prevention strategies should be considered.[11] In patients undergoing cardiac surgery for other reasons, the left atrial appendage excision, ligation, or amputation may be the best option.[11] If patients are already undergoing a procedure and are a good candidate for the Watchman device it makes sense to do two procedures in one and to give them a future with a lower bleeding risk.

Al-abacha et al conducted a meta-analysis included studies that met the following criteria: the study was published in a peer-reviewed journal, and the study compared the outcomes of NVAF treated with LAAC device vs medical management.[12] The primary endpoint of this meta-analysis was a composite of stroke, systemic embolism and cardiovascular death.[12] Five studies were included with a total of 4778 patients. The median-weighted follow up period was 2.6 years.[12] A limitation or possible negative part of this meta-analysis is only using 5 trials, however the trials were large and therefore they still have a wide patient population. The studies they chose were PROTECT AF, PREVAIL, Prague-17, APPLY and Neilsen 202, the first three of five are RCTs that used the Watchman device and the last two used the AMULET device.

This meta-analysis found that the data showed a statistically significant lower risk of the composite primary outcome in the LAAC device arm when compared to medical therapy.[12] The risk of all-cause mortality was significantly lower in the LAAC device arm when compared to the medical management arm.[12] There was also a significantly lower risk of cardiovascular death

in the LAAC device arm when compared to the medical management arm.[12] There was no statistically significant difference in the risk of all stroke, ischemic stroke or systemic embolism in the LAAC device arm when compared to medical management, however the risk of hemorrhage stroke was significantly lower risk of in the LAAC device arm when compared to the medical management arm.[12] Our pooled data showed a significantly lower risk of composite outcomes of stoke, systemic embolism, and cardiovascular death in the LAAC device arm. These results show that nearly across the board, the LAAC device arm is the safer option when compared to regular medical management of nonvalvular atrial fibrillation, which is typically Warfarin. This shows that this is a great option for all NVAF patients who cannot tolerate OAC's but also for people who don't want to take OAC, find them to be costly or are unable to follow a scheduled pill routine. The low risk of cardiovascular mortality in the LAAC device arm was consistent between the studies, and was reported in a previous meta-analysis by Holmes et al[12] which was discussed above.

The main goal of anticoagulation or the Watchman device is stroke prevention. The neurologist should be an important member of the AF management team, adding valuable input as to the diagnosis of AF-related ischemic stroke, understanding both the embolic and hemorrhagic stroke risk in individual patients and selection of appropriate preventive measures.[13] Gokcal et al conducted a review to help neurologists best manage their patients with afib and prevent strokes. AF-related embolic strokes are typically more severe than other ischemic strokes and they are associated with a significantly higher risk of recurrence and poorer long-term outcomes.[13] It is important to be looking at all anticoagulant or surgical interventions for your patient and determining which best decreases their stroke risk.

Gokcal et al really focuses on detecting AF through the long-term loop recorders which is an ambulatory ECG monitoring device that store the heart's electrical signals only when the monitor is triggered by a patient or by abnormal heart rhythm.[13] The longer-term AF monitoring systems resulted in the relatively common detection of short AF episodes. This advance challenged the previous paradigm that AF should last longer than 24 h to result in embolism formation.[13] With these long-term loop recorders the incidence of catching AF will be higher and therefore lead to quicker treatment and better outcomes. Gokcal et al also argue that the grading system CHAD-2-VASC is inferior to the newer grading system ATRIA. The risk factors in the ATRIA score are age (categorized as < 65, 65–74, 75–84, and ≥ 85 years), female sex, diabetes mellitus, heart failure, hypertension, proteinuria, and renal disease. The ATRIA score predicts ischemic stroke risk better than $CHADS_2$ or CHA_2DS_2-VASc, also with an enhanced ability for severe stroke prediction.[13] Determining hemorrhagic stroke risk and bleeding risk in general is crucial before deciding on treatment with Warfarin, NOAC or a device like the Watchman is used.

Once the physician has determined the hemorrhagic stroke and bleeding risk, making the decision on how to treat their AF can be complex. Intracranial hemorrhage is by far the most feared complication of long-term systemic anticoagulation and the main reason for undertreatment of AF patients worldwide.[13] Warfarin has a large risk for bleeding and as discussed earlier has many drug and food interactions. Novel oral anticoagulants are a better option because there doesn't need to be INR monitoring and less drug interactions. However, the disadvantages of NOACs are increased risk of gastrointestinal side effects and hemorrhage, increased bleeding risk especially in renal failure, availability and efficacy of specific antidotes, higher cost, and finally poor patient compliance.[13] This is why the Watchman device is a great

alternative and with real-world post-approval experience showing high rates of successful WATCHMAN implantation with lower complication risks (pericardial effusion/tamponade, device migration).[13] The incidence of procedure-related stroke or death was 0.08% each.[13] Modern LAAC procedures such as FDA-approved WATCHMAN should be discussed as an anticoagulant sparing stroke prevention approach in NVAF patients at high risk for ICH based on an individual patient's clinical and neuroimaging characteristics.[13]

As discussed above it is a critical decision made by the physician along with the patient on how to prevent stroke from occurring with a diagnosis of atrial fibrillation. There are the scoring systems that have been mentioned like CHAD-2-VASC and HAS-BLED but Dar et al looks into the indication and patient selection for Left Atrial Appendage Occlusion, Watchman device. The approval of the Watchman specified indications for use in patients with nonvalvular AF who are either at increased risk of stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores; are deemed by their physicians to be suitable for warfarin therapy; and finally, have an appropriate rationale to seek a nonpharmacologic alternative to warfarin, taking into account the safety and efficacy of the device compared with warfarin.[14]

What does the patient population who would benefit from the Watchman device look like? Based on the plentiful data from different registries about successful use of LAAC in patients with contraindication to anticoagulation and also on the efficacy and safety of different antithrombotic protocols post-procedure,[14] people with thrombocytopenia or known coagulation defects, recurrent GI bleeding, prior ICH or severe bleeding, patients currently on "triple therapy" aka dual-antiplatelet therapy plus anticoagulation and people who have poor compliance with their OACs would all benefit having the discussion about LAAC with Watchman device. It is recommended to collect scores and data like CHAD-2-VASC,

HAS-BLED, prior experience with OAC, prior history of bleeding, any contraindications to anticoagulation, the patient's cardiac structure and function including LAA anatomy[14] before considering the use of the Watchman device.

With any procedure there come risks with things like anesthesia but also with the Watchman device there is a risk of device-related thrombus (DRT). Main et al conducted a randomized control trial to develop consensus echocardiographic diagnostic criteria for DRT, estimate the incidence of DRT and determine clinical event rates in patients with DRT.[15] This trial was building off the PROTECT-AF trial where specific criteria for DRT identification are not available nor is the true incidence or clinical significance of DRT known.[15] This study evaluated 93 follow-up TEEs in 35 PROTECT-AF device patients who underwent Watchman device implantation in which the study site investigator and/or echocardiography core laboratory suspected DRT (33 at 45-day follow-up, 33 at 6-month follow-up, and 27 at 1-year follow-up).[15]

DRT was adjudicated as present in 15 of 26 TEEs (58%) evaluated in phase three. Overall, at least 1 TEE was DRT positive in 27 PROTECT-AF patients. Incident of DRT was present at 45 days in seven patients, with highest prevalence at six and 12 months.[15] Those with DRT were older and more commonly had permanent AF versus those without DRT in the PROTECT-AF trial.[15] Main et al found the prevalence of LAA-associated thrombus in PROTECT-AF to be 5.7% of patients, with DRT much less likely at 45 days while patients remained on warfarin, versus six and 12 months follow-up when discontinuation was allowed.[15] The marked increase in DRT incidence at six and 12 months (19 and 12 patients, respectively) suggests that endothelialization in some patients may require more time and the combination of aspirin and/or clopidogrel after 45 days may be ineffective in preventing DRT in some patients.[15] This study shows that the risk of DRT can be present up until roughly a year after the procedure

but a lot depends on patient risk factors. It is important to note this trial only looked at 93 of the TEE's from the PROTECT AF trial.

Device related thrombus is not the only risk with the Watchman device procedure. Sahay el al meta-analysis was done to assess the efficacy (mortality and stroke/SE) and safety (major, intracranial and gastrointestinal bleeding) of LAAC as compared with medical prophylactic therapy for stroke prevention in patients with non-valvular AF. The population of interest included patients with non-valvular AF and the intervention was medical or percutaneous treatment for stroke prophylaxis assessed in RCT.[16] Trials with fixed-dose warfarin, a combination of APT with NOAC or any other comparison without including VKA were excluded from the analysis.[16] For each direct comparison between treatments, where information from more than one trial was available, we performed a traditional random-effect model.[16] A total of 2929 citations were identified using the search terms. Of these, 488 were screened at the abstract level and 413 records were excluded. The remaining 75 publications were carefully screened and after analysis of the full text, with 19 studies being included in this meta-analysis.

Of 87,831 randomized patients 36,645 were assigned to warfarin, 43,314 to NOACs, 6215 to APT, 925 to placebo and 732 patients were assigned to Watchman device implantation.[16] The results from the meta-analysis showed that All-cause mortality and stroke/SE incidence was reported in 16 and 17 studies. Direct comparison revealed a mortality benefit with NOAC and no difference with LAAC as compared with VKA.[16] LAAC led to a non-significant reduction in the incident of stroke as compared with VKA.

An important factor to consider with any procedure or treatment option in medicine, is cost. Panniker et al condueted a randomized control trial in order to analyze real-world outcomes of patients with non-valvular atrial fibrillation (NVAF) undergoing left atrial appendage closure

(LAAC) with the Watchman device and to compare costs with available antithrombotic therapies. They gathered two databases of patients who recieved LAAO with Watchman, were collected from 110 patients with NVAF at risk of stroke, suitable and unsuitable for long-term anticoagulation.[17] They used the databases to compare outcomes and cost of the Watchman versus Warfarin, NOACs like dabigitran, rivoroxaban, epixaban and aspirin as well as no treatment at all. Costs were estimated over a 10 year horizon.[17] Follow-up was 24.1 ± 4.6 months, during which annual rates of stroke, major bleeding, and all-cause mortality were 0.9% (2/223 patient-years), 0.9% (2/223 patient-years), and 1.8% (4/223 patient-years), respectively.[17]

The results from Panniker et al showed LAAC stroke and major bleeding rates were significantly lower than PROTECT AF results: mean absolute difference of stroke, 0.89% ($P = 0.02$) and major bleeding, 5.48% ($P < 0.001$).[17] This reaffirms that the PROTECT AF results were somewhat skewed and when you look at the long term serious adverse events, they are minimal. The results for the cost difference between treatment options showed that there is a high initial cost of LAAC, as with most implantable devices; however, this is offset by lower rates of ischaemic stroke, major bleeding, and death over 10 years when compared with the other agents.[17] Results also may have some variation depending on insurance companies that were used. After comparing they found that over a 10-year period PROTECT AF LAAC was cost-saving compared with all other treatment options.[17] When comparing to Warfarin based on PROTECT AF, LAAC appeared more costly than warfarin at 10 years. It is important to consider that Warfarin is one of the cheapest options for anticoagulation compared to the newer NOACs. However, with the monitoring, food and drug interactions of Warfarin the lifestyle changes needed for Warfarin may not be worth the cheaper cost.[17]

Left Atrial appendage occlusion is a relatively new procedure, so why is the Watchman device the device of choice? The Watchman Device was the first device tested in the PROTECT AF trial which was discussed earlier on but the risks of the Watchman are still being considered and should be well understood when educating patients on their options. Bode et al conducted a meta-analysis to evaluate the procedural safety and complications of all transcatheter LAAO devices and compare procedural events across different LAA closure devices.[18] All studies reporting the peri-procedural events of transcatheter LAAO with a sample size ≥ 25 were included in this analysis. [18]

Forty-nine studies involving 12,415 patients were included in this meta-analysis, and the pooled proportion of successful implantation of LAA closure devices was 96.2%.[18] Pooled proportion of ischemic stroke was 0.3% (0.2-0.5%) and hemorrhagic stroke was 0.1%.[18] A big concern is post procedural stroke and this meta-analysis shows that the risk is fairly low for both ischemic and hemorrhagic stroke. Another risk of the procedure is bleeding requiring a transfusion. Pooled proportion of major bleeding requiring transfusion was 1.2%, gastrointestinal bleeding was 0.3% and intracranial bleeding was 0.2%[18] which shows based on 49 different trials the risk of post procedural LAAO has a low risk of bleeding requiring transfusion.

The principal finding of this study is that LAAO is an efficacious procedure. All devices included in this meta-analysis had similar efficacy in LAAO with an implantation success rate of 96.2%. [18] This shows that the Watchman is not significantly safer or better than the other LAAO devices like the Amulet or Lariat but it is the most regularly studied and has been compared to oral anticoagulants. Due to their being the most research and a higher popularity the Watchman device may be the device of choice for surgeons. The Watchman device reported 0.1% stroke, ACP with 0.9%, Amulet had 0.3 and Lariat had 0.2.[18] This however, was not found to be

statistically significant. This meta-analysis establishes the safety and efficacy of LAAO as an alternative for patients with NVAF that seek nonpharmacologic approaches for stroke prevention.[18] The FDA circulatory and Device Panel reviewed the Watchman data three times before finally granting approval. However, with the maturation of this technique, the post-procedural risks have been significantly reduced for all devices.[18]

The patient population being treated for NVAF are typically older or elderly patients. Briceno et al conducted a meta-analysis comparing treatment of NVAF with NOACs versus Warfarin versus the Watchman, in addition to a subgroup analysis of the elderly population. Seven phase III RCTs were available comparing the efficacy and safety of NOACs or Watchman device with warfarin for stroke prevention in patients with NVAF. An additional search limited to the elderly population (≥75 years of age) with NVAF was done including six phase III RCTs were found comparing NOACs and Watchman device to warfarin for stroke prevention in this population.[19] The primary endpoint was the incidence of SSE. The secondary end point was all-cause mortality.[19]

The 6 RCTs reported SSE. No data were available for all-cause mortality and safety outcomes in the DEVICE group for the elderly, therefore, only the primary end point was analyzed in this subgroup[19] There were a total of 1211 SSE in this group: 3.3% (544/16 280) in the NOAC and 11% (42/388) in the DEVICE group.[19] Briceno et al found stroke prevention benefit was also observed in a subgroup analysis of the elderly population. It was concluded that the DEVICE is a reasonable noninferior alternative to warfarin for stroke prevention, but cautious use is essential given safety concerns No definitive conclusion can be drawn in the elderly population in regard to the bleeding risk or procedure-related complications given lack of published data in the DEVICE group.[19]

Tereshchenko et al conducted a meta-analysis with the goal of comparing the relative effectiveness of several antithrombotic drug therapies such as warfarin, aspirin and NOACs as well as the LAA occlusion device for stroke prevention in nonvalvular AF. A study was considered eligible if it was an RCT that enrolled patients with nonvalvular AF and presented efficacy and safety outcomes data.[20] They included RCTs that tested the following antithrombotic interventions: aspirin, VKA, 4 NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban), and the Watchman LAA occlusion device.[20] The combined outcome of stroke (both embolic and hemorrhagic) and systemic embolism served as a primary efficacy outcome. Transient ischemic attacks were not included.[20] The primary safety outcome was a combined outcome of major extracranial bleeding and intracranial hemorrhage (including epidural, subdural, and subarachnoid hemorrhage) or major Watchman device implantation–related complications.[20]

A total of 21 RCTs with 29 study arms were included in this NMA, including 96,017 nonvalvular AF patients with a median age of 71.5 years; 65% were males.[21] They did not report on why the percentage of males was much higher than females, but this is something that should be considered when interpreting their results. Compared with aspirin, VKA and NOACs reduced the risk of stroke or systemic embolism by around 50% to 60%, both in unadjusted and adjusted analyses. There was no statistically significant difference in effects of aspirin and the Watchman device.[20] After adjustment for RCT population characteristics, risk of major bleeding in all groups of antiembolic interventions, including risk of procedure-related complications in the Watchman device group, did not differ significantly from risk of major bleeding in the placebo/control group.[20] This agrees with the Al-abacha meta analysis as discussed above that major bleeding was statistically significantly lower with the Watchman device.

There was no single winner for the primary efficacy outcome: The probability of being the best intervention to prevent stroke and systemic embolism did not exceed 50% (ie, pure chance) for any of the treatment options.[20] The Watchman device was the best life‐saving intervention in nonvalvular AF, with a probability of around 72%.[20] The Watchman device was the single representative of a cluster of "the most effective and the most dangerous." VKA and edoxaban formed a cluster of "reasonably effective and reasonably safe."[20] The Watchman device is likely rated most dangerous due to risks from having to undergo a procedure but if you considered long term risks of Warfarin (VKA) it would likely outweigh the risks of the device procedure. Unfortunately, there is no long term data to support this hypothesis. When looking at interventions for reduction of stroke and overall mortality, in unadjusted and adjusted analysis all 4 NOACs and the Watchman device formed a single cluster of "the most effective and life‐saving" interventions. VKA alone formed a cluster of "moderately effective" treatments.[20]

Discussion/Analysis

Based on the literature presented above, the Watchman device is a strong option for non-valvular atrial fibrillation treatment in the prevention of stroke. None of the RCTs so far have determined that the Watchman device is superior to warfarin. However, when analyzing meta-analysis of long term outcomes and serious adverse events, the Watchman device seems like a better option in the right candidate. Common reasons for a patient to be recommended the Watchman device is previous stroke, major risk of bleeding, high falls risk and people who are unable to regularly take a pill. Another benefit that appeals to patients is there are no drug interactions, where Warfarin has a lengthy list of drug and food interactions. Warfarin also has

continuous monitoring of INR which can be timely and a burden to be getting checked every week.

The main trial that was originally conducted for the Watchman device, the PROTECT AF trial, found that the device was non-inferior to Warfarin. This trial lacked a follow up which now other studies have been done to do this, but including these results in their trial may have changed their results. Reddy et al conducted the five year follow up RCT from the PROTECT AF and PREVAIL trails. This study demonstrates that LAAC with Watchman provides stroke prevention in nonvalvular atrial fibrillation comparable to warfarin, with additional reductions in major bleeding, particularly hemorrhagic stroke, and mortality.[5] When getting the whole picture that includes a follow up, the device and Warfarin are very comparable. Other things considered in this paper are things like cost. Does twenty plus years of warfarin cost substantially more than the cost of getting the Watchman implanted? Panniker et al found that left atrial appendage closure achieves cost parity in a relatively short period of time and may offer substantial savings compared with current therapies. Savings are most pronounced among higher risk patients and those unsuitable for anticoagulation.

If the device is cost effective and works just as effectively as Warfarin, why would you not consider the device? Safety of the procedure is an important consideration when recommending this to a patient or not. If the risks of the procedure are high, it would make sense this is not the best option for your patient. However, there is always a gray area and it's important to consider if they are a good candidate, can handle anesthesia and how likely they are to have post-op complications. Common post-op complications reported were gastrointestinal bleeding, intracranial bleeding, anemias requiring a transfusion and stroke, however the incidence of these were low.

Though there are newer anticoagulant therapies on the market now instead of warfarin, these pills still come with a bleeding risk. The NOACs also can be quite expensive depending on insurance companies and insurance plans. To be able to eliminate the risk of severe bleeding, bleeding after a fall and the worry of having to take a pill can all be possible with the Watchman device. The post-op complications were not a significant percentage of participants and the five year outcomes were so positive that it must be considered a strong option for the treatment of non-valvular atrial fibrillation. The original PREVAIL trial which was a follow up after the PROTECT AF trial showed that although noninferiority was not achieved for overall efficacy, event rates were low and numerically comparable in both arms. Procedural safety has significantly improved.[8] Since it has now been almost ten years since the device has come out, doctors have had the time to perfect the placement of the device and decrease poor procedural outcomes. The success rate of implantation will only continue to get better.

Stroke is a main concern of atrial fibrillation due to the production of clots in the left atrial appendage. LAAC with the Watchman device seems to be good at reducing the risk of hemorrhagic stroke. Not all studies clarified between hemorrhagic stroke and ischemic stroke. Al-Abcha found that a lower all-cause mortality, cardiovascular mortality, hemorrhagic stroke, major bleeding, non-procedural major bleeding and the composite of stroke, systemic embolism, and cardiovascular death was in the LAAC device arm when compared to OAC. Gokcal et al and Reddy et al also came to the same conclusion that the Watchman device was best at reducing specifically hemorrhagic stroke. It would be beneficial to have more trials conducted with ten year follow up to see if there is a reduction in more hemorrhagic strokes or ischemic strokes.

Though no study said definitively the Watchman device is better at preventing stroke when compared to Warfarin, many of the studies presented above give the groundwork and

results that it is highly comparable to Warfarin and more long-term results may more solidly define that. Besides procedural risks and initial costs, the Watchman device seems to have less long term risks of serious adverse events and works effectively in reducing the risk of stroke and overall mortality. With Warfarin's monitoring, food and drug interactions and continuous bleeding risk the Watchman device is a great option for non-valvular atrial fibrillation treatment for patients who do not want to worry about those things. When considering all treatments for NVAF: aspirin, Warfarin, NOACs and devices like the Watchman the Watchman has things that make it more beneficial than the others depending on the patient. When recommending the Watchman device to patients it is important to consider their past medical history, current bleeding risks, stroke risks and how likely they can handle the procedure and any post-op complications. The Watchman is still a fairly new device but has so far had a successful role in the treatment of non-valvular atrial fibrillation.

Conclusions

The goal of this literature review is to examine studies for patients with non-valvular atrial fibrillation to determine the superiority of the Watchman device versus warfarin (Coumadin) in the prevention of stroke. The studies overall showed that the Watchman device is a great option for patients who can not reliably take their oral anticoagulants, do not want to be on anticoagulation, have a fall risk or risk of prior bleeding. This decision is ultimately up to the patient and the surgeon. There are procedural risks that must be considered and discussed if the device benefits outweigh the risks of the procedure. It also is important to consider the patient's previous medical history of stroke and risk calculations like HAS-BLED and CHADS2VASC to determine their risk of a new stroke. The PROTECT AF and PREVAIL trials laid the groundwork for the Watchman Device and it is currently the most studied LAAO device against other atrial fibrillation options.

The studies that were reviewed above analyzed the safety, efficacy, patient population that would benefit from the Watchman device and the negative potential side effects from the Watchman device and the procedure itself. Overall, the Watchman device was deemed safe but in the PROTECT AF trial it was not proven superior to Warfarin. Due to this finding, many meta-analysis and follow up trials were conducted to see if their results were accurate. Multiple studies found that the device is a great option to consider for the treatment of atrial fibrillation and it seems the long term benefits of the device have the ability to be better than Warfarin long term.

More trials can be conducted to evaluate the effectiveness of the Watchman device as there will now be a population of patients who have had it for 10 plus years. It will now be possible to get long term data on bleeding events and incidents of strokes. I think further research could be done to see if you can decrease the time patients need to be on anticoagulation after the Watchman device implantation. It would decrease the cost of having to buy oral anticoagulants and help lower a bleeding risk. Overall, the review of the literature shows that the Watchman device is a great, new option for the treatment of non-valvular atrial fibrillations for decreasing stroke risk.

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Appendix A

Author	**Title**	**Design**	**Source**	**Findings**	**Year Published**

Boston Scientific Corporation	WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients With Atrial Fibrillation (PROTECT AF)	RCT	Clinicaltrial.gov	This is a multi-center, prospective, randomized study, stratified by center, comparing the WATCHMAN device to long term warfarin therapy, demonstrating that the treatment arm is non-inferior to the control arm	2015
Holmes DR Jr	Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial	RCT	PubMed	LAA occlusion was noninferior to warfarin for ischemic stroke prevention or SE >7 days' post-procedure. Although noninferiority was not achieved for overall efficacy, event rates were low and numerically comparable in both arms. Procedural safety has significantly improved	2015
KP, Phillips	Combining Watchman left atrial appendage closure and catheter ablation for atrial fibrillation: multicentre registry results of feasibility and safety during implant and 30 days follow-up	Multicenter Study	PubMed	The outcomes from these international, multicentre registries support the feasibility and safety of performing combined procedures of ablation and Watchman LAAC for patients with non-valvular AF and high stroke risk	2018
Price, MJ	Bleeding Outcomes After Left Atrial Appendage Closure Compared With Long-Term Warfarin: A Pooled, Patient-Level Analysis of the WATCHMAN Randomized Trial Experience	RCT	PubMed	There was no difference in the overall rate of major bleeding in patients assigned to LAA closure compared with extended warfarin therapy over 3 years of follow-up. However, LAA closure significantly reduced bleeding beyond the procedural period, particularly once adjunctive pharmacotherapy was discontinued	2015

L, Ueberham	Pharmacological and Non-pharmacological Treatments for Stroke Prevention in Patients with Atrial Fibrillation	Review	PubMed	For patients with a high bleeding risk and thus not suitable for oral anticoagulation, a palette of surgical and non-surgical methods for LAA occlusion are available	2017
A, Al-Abcha	Left Atrial Appendage Closure Versus Oral Anticoagulation in Non-Valvular Atrial Fibrillation: A Systematic Review and Meta-Analysis	Meta-Analysis	PubMed	Our meta-analysis showed lower all-cause mortality, cardiovascular mortality, hemorrhagic stroke, major bleeding, non-procedural major bleeding and the composite of stroke, systemic embolism, and cardiovascular death in the LAAC device arm when compared to OAC	2021
VY, Reddy	5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials	RCT	PubMed	These 5-year outcomes of the PREVAIL trial, combined with the 5-year outcomes of the PROTECT AF trial, demonstrate that LAAC with Watchman provides stroke prevention in nonvalvular atrial fibrillation comparable to warfarin, with additional reductions in major bleeding, particularly hemorrhagic stroke, and mortality	2017
E, Gokcal	Atrial Fibrillation for the Neurologist: Preventing both Ischemic and Hemorrhagic Strokes	Review	PubMed	LAAC can be considered in patients at higher hemorrhagic risks while warfarin/DOAC use should be individualized in the majority of AF patients at a low risk of bleeding.	2018
T, Dar	Indication, Patient Selection, and Referral Pathways for Left Atrial Appendage Closure	Meta-Analysis	PubMed	Observational data support extension of LAAC to patients most in need with excellent results thus far. Its use must continue to be tailored to the individual	2018

				patient, occasionally with less vigorous post-procedure antithrombotic regimens than those traditionally used	
ML, Main	Assessment of Device-Related Thrombus and Associated Clinical Outcomes With the WATCHMAN Left Atrial Appendage Closure Device for Embolic Protection in Patients With Atrial Fibrillation	RCT	PubMed	Found the prevalence of LAA-associated thrombus in PROTECT-AF to be 5.7% of patients, with DRT much less likely at 45 days while patients remained on warfarin, versus 6 and 12 months follow-up when discontinuation was allowed	2016
S, Sahay	Efficacy and safety of left atrial appendage closure versus medical treatment in atrial fibrillation: a network meta-analysis from randomized trials	Meta-Analysis	PubMed	The findings of this meta-analysis suggest that LAAC is superior to placebo and APT, and comparable to NOAC for preventing mortality and stroke or SE, with similar bleeding risk in patients with non-valvular	2017
S, Panniker	Outcomes and costs of left atrial appendage closure from randomized controlled trial and real-world experience relative to oral anticoagulation	Meta-analysis	PubMed	Left atrial appendage closure in both settings achieves cost parity in a relatively short period of time and may offer substantial savings compared with current therapies. Savings are most pronounced among higher risk patients and those unsuitable for anticoagulation	2016
WD, Bode	Left atrial appendage occlusion for prevention of stroke in nonvalvular atrial fibrillation: a meta-analysis	Meta-analysis	PubMed	The data suggest that LAAO is a reasonable option for stroke prophylaxis in AF when anticoagulation is not an option, and the risk for stroke outweighs the risk of procedural complications	2015

DF, Briceno	Left Atrial Appendage Occlusion Device and Novel Oral Anticoagulants Versus Warfarin for Stroke Prevention in Nonvalvular Atrial Fibrillation: Systematic Review and Meta-Analysis of Randomized Controlled Trials	Meta-Analysis	PubMed	DEVICE is a reasonable noninferior alternative to warfarin for stroke prevention, but cautious use is essential given safety concerns	2015
LG, Tereshchenko	Comparative Effectiveness of Interventions for Stroke Prevention in Atrial Fibrillation: A Network Meta-Analysis.	Meta-Analysis	PubMed	The entire spectrum of therapy to prevent thromboembolism in nonvalvular AF significantly reduced stroke/systemic embolism events and mortality	2017

Research Proposal
Introduction

Atrial fibrillation is a common heart arrhythmia that leads to an increased risk of stroke. Warfarin was the original choice of oral anticoagulation that would be used as the treatment for atrial fibrillation. However, there are people who have contraindications to anticoagulation or are a high fall risk and shouldn't be on Warfarin. The Watchman Device was originally designed in 2005 as a way to close the left atrial appendage where clots are usually formed with atrial fibrillation. The watchman may be a superior way to help reduce the risk of stroke compared to the traditional use of Warfarin. From research so far, there has been no definitive answer if the Watchman is superior to Warfarin at preventing stroke in pateints with a fib. The goal of this research proposal is to determine if the Watchman device or Warfarin over the span of ten years

is more successful at preventing stroke and to look at how many hemorrhagic strokes versus ischemic strokes.

Research Design

The PROTECT AF and PREVAIL trials were the original clinical trials that tested the Watchman device. Using the two databases of participants from the trials a survey will be sent out too all participants. If they answer the questions on the survey and allow access to their medical records their medical data will be included in the trial. We will then be contacting patients from local hospitals who are on Warfarin. They will be provided a survey and given they fill out the survey they will be included. The goal is to have roughly equal numbers of people in the Watchman device group and Warfarin group.

Based on the responses from the survey we will be able to combine the data to see how many patients have had ischemic strokes are hemorrhagic strokes or other serious adverse events from either the device or Warfarin use. If any survey is incomplete or medical records are not allowed access, they will not be included in the trial. Collection of the survey will take roughly a month and then there will be a lengthy time period of going through the survey responses and obtaining medical records. Once all data is gathered and has been looked over the analysis will begin.

Participants

Participants in this study must have been a part of the PROTECT AF or PREVAIL trials for the Watchman device. These were the two leading trials for the device and have the largest pool of patients, which is why we are using their databases. By word of mouth and going to surrounding hospitals we will inform providers about our study and ask them to hand a flyer out to their patients who are on warfarin and fit the criteria of the study. The criteria the patient must

meet are as follows: need to have non-valvular atrial fibrillation, need to have been on Warfarin for ten years or have had the device for ten years, need a CHADS2 VASC score of 1 and need to be willing to allow access to medical records to confirm they had a stroke if they reported so and what type of stroke it was. The participants will be given a description of the study and contact information if they choose to later on revoke their information in the study. No patient identifiers or names will be used in the study or paper. They will not be rewarded monetarily but rewarded knowing they are helping in the advancement of treating atrial fibrillation.

Participants will have no mental, physical or emotional risk in participating in this trial. There is no in person contact or meetings they would need to attend. They need to fill out the survey and mail it back to us, and postage will be provided. The survey will roughly take them five minutes to complete. Their doctors are also welcome to help them fill it out if they are unable to do so on their own. There will be a phone number and email address they are able to contact us at with any questions.

Methods and Data Collection

Once surveys are mailed back in, they will be sorted and data will be inserted into a spreadsheet to organize responses to survey questions. If access is denied to medical records that survey will be thrown out and no data from the survey will be recorded. There will be two surveys, one for the device group and one for the Watchman. They will be short surveys and participants will not be rewarded monetarily for participating. Questions will be their current age, the age they got the device implanted, any serious adverse events from the procedure, any strokes since the watchman was implanted. An optional question will be listing a pro and con for the Watchman device you've experienced. The Warfarin survey will be identical but in the context of Warfarin.

After going through the PROTECT Af and PREVAIL trial databases, the surveys will be mailed out to all participants. They will have one month to fill out the survey and mail it back. We then will be going to providers in the area to have them ask patients on Warfarin if they are willing to participate. After collecting close to equal number of people on Warfarin- hopefully more since we do not expect a one hundred percent response rate, we will give the Warfarin group one month to reply.

Following a month of collecting and waiting for responses the timeframe for responses will close and data collection will begin. Anyone who did not completely fill out the survey or did not grant us access to their medical records will be excluded from the trial.

Statistical Analysis

Using a spreadsheet all responses from the survey will be entered. The main data that will be analyzed is if the patient has had a stroke. We will then use their medical records to confirm they had a stroke and which kind of stroke it was. This will all be recorded and then later calculated for statistical significance. Similarly, the Warfarin groups data will also be entered into a separate spreadsheet and the main focus will be if they replied yes to having a stroke. Like the device group their medical records will be checked to confirm and determine which kind of strokes. Transient ischemic attacks will not be included in the main analysis but it will be noted if that is what the patient deemed as a stroke.

Once all data is in the spreadsheet and medical records have been confirmed we will conduct a comparative analysis on the number of strokes total and a further breakdown of which type of stroke. In our analysis we will calculate things like average age, which sex were stroke rates higher in, did they have a history of a previous stroke, ect. Everything will be conducted on

a P value standardized scale to determine statistical significance. There will be a further analysis of the optional questionnaire on the survey about the pros and cons of either treatment option.

Challenges of the study

The main challenges with the study will be getting enough responses from both groups. Issues getting responses may be due to lack of any monetary compensation, change of address, deceased or not wanting to grant access to medical records. I do not foresee problems with validity because they can answer wrong on the survey, but if medical records say otherwise we will be able to double check. Another problem with the study is we are not incorporating the use of NOACs or aspirin which are two other treatment options for atrial fibrillation. NOACs are much newer but tend to be more popular because you do not need INR testing like you do with Warfarin. However, since warfarin was the first staple treatment for a fib it seems to be a good comparison to the Watchman. This study will also not be a complete picture due to the smaller sample sizes. More Watchman devices have been planted but will not fall into the post-op ten years which is required for the study.

Conclusion

The goal of this study is to determine if the Watchman device is superior to Warfarin for preventing strokes in patients with atrial fibrillation. Stroke is a very large risk that comes with the diagnosis of a.fib. It usually requires a patient to be on an anticoagulation for the rest of their life, until the Watchman device was invented. Warfarin typically has weekly monitoring of the patient's INR and comes with a large bleeding risk. This study aims to discover if there is better chance of reducing stroke using the device versus Warfarin and in return would eliminate the bleeding risks, costs of anticoagulation and would have no INR monitoring.

A secondary outcome we are looking at is out of all the strokes are there more hemorrhagic or ischemic strokes. The goal of this study is to hopefully get a better understanding of long term benefits of the Watchman device or Warfarin for reducing stroke risk in patients with atrial fibrillation. Since the device is so new, there hasn't been more than a five year follow up. With an analysis ten years out of the patients who have had the device implanted and getting data on how many strokes and what kind of stroke can hopefully more clearly show us if a treatment is more effective than the other.

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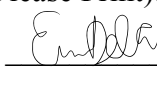
Author's Signature:  Date: 07/20/2022

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