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WATCHMAN compared to Warfarin in reducing risk of stroke in patients with non-valvular atrial fibrillation

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WATCHMAN Compared to Warfarin in Reducing Risk of Stroke in Patients With Non-Valvular Atrial Fibrillation

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Abstract

Objective: To determine if the WATCHMAN device is as efficacious as warfarin for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) using a systematic review. **Methods:** Pubmed and Google Scholar databases were used to evaluate clinical trials using the search terms atrial fibrillation, watchman, warfarin, and stroke prevention. **Results:** Three studies met inclusion criteria, with 2 being randomized control trials (RCT), and 1 being a prospective cohort study. *Reddy et al* found that after 3.8 years of follow-up, patients with percutaneous closure of Left atrial appendage (LAA) met criteria for both non-inferiority and superiority, compared with warfarin for preventing combined outcome for stroke. *Holmes et al* showed at 18 months follow-up that the WATCHMAN device and warfarin therapy groups had similar efficacy endpoints. The device group was shown to be non-inferior to the control group in late-ischemic stroke 7 days post procedure, and was found to be equally as safe. *Boresma et al* showed that at the 1-year follow-up there was a lower risk of stroke in the device group, and that the earliest discontinuation of anticoagulant therapy had the lowest risk of bleeding. **Conclusion:** This systematic review shows evidence that the WATCHMAN implantable LAA device may be a suitable alternative to prevent thromboembolism in patients with NVAF who may have a contraindication for long-term warfarin or anticoagulation use. Due to the novel technology of the WATCHMAN implant, more studies should be completed to determine its long-term efficacy and adverse events.

Introduction:

Stroke is a leading cause of long-term disability in the United States. Stroke also accounts for approximately 140,000 deaths every year and it is the fifth leading cause of death among Americans, according to the Center for Disease Control [1]. In the United States someone has a stroke every 40 seconds, and someone dies of a stroke every 4 minutes[1]. A major risk factor for ischemic stroke is atrial fibrillation (AFib). AFib increases the risk of stroke four to five-fold compared to those without AFib[2]. Due to the irregular contraction of the atria, blood clots can form and embolize to the brain. Among various treatments for AFib, such as the WATCHMAN procedure, anticoagulants have been the mainstay of treatment in prevention of clot formation leading to stroke.

Warfarin (Coumadin) was the only known anticoagulant for years, reducing risk of stroke by 50-70%[3]. Warfarin affects the extrinsic pathway, blocking the formation of vitamin K dependent factors[3]. With this, there is an increased risk of bleeding while on warfarin. To monitor blood levels, an international normalized ratio (INR) is performed every 4-6 weeks to maintain a therapeutic range[4]. A diet high in leafy green vegetables, vitamin K supplements, various medications such as antibiotics and non-steroidal anti-inflammatory drugs, and alcohol can all affect the levels of warfarin causing drastic changes in the INR. The dangerous risk of bleeding as well as inconveniences related to warfarin use in day-to-day life has led to further development of new technologies to reduce the risk of stroke.

A new treatment that has been FDA approved for the reduction of strokes in patients with NVAF is the WATCHMAN implant. It is a device that is implanted into the left atrial appendage, which is where more than 90% of stroke forming clots form[5]. This filter prevents clots from forming in the LAA by allowing heart tissue growth over the implant to permanently seal in order to prevent

embolisms to the brain[5]**.** Three studies looking at the efficacy of the WATCHMAN device are reviewed here.

PICO:

Population: Adults with non-valvular atrial fibrillation
Intervention: WATCHMAN device
Control: Warfarin as anticoagulant therapy
Outcome: preventing blood clots that lead to stroke

Clinical Question:

Is the WATCHMAN device as efficacious as warfarin at reducing the risk of stroke in patients with non-valvular AFib?

Methods

An initial Pubmed and Google Scholar search was performed in September 2019 using the following key search terms: WATCHMAN, warfarin, atrial fibrillation, stroke, prevention, and comparison which yielded 47 articles in PubMed and 49 in Google Scholar. 83 articles were reviewed once the duplicates were removed, of which 73 articles were then removed because they were systematic reviews, comparing different NVAF treatment procedures, or various closure techniques of LAA procedure. The 10 remaining articles were reviewed, of which 7 were excluded due to not being full-text articles, were meta-analysis, or study end-points different than that of our objective.

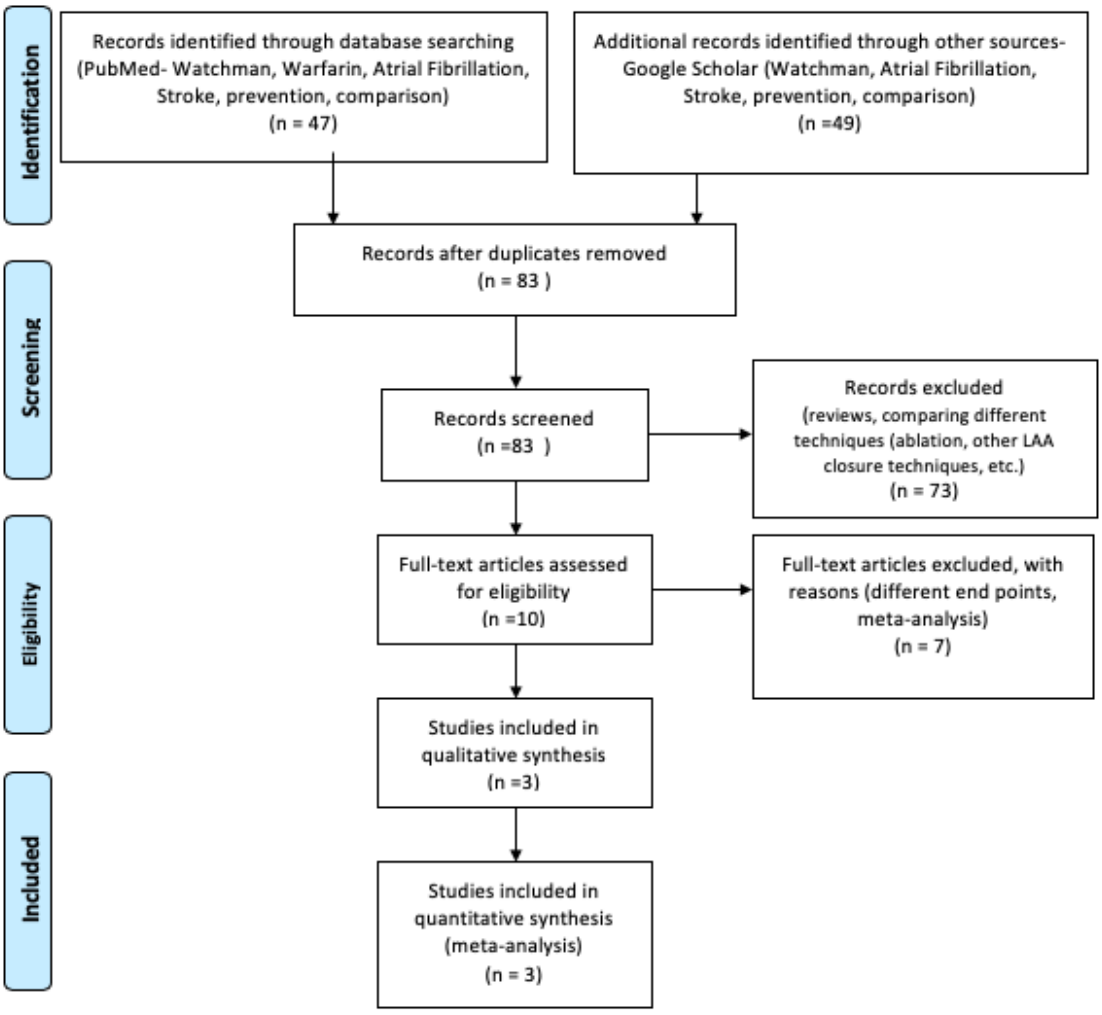

Figure 1. PRISMA flow diagram

Study 1: *Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. Reddy et. al. PROTECT AF*

Study objective: To determine whether a local strategy of mechanical left atrial appendage (LAA) closure was noninferior to warfarin.

Study design: The study (PROTECT AF) was a multicenter, randomized (2:1) unblinded, Bayesian- designed study conducted at 59 hospitals with 707 patients with nonvalvular AF and at least one other stroke risk factor ($CHADS_2 \geq 1$).[6] Enrollment occurred between February 2005 and June 2008 and included a 4 year follow up through October 2012. Noninferiority required a posterior probability greater than 97.5% and a superior probability of 95% or greater; the noninferiority margin was a rate ratio of 2.0 comparing event rates between treatment groups.

Table 1: Inclusion and Exclusion Criteria for study participants

Inclusion criteria	Exclusion criteria
1. 18 years of age or older 2. Paroxysmal, persistent, or permanent nonvalvular AF 3. 1 or more $CHADS_2$ risk factors (age >75 years, hypertension, diabetes, heart failure or left ventricular systolic dysfunction, prior transient ischemic attack (TIA) or stroke) 4. Eligible for long term anticoagulation for warfarin	1. Patent foramen ovale with atrial septal aneurysm 2. Atrial septal defect, mechanical valve prosthesis, LV ejection fraction less than 30%, mobile aortic atheroma, and symptomatic carotid disease.

Results

The study included 707 patients, 463 of which were randomized to the device group and 244 to warfarin. There were 39 primary efficacy events (stroke, systemic embolization, and cardiovascular or unexplained death) among 463 device patients (8.4%, 2.3 events per 100 patient-years, 95% credible interval 1.7-3.2) vs 34 events among 244 warfarin patients (13.9%, 3.8 events per 100 patient-years, 95% credible interval, 2.5- 4.9) (RR, 0.60 favoring device; 95% credible interval, 0.41- 1.05), meeting criteria for both noninferiority (posterior probability, >99.9%) and superiority (posterior probability, 96.0). The ischemic stroke rate in the device group (1.4%/year, 24/463 patients) was not significantly greater than in the warfarin group (1.1%/year, 10/244 patients, P = .49). Fewer hemorrhagic strokes occurred in the device group (3/463 patients, 0.6%) than in the warfarin group (10/244 patients, 4.0%). In addition, fewer cardiovascular deaths occurred in the device group (17/463 patients, 3.7%) than in the warfarin group (22/244 patients, 9.0%).

Critique:

Strengths of this study include the relatively long follow up of 3.8 years and a relatively large sample size of 707 patients. In addition, the majority of randomized patients received the intended therapy, with 99% of patients in the warfarin group receiving the anticoagulant. Adherence with therapy (the time in therapeutic range) was high compared to other studies at 70% for the warfarin group. In patients randomized to receive the device, 88% were successful in implantation. Weaknesses of the study include patients and physicians not being blinded in this study, which may contribute to treatment bias among the two groups. The safety endpoint required unblinding for assessment of procedure relationship, as well as assessment for potential thrombus on the device in stroke events. The study also reflected a predominantly male population (70.4% in the device group vs. 70.1% in the warfarin group) and a predominantly causasian population (91.8% in device group vs. 91% in the warfarin group). In addition, patients receiving the LAA device had to adhere to 6 months of anticoagulation or antithrombotic intervention (or both) to protect patients from defined primary efficacy endpoints. This study did

not address patients with absolute contraindications to warfarin unable to tolerate this initial anticoagulation transition.

Study 2. *Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. Holmes, et al*

Objective: To assess the safety and efficacy of LAA occlusion for stroke prevention in patients with NVAF compared with long-term warfarin therapy.

Design: The PREVAIL trial was a multicentered, randomized study that included 50 sites in the United States. There was a total of 475 patients enrolled with NVAF and a $CHADS_2$ score of $\geq$ 2, or a score of 1 plus another risk factor (Table 2) to undergo a LAA occlusion with the WATCHMAN procedure and discontinuation of warfarin, or either to receive chronic warfarin treatment. This study has three coprimary endpoints: 1) primary efficacy including a composite of hemorrhagic or ischemic stroke, SE (systemic embolism), and cardiovascular/unexplained death, 2) late-ischemic efficacy, a composite of ischemic stroke or SE, excluding the first 7 days after randomization, 3) a coprimary endpoint being early safety, a composite of all-cause death, ischemic stroke, SE, or device-/procedure-related events requiring open cardiovascular surgery or major endovascular intervention between randomization and within 7 days of the procedure or during hospitalization.

Table 2. Inclusion and exclusion criteria for participants in the PREVAIL trial

Inclusion Criteria	Exclusion Criteria
1. $CHADS_2$ score $\geq$2 2. $CHADS_2$ score of 1 if: • Female >75 years of age • Baseline ejection fraction >30%, but < 35% • Age 65-74 years with diabetes or coronary artery disease • Age $\geq$65 years with CHF	1. Requirement for long-term anticoagulation therapy for reasons other than AF 2. Contraindication to warfarin or aspirin 3. Previous stroke/transient ischemic attack within 90 days of enrollment 4. Symptomatic carotid disease 5. A patent foramen ovale or atrial septal defect requiring treatment 6. Patients in whom clopidogrel therapy was indicated

Results: 269 patients were randomized to the device group, and 138 to the control group. The LAA occlusive device was successfully implanted in 95.1% of patients in which it was attempted, with 4 patients in which the implant was not attempted even though they were assigned the device group due to not stopping anticoagulation therapy, a new LAA thrombus detected, and LAA size and shape were not optimal for the device. All patients had a 6 month

minimum follow-up in which 92.2%, 98.3%, and 99.3% of patients were able to discontinue their warfarin after 45 days, 6 months, and 12 months, respectively.

The primary endpoints of efficacy at 18 months were similarly low in both the device (0.064) and the control group (0.063), with one stroke/SE occurring with warfarin therapy. The second endpoint of late-ischemic primary efficacy for the rate of stroke or SE > 7 days after randomization for the device group (0.0253), and control group (0.0200) had a 95% CI, achieving noninferiority of the device group was shown compared to the control group. The last endpoint of early safety was only evaluated in the device group, and was successful if the percentage of patients experiencing one of the SE was statistically less than the performance goal of 2.67% with an upper bound of the 1-sided 95% CI. Only 6 events occurred in the 269 patients with the LAA device demonstrating 2.2% experienced an event, and the 1-sided upper bound was 2.652% which successfully achieving the endpoint. This study supports that the WATCHMAN device remains a reasonable, safe, and efficacious alternative to chronic long-term warfarin therapy for prevention of stroke in patients with NVAF.

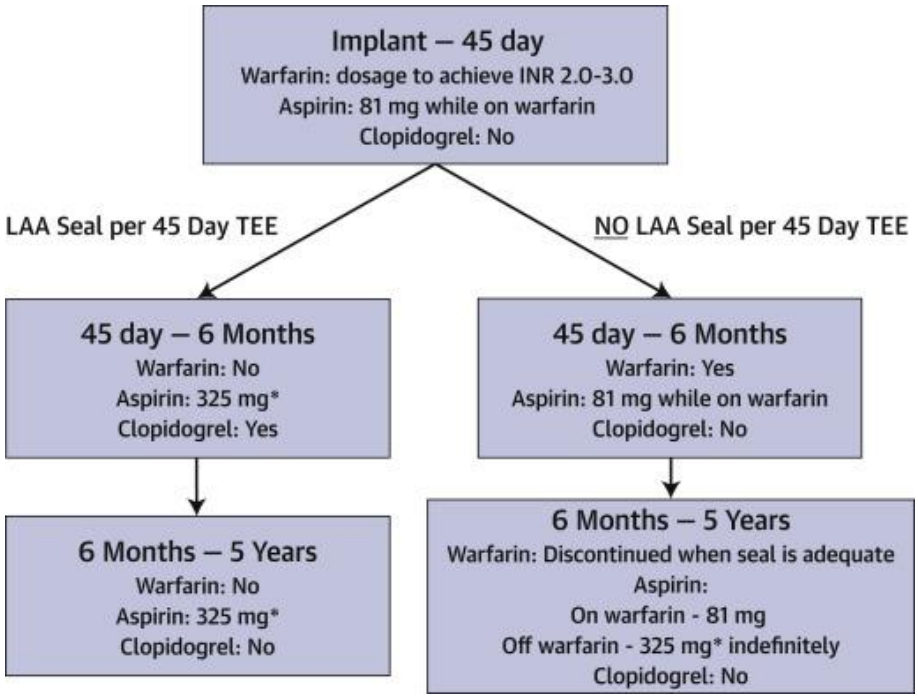

Figure 1. Medication regimen for LAA occlusion

Critique: This PREVAIL trial adds new information to supplement the previous PROTECT AF trial. The first primary endpoint of this study showed similar absolute event rates which did not demonstrate that LAA occlusion is noninferior to warfarin, which is possibly due to the lower-than-expected number of events that occurred. This is mainly due to the control group which was found to be an "unexpected, overperforming group" which is likely due to the time-in-therapeutic range of 68%, which is known to be higher than similar study designs. This study did

not include patients whom anticoagulation is contraindicated in, contributing to the lack of data in this population.

Study 3. *Evaluating Real-World Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology. Final 2-Year Outcome Data of the EWOLUTION Trial Focusing on History of Stroke and Hemorrhage. Boresma, et al.*

Objective: To obtain data on the overall safety, efficacy, procedural success, complications, and long-term patient outcomes of the WATCHMAN device including subgroups at high risk of stroke and bleeding, including patients with prior ischemic and hemorrhagic stroke and those with prior major bleeding.

Study Design: This study is a multicenter, prospective, non-randomized cohort study. The study began in October 2013 and was completed in May 2015, enrolling patients if they were eligible to receive the WATCHMAN device according to the appropriate guidelines, not participating in another trial, were not pregnant, and were able to provide informed consent. Follow-up included a clinic visit between 1-3 months post-implant, LAA imaging, and annual follow-up visits. This study included documentation of serious adverse events including all-cause death, strokes, TIA, SE, perforation, tamponade, neurological events, thrombosis, and bleeding that occurred within seven days of the implant. Study sites received on-site monitoring ranging from 2-5 times depending on the number of patients and compliance review.

Results: A total of 1,020 patients received the WATCHMAN implant from 47 centers in 13 countries. Of the implanting physicians, 78% had <2 years of experience with the device and performed 75% of the study participants procedures. No irregularities or discrepancies were detected between study sites using transesophageal echocardiography (TEE) findings and first follow up visits. At the 2-year follow-up 161 patients had died, with non-cardiovascular causes being the most common (75), cardiovascular causes (46), bleeding (10), and unknown causes (30). Out of the 1% bleeding as cause of death, 6 were gastrointestinal, and 4 were cerebral. Of the cerebral bleeds, 1 was on dual antiplatelet therapy (DAPT), 1 on single antiplatelet therapy (SAPT), 1 on warfarin, and 1 using no anticoagulation.

At hospital discharge 16% of patients were using warfarin, 11% using a novel anticoagulant anti-coagulant (NOAC), 60% a DAPT, 58% on SAPT, and 6% on no anticoagulation. At the 2 year follow up, 8% of active patients were still on a NOAC, 7% were on DAPT, 71% were on SAPT, while 14% were not using any anticoagulant. The conversion time to just SAPT or no anticoagulation was 46% at 6 months, 75% at 1 year, and 95% at 2 years.

Most patients were placed on a type of anticoagulant directly after the procedure to prevent a device-related thrombus (DRT). Out of 835 patients with follow-up imaging, 34 patients had a DRT with 31 of them found within the first 90 days post-procedure, with the majority of clots being non-mobile. There was no statistical significance found between the type of anticoagulant used; but the patients on warfarin, NOAC, or DAPT were found to have the non-mobile clots. The mobile type was seen in all patients except for patients on warfarin. In 21 patients who experience a stroke during the 2-year period with LAA imaging performed, only 1 DRT was found.

At the 2-year follow-up 47 patients were found to have experienced major non-procedural bleeding. These patients were categorized by discontinuing DAPT <105 days, and those that

discontinued >105 days. The lowest rates of bleeding were seen in the patients with earliest discontinuation, although not found to be statistically significant. Ischemic stroke risk was 7.2/100 patient-years with a composite risk of 10.2/100 patient-years, and an observed stroke rate of 1.3/100 patient-years. When this cohort was divided into low risk (n=118) and high risk (n=902) for stroke, no ischemic stroke/TIA/SE was observed in those with a $CHADS_2$ score <3.

After 1-year follow-up there was lower overall stroke, TIA, and SE. The discontinuation of DAPT and NOAC therapy in patients at 2 years showed a 46% lower major bleeding risk compared to the control group. In summary, the WATCHMAN LAA is a very effective and safe alternative in preventing thrombo-embolitic events in patients with NVAF with high risk of stroke and bleeding.

Critique: EWOLUTION is the largest prospective study on the WATCHMAN device reporting on 2-year follow up outcomes. This study is not as strong as the previous studies due to being a prospective cohort study rather than an RCT directly comparing WATCHMAN to warfarin use. The study utilized center-dependent data completeness, imaging, and follow-up being the responsibility of local investigators. This study also had a continuation of some form of NOAC in most patients which could contribute to the additional stroke/TIA/SE prevention. The study failed to mention the specific SAPT, DOAC, or NOAC therapies. It was mentioned that continuing use of oral anticoagulants along with the device may also contribute to further stroke prevention.

Discussion:

This review focused on the use of the WATCHMAN device as an alternative to warfarin therapy for reducing the risk of stroke in patients with nonvalvular AFib. The PROTECT-AF and PREVAIL studies were both unmasked randomized control trials, while the EWOLUTION study was a prospective, non-randomized cohort study. The PROTECT-AF and PREVAIL studies had similar inclusion criteria of $CHADS_2$ score >1.[6,7] The EWOLUTION study had a vast majority of patients with much higher $CHADS_2$ score> 4 (73.1%).[8] The PREVAIL study had a primary efficacy endpoint of 0.064 for the device group vs. 0.063 for the control group, yielding a mean 18-month rate ratio of 1.07 (95% CrI: 0.57 to 1.89)[7]. The upper bound of 1.89 was not lower than the prespecified noninferiority margin of 1.75 predefined in the statistical analysis plan, therefore, statistical noninferiority was not achieved. However, the rate of stroke or SE >7 day after randomization was 0.0253 for the device group and 0.0200 for the control group with an 18-month risk difference 0.00533 (95% CrI- 0.0190 to 0.0273). Since the 95% CrI of the risk difference was < 0.0275, noninferiority was achieved.[7]

The PROTECT AF study had a primary efficacy endpoint (which included stroke, systemic embolism, or cardiovascular death and unexplained death) of 39 events among 463 device patients (2.3 events per 100 patient years) compared to 34 events among 244 warfarin patients (3.8 events per 100 patient years). This met criteria for both noninferiority (posterior probability, >99%) and superiority (posterior probability, 96%)[6].

The EWOLUTION study had a historical ischemic stroke risk of 7.2/100 patient years and showed a composite risk of ischemic stroke/TIA/SE of 10.1/100 patient-years. The observed stroke rate was 1.3/100 patient-years, conferring a reduction of 83% from what was expected. The combined endpoint of ischemic TIA/SE, found the observed rate at 2.0/100 patient-years, conferring a risk reduction of 80%.[8]

Each of the studies varied in their strengths and weaknesses due to sample size, length of study, and their endpoints. The EWOLUTION study had the largest population of patients with 1,020 participants receiving the WATCHMAN device, whereas the PROTECT AF had 463 patients receiving WATCHMAN, while the PREVAIL study had the least amount receiving the WATCHMAN at 269 [6,7,8]. In addition, all 3 studies were of varying duration, with the PREVAIL study being 18 months, compared to EWOLUTION being 2 years, and the PROTECT AF study had a duration of 4 years. The variability in duration of the studies may have affected the outcomes, especially when reviewing a serious adverse event such as stroke, TIA or systemic embolism. The major findings of the PREVAIL trial were that LAA closure with the WATCHMAN was not noninferior to warfarin for primary efficacy composite endpoint of all-cause stroke, SE, cardiovascular, or unexplained death, although the event rates for warfarin were significantly lower than expected, which affected the ability of the study to establish noninferiority.[7] The PROTECT-AF study found that the WATCHMAN device met criteria for both noninferiority and superiority, compared to warfarin therapy, for preventing the combined outcome of stroke, systemic embolism, and cardiovascular death, while also being superior for cardiovascular mortality and all-cause mortality.[6]

The EWOLUTION study had more female participants (40.1%) in the device groups compared to PROTECT AF and PREVAIL studies (29.6% and 32.3%respectively).The study found that the WATCHMAN device had consistently low rates of stroke and nonprocedural bleeding, however most were contraindicated to oral anticoagulation and only used single antiplatelet therapy.[8]

Conclusion:

This systematic review shows evidence that the WATCHMAN implantable LAA device may be a suitable alternative to prevent thromboembolism in patients with NVAF who may have a contraindication for long-term warfarin or anticoagulation use. There are numerous factors that could affect the outcomes of patients receiving the WATCHMAN device, such as the physicians' experience with the procedure, health status of the individual, and any history of major bleeding.

There are various risks associated with device placement, such as device related thrombus, post-procedure related bleeding, and thromboembolic related events such as stroke. One of the benefits of WATCHMAN is not being on lifelong anticoagulation which is the alternative in patients currently with NVAF to reduce risk of stroke. The studies reviewed here showed WATCHMAN was noninferior to warfarin for preventing stroke. However, we believe that more trials showing efficacy of WATCHMAN need to be performed, especially in populations that were not greatly represented in the studies reviewed here, including women and minority races. There are currently two additional randomized control trials looking at the efficacy of the WATCHMAN device in stroke risk reduction, the ASAP-TOO and the OPTION. These trials are further researching other oral anticoagulants and their efficacy compared to WATCHMAN.

References

1. Stroke Facts. CDC.gov. https://www.cdc/gov/stroke/facts.htm. Published March 15, 2019. Accessed 18 September 2019.

2. Atrial fibrillation fact sheet|data & statistics|dhdsp|cdc. https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_atrial_fibrillation.htm. Published November 2, 2018. Accessed 18 September 18 2019

3. What medicines treat afib? WebMD. https://www.webmd.com/heart-disease/atrial-fibrillation/what-medicines-treat-afib. Accessed 18 September 2019.

4. Tideman PA, Tirimacco R, St John A, Roberts GW. How to manage warfarin therapy. *Aust Prescr*. 2015;38(2):44-48. doi:10.18773/austprescr.2015.016. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4653986/. Accessed 18 September 2019.

5. About the watchman procedure for physicians. https://www.watchman.com/en-us-hcp/about-the-procedure.html. Accessed 21 September 2019

6. Protect AF trial
Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, Huber K, Whisenant B, Kar S, Swarup V, Gordon N, Holmes D; PROTECT AF Steering Committee and Investigators. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA*. 2014;312(19):1988-1998. doi:10.1001/jama.2014.15192. https://www.ncbi.nlm.nih.gov/pubmed/25399274. Accessed 12 September 2019

7. PREVAIL trial
Holmes DR, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol*. 2014;64(1):1-12. doi:10.1016/j.jacc.2014.04.029r. https://www.ncbi.nlm.nih.gov/pubmed/24998121**.** Accessed 12 September 2019.

8. EWOLUTION STUDY
Boersma LV, Hueseyin I, Kische S, Pokushalov E, Schmitz T, Schmidt B, GoriT, Meincke F., Protopopov AV, Bettst, Mazzone P, Foley D, Grygier M, Sievert H, De Potter, Vireca E., Stein K., BergmannMW. Evaluating real-world clinical outcomes in atrial fibrillation patients receiving the watchman left atrial appendage closure technology. *Circulation: Arrhythmia and Electrophysiology*. 2019;12(4): e006841. doi:10.1161/CIRCEP.118.006841. https://www.ahajournals.org/doi/10.1161/CIRCEP.118.006841'. Accessed 15 September 2019.