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Analysis of the WATCHMAN on the Reduction of Stroke Compared to Anticoagulants: A Systematic Review of the Literature

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Abstract

Objective: Anticoagulants have been approved and used for decades as highly effective blood thinners. The objective of this study is to analyze the clinical trials in order to determine if the Watchman reduces the risk of stroke in patients with atrial fibrillation compared to those prescribed the traditional anticoagulants. This will contribute to the current body of knowledge and possibly provide beneficial clinical guidance with respect to providing an alternative option for those suffering from non-valvular Atrial fibrillation. **Methods:** A systematic literature search through the Saint James School of Medicine library resources as well as PubMed, Medscape, Google Scholar was conducted. Studies were included if the literature examined the comparison between the Watchman device and four specific anticoagulants (Xarelto, Eliquis, Pradaxa, and Warfarin) in association with reduction of risks of strokes in an atrial fibrillation population. The study includes a qualitative sub-analysis to explore additional clinical aspects that may affect risk of stroke and response of treatment. **Results:** Outcomes were significant for similar stroke occurrence, when compared to published clinical trials. Alternatively, there was a significant reduction in risk of bleeding and all-cause mortality in the Watchman™ device compared to traditional NOACs and warfarin. While examining the studies and trials, overall, the Watchman™ device offers a better long-term outcome therapy for non-valvular atrial fibrillation populations who are not possibilities for extended anticoagulation. The studies used for analysis examining the dosage found higher fatality with increased use of NOACs and more hospitalizations with decreased use. **Conclusion:** From the

presented data, it is safe to say that the Watchman™ device is a viable and effective alternative for stroke prophylaxis in certain patient populations. Compared to traditional anticoagulant therapies for non-valvular atrial fibrillation, these studies suggest that the Watchman™ device can reduce bleeding time and, in most cases, the risk of stroke is less than or equal to traditional anti-coagulants.

Keywords

Watchman, Stroke Risk Reduction, Anticoagulation

1. Introduction

The use of oral anticoagulants, such as apixaban (Eliquis), rivaroxaban (Xarelto), dabigatran (Pradaxa), and warfarin (Coumadin), are FDA approved and have been a mainstay long-term therapy for stroke prophylaxis in patients with diagnosed with non-valvular Atrial Fibrillation (NVAF) [1]. These oral anticoagulants have been shown to reduce the risk of stroke in NVAF patients; however, adverse events and certain pharmacokinetics limit the use of these drugs. In March 2015 the FDA approved the Watchman™ device (Boston Scientific Corporation; Natick, MA) as an alternative prophylactic measure to long-term oral anticoagulation in patients with Nonvalvular Atrial Fibrillation (NVAF) requiring stroke prophylaxis. The goal of this systematic review is to assess the effectiveness of stroke reduction of the Watchman device in indirect comparison to the aforementioned oral anticoagulants in individuals with NVAF as a viable alternative of stroke prophylaxis.

AF is a supraventricular arrhythmia and is characterized by a rapid, irregular heartbeat [2]. Under normal circumstances, the sinoatrial (SA) node generates electrical complexes that travel through the atrioventricular (AV) node, then to the bundle branches and into Purkinje fibers. When small random segments of depolarization occur in the atria at irregular intervals, this can result in a random irregular pattern of QRS complex which generates an irregular rhythm. Although pathogenesis is likely multifactorial, cellular hypertrophy and atrial remodeling have been associated with new onset and perpetuation of atrial dysrhythmia events [3]. In clinical practice, readings of rapid oscillatory (fibrillary) waves lacking defined P waves with RR intervals occurring at irregular rates can be observed via a twelve-lead electrocardiogram (ECG), the reference standard [4]. In the setting of suspected paroxysmal AF, continuous ambulatory ECG (Holter monitor) may be warranted. In a randomized trial the Holter monitor demonstrated a 48% diagnostic yield of a 24-hour monitoring period.

Photoplethysmogram (PPG) is a non-invasive, low-cost, optical measurement that can be used to detect variations of blood volume [5]. The peripheral pulse signal captured by the PPG can be processed via an algorithm to reflect RR in-

terval signals. Although PPG is not useful for diagnoses, this may allow for more practical methods of patient-centered tracking in a wider population [6].

A feared complication of AF is thrombosis formation in the LAA which can become dislodged and lead to an embolic stroke. The LAA is a small extension or outpouching of cardiac tissue in the superior portion of the left atrium with varying morphology. Previous literature supports the LAA being the most common site of thrombosis generation with ensuing embolism into circulation and consequent stroke [7]. In the setting of AF, the blood pools in the LAA leading to stasis and coagulation. For this reason, long-term thromboembolic prophylaxis is indicated to reduce the risk of thromboembolic events [8].

In regards to diagnostic criteria for AF, the 2020 European Society of Cardiology (ESC) and European Association of Cardio-Thoracic Surgery (EACTS) guidelines state a standard 12-lead ECG recording or a single-lead ECG tracing of $\geq$30 seconds showing heart rhythm with no discernible repeating P wave and irregular RR intervals (when AV conduction is not impaired) is diagnostic of clinical AF.

American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS), American College of Cardiology/American Heart Association (ACC/AHA), European Society of Cardiology (ESC), and National Institute for Health and Care Excellence (NICE) have a similar risk-based approach to guide anticoagulation prophylaxis recommendations. This method involved using the CHA_2DS_2-VASc score which incorporates major risk factors to aid in identifying low-risk individuals who shouldn't be offered anticoagulant therapy (Lip *et al*., 2010). The reference values include congestive heart failure (1 point), hypertension (1 point), age $\geq$ 75 years (2 points), diabetes mellitus (1 point), prior stroke or TIA or thromboembolism (2 points), vascular disease (1 point), age 65 - 74 years (1 point), and sexual category (*i.e*., female sex is 1 point). While stroke prophylaxis is recommended to patients with NVAF and $\geq$1 non-sex CHA_2DS_2-VASc risk factor per CHEST guidelines, the AHA/ACC/HRS updated their recommendations for stroke prophylaxis in patients with NVAF and $\geq$2 non-sex CHA_2DS_2-VASc risk factors. Another risk stratification tool of note is the Age, Biomarker, Clinical history (ABC) score. The ABC stroke risk score accounts for age, cardiac biomarkers N-terminal fragment B-type natriuretic peptide (NT-proBNP) and cardiac troponin high-sensitivity (cTn-hs) and is comparable to CHA_2DS_2-VASc in predicting thromboembolic risk [9].

While previous literature shows OACs to decrease the risk of stroke, certain patient populations have contraindicated bleeding risk which may prevent OAC use. The ACCP strongly recommends using the bleeding risk scheme HAS-BLED to evaluate OAC appropriateness in AF patients. Also called the Birmingham AF bleeding schema, HAS-BLED accounts for hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), and drug/alcohol concomitantly [8]. In a cohort of 1,279 patients with NVAF, a renal function biomarker Beta-trace protein (BTP) to the HAS-BLED

score showed improvement in bleeding risk prediction [10]. A score of 1 to 2 points indicates moderate risk and >3 points is considered high risk.

Lifestyle education is a very important key component in analyzing patients with non-valvular atrial fibrillation trying to lower their risk of ischemic stroke. The prevalence of atrial fibrillation and trying to decrease it is very important when considering some vastly common risk factors that many face today, for example; older age, hypertension, obesity, diabetes mellitus, sleep apnea, cardiac diseases, smoking, alcohol and substance abuse [11]. Factors that can be reversible or controllable with patient education regarding lifestyle modifications can have an effect on risk of stroke and potentially decrease the use of OACs. Suggested interventions are lifestyle adjustments such as weight loss, smoking discontinuation, healthier food habits and the termination of alcohol and substance use.

As previously stated, the aim of this study is to determine if the Watchman device is a viable alternative to OACs. The use of interventional therapy should be based on patient specific needs and guideline recommendations. The following results are to the researchers' best ability as medical students, and to stay in accordance with the proposed timeline and resources approved by Saint James School of Medicine.

2. Methods

The aim of this research was to conduct a comprehensive systematic literature review search through a variety of resources including: PubMed, Google Scholar, Medscape, and EBSCO electronic as well as the Saint James School of Medicine library resources. Search terms "atrial fibrillation", 'rhythmia dysfunction", "left atrial appendage", "clotting risk", "stroke prevention", "primary risk of stroke", "bleeding risk", "anticoagulant contraindications", "clinical trial", and "adverse effect" were used to identify and analyze relevant findings to discuss the efficacy profiles of the Watchmen device, Xarelto, Eliquis, and Pradaxa. Citations were screened and assessed via Rayyan, a web application. This being said, if an article met the list of exclusions below, it was excluded from the analysis. Two review authors carefully assessed study eligibility and risk bias, with another two authors settling any discrepancies.

The inclusion criteria for this systematic review were based on: relevant articles published within the last 15 years, peer-reviewed or scholarly articles, studies published in the English language, and studies in which the population involved had taken anti-coagulants for a period of at least one month (refer to **Figure 1**). Over the past decade and a half, medical technology has witnessed rapid development in both design and requirements for medical device approval. By limiting our timeline of evaluation, we ensure our research reflects the current clinical guidelines and technological design, providing a more accurate assessment of the Watchman device. The articles chosen were those examining relevant clinical trials pertaining to the relative risks of strokes in participants with Atrial fibrillation who were either prescribed traditional anticoagulants, specifically

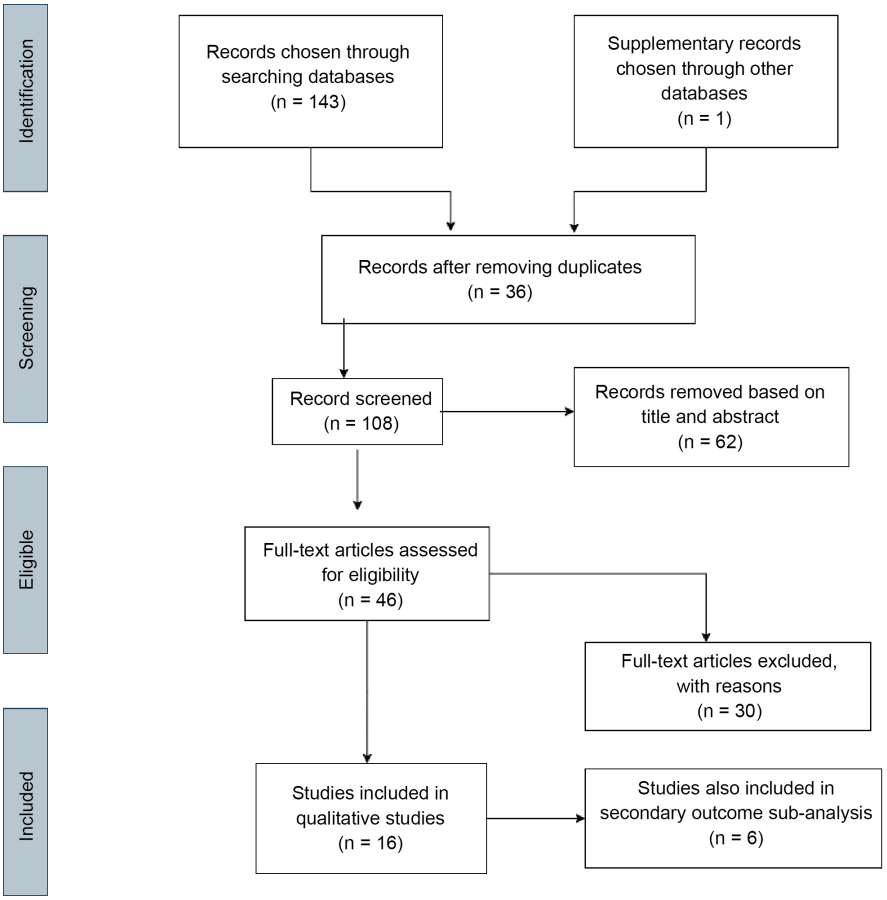

Figure 1. Anticoagulant therapy and their risks of stroke or systemic embolism based on trials.

Warfarin, Xarelto, Eliquis and Pradaxa versus those who were prescribed/recommended the Watchman Device. Excluded articles were based on publications that had been originally written in a foreign language, used for marketing purposes or financial gain, articles dated prior to 2006, duplicate articles, systematic review, and literature reviews.

In order to establish an accurate and thoroughness of the study selection process, the reviewers involved in this systematic review consisted of medical students with diverse backgrounds in various science fields. They had previously completed foundational medical education, which equipped them with a strong comprehension of fundamental medical concepts and research methodologies. In particular medical research classes, these research classes provided comprehensive instruction on various aspects of conducting research in the medical field, such as study design, data collection and analysis, literature review, and critical appraisal of scientific literature. Furthermore, these classes familiarized the students with research ethics and the importance of precise methodology in generating reliable evidence.

Additionally, their educational backgrounds encompassed a range of science disciplines. The coursework in these disciplines helped develop a strong founda-

tion of scientific knowledge and analytic skills, which are crucial for conducting systematic reviews and critically evaluating the selected studies. To equip the reviewers with the essential skills for conducting a systematic review, they underwent a comprehensive training program specifically designed to meet the requirements of this study. This training expanded on the knowledge acquired from their research course and with guidance on productive literature search strategies, study selection criteria, risk bias assessment techniques, and data extraction methods. During the review process, the reviewers received continuous supervision and mentorship from experienced researchers and medical professionals, assuring the quality and accuracy of their assessments. The active involvement of these reviewers was overseen by senior researchers who provided guidance and oversight, therefore maintaining the integrity and standards of the review process.

The primary outcome was incidence of stroke based on alternative therapies. This is defined as a record of diagnosis of non-valvular atrial fibrillation with prescribed Warfarin, Xarelto, Pradaxa and Eliquis, versus the alternative Watchman device. Other outcome measures included increase in prothrombin time (PT), partial thromboplastin time (PTT) and D-dimer.

Besides the quantitative analysis comparing the WATCHMAN device to anticoagulants in lowering risk of stroke, the qualitative sub-analysis was performed to examine other possible clinical factors that may contribute to stroke risk and influence therapeutic outcomes. The qualitative sub-analysis aimed to better comprehend environmental factors, personal experiences, and perceptions surrounding the use of the WATCHMAN device and anticoagulants in the specific patient group. Furthermore, qualitative sub analysis was performed for the following secondary outcomes: to examine any prior stroke or transient ischemic attack, history of hypertension, CHA2DS2-VASc score, HAS-BLED score, age and diabetes.

The selection criteria of the qualitative sub-analysis included studies that reported healthcare provider's opinion, patient experiences, and contextual factors.

Data extraction for the qualitative sub-analysis in this systematic review was conducted meticulously, assuring the careful retrieval of pertinent information on the identified clinical factors. The factors encompass various aspects such as patient medication preferences, adherence to treatment, recognition risks and benefits, health provider recommendations, and therapy restrictions, among others.

As with every study, it is vital to acknowledge possible limitations related with qualitative sub-analysis. These may involve unstandardized quality and reporting of the studies, potential selection bias from search strategy, and possible biases in data collected. Nevertheless, efforts were made to minimize bias and enhance the quality of the sub-analysis by utilizing transparent data retrieval process, high-quality data analysis strategies and systematic search methods. This analysis is valuable as it offers insights into subjective occurrences, standpoints, and

unforeseen factors that may exacerbate or influence the risk of stroke and variation in the therapy outcomes within this population. By incorporating qualitative data, the objective of this sub-analysis is to enrich quantitative results and provide a more profound understanding of clinical factors contributing to stroke risk and treatment outcomes in patients with atrial fibrillation treated with the WATCHMAN device compared to anticoagulants.

This systematic review concentrated on evaluating the effectiveness of alternative therapies for stroke prophylaxis in patients with non-valvular atrial fibrillation. The primary outcome measure of interest was the incidence of stroke among the participants who received these therapies. This measure was chosen to determine efficacy of the alternative treatments in preventing strokes in this specific patient population.

It is essential to provide a justification for the selection of these specific outcome measures and their clinical significance. The choice of the primary outcome measure, the incidence of stroke prophylaxis in patients with non-valvular atrial fibrillation. The secondary outcome measures, including PT, PTT, and D-dimer, were chosen based on set associations with the coagulation system and their capabilities to provide objective data on the effectiveness and safety of the alternatives therapies. For example, an increase in PT, PTT, or D-dimer levels may suggest a potential disruption in the balance of the coagulation system, indicating a greater risk of abnormal blood clot formation. This information is vital in assessing the safety of the other therapies and monitoring their impact on the clotting mechanisms in patients with non-valvular atrial fibrillation.

Summary of Primary Outcome Findings

Author (Year)	Design /Study Size	Treatment being studied	Mean (Year)	Findings (refer to **Figures 2-5**)
		Anticoagulant therapy and incidence of stroke		
Patel, M. R. *et al.* (2011)	Randomized Clinical trial (n = 14,264)	Rivaroxaban (Xarelto) 20 mg or 15 mg daily for patients with a creatinine clearance of 30 to 49 mL per minute vs. dose adjusted (target international normalized ratio [INR], 2.0 to 3.0) Warfarin	71.2 ± 9.42 (73 years (1/4 of patients were 78 years and older) and 39.7% of the patients were women)	Rivaroxaban was noninferior to Warfarin. Stroke or systemic embolism occurred in 269 patients in the rivaroxaban group and in 306 patients in the warfarin group (hazard ratio, 0.88; 95% CI, 0.74 to 1.03; P < 0.001 for noninferiority; P = 0.12 for superiority) [12].
Rutherford, O. C. W. *et al.* (2020)	Randomized cohort trial (n = 20,504)	Dabigatranvsrivaroxaban	Dabigatran 70.9 ± 10.95 Rivaroxaban 70.9 ± 11.21	Stroke/SE occurred with an event rate of 1.84/100 person-years compared with 2.21/100 person-years in the rivaroxaban group [HR 0.88; 95% confidence interval (CI) 0.76 - 1.02].

Continued

	Randomized cohort trial (n = 27,298)	Rivaroxaban vs. apixaban	Rivaroxaban 72.7 ± 11.08 Apixaban 72.7 ± 11.66	Rate of stroke/SE was 2.65/100 person-years for the apixaban group vs. 2.31/100 person-years for the rivaroxaban group (HR 1.00; 95% CI 0.89 - 1.14) [13].
Li (2018)	Retrospective Cohort (n = 80,279)	Apixaban 2.5,5mg vs. warfarin respectively	Apixaban 5 mg 68.6 ± 11 Apixaban 2.5 mg 82.5 ± 9.5 Warfarin (5 mg matched) 69.2 ± 11.7 Warfarin (2.5 mg matched) 80.1 ± 8.5	Apixaban 5 mg BID associated with lower risk of stroke/SE ([HR]: 0.70, 95% [CI]: 0.60 - 0.81). Apixaban 2.5 mg BID is also associated with a lower risk of stroke/SE (HR: 0.63, 95% CI: 0.49 - 0.81) [14].
Siontis (2019)	Retrospective Cohort (n = 25,523)	NVAF and ESKD Apixaban vs. warfarin	68.22 ± 11.89	No difference in risk of stroke (HR 0.88, 95% CI 0.69 - 1.12; P = 0.29) [15].
Bristol-Myers Squibb (2017) AVERROES NCT00496769	RCT (n = 5,598)	Apixaban (2.5, 5 mg) vs ASA (81-324 mg)	69.9 ± 9.58	Apixaban demonstrated superiority vs ASA; 1.62%/Year vs 3.63%/Year (HR 0.45; 95% CI 0.32 to 0.62, P < 0.001) in stroke/systemic embolism prevention, respectively. Episodes of major bleeding: apixaban 1.4%/Year, and ASA 1.2%/Year (HR 1.13; 95% CI 0.74 to 1.75; P = 0.57).
Bristol-Myers Squibb (2018) NCT02415400	RCT (n = 4,614)	Apixaban + ASA Apixaban + placebo Warfarin + ASA Warfarin + placebo	69.9 ± 9.17	Apixaban (15.85%/yr) vs warfarin (17.17%/yr) with placebo were similar is stroke prevention (HR 0.92; 95% CI 0.75 to 1.13, P = 0.4370). Adjuvant therapy with ASA (15.28%/yr) vs placebo (17.73) did not show significance (HR 0.86; 95% CI 0.70 to 1.07, P = 0.1742).
Boehringer Ingelheim (2009) RE-LY NCT00262600	RCT (n = 5,883)	Group 1: Dabigatran 110 mg PO BID Group 2: Dabigatran 150 mg PO BID Group 3: Warfarin (INR 2 - 3)	71.5 ± 8.7	Group 1 NI vs. group 3 (HR 0.90; 95% CI 0.74 to 1.10, P < 0.0001) in stroke prevention. Group 2 NI vs. group 3 (HR 0.65; 95% CI 0.52 to 0.81, P < 0.0001) in stroke prevention. Group 2 met superiority vs. group 3 in reducing stroke or systemic embolism (HR 0.83; 95% CI 0.74 to 0.93, P = 0.0015).

Continued

Watchman™ Device and incidence of stroke				
				NVAF at increased risk for stroke or bleeding. LAAC resulted in improved rates of hemorrhagic stroke, cardiovascular/unexplained death, and nonprocedural bleeding compared to warfarin.
Holmes, D. R. *et al.* (2015) (PROTECT AF) (PREVAIL) (CAP) (CAP2)	Meta-Analysis (n = 2,406) (PROTECT AF n = 707) (PREVAIL n = 407) (CAP n = 566) (CAP2 n = 579)	Watchman vs Warfarin	PROTECT AF 72.0 ± 8.9 PREVAIL 74.3 ± 7.4 CAP 74.0 ± 8.3 CAP2 75.3 ± 8.0	Watchman device had fewer hemorrhagic strokes (0.15 vs. 0.96 events/100 patient-years [PY]; hazard ratio [HR]: 0.22; 95% CI: 0.08 to 0.61; P = 0.004), cardiovascular/unexplained death (1.1 vs. 2.3 events/100 PY; HR: 0.48; 95% CI: 0.28 to 0.81; P = 0.006), and nonprocedural bleeding (6.0% vs. 11.3%; HR: 0.51; 95% CI: 0.33 to 0.77; P = 0.006) compared with warfarin. All-cause stroke or systemic embolism was similar between both strategies (1.75 vs. 1.87 events/100 PY; HR: 1.02; 95% CI: 0.62 to 1.7; P = 0.94). There were more ischemic strokes in the device group (1.6 vs. 0.9 and 0.2 vs. 1.0 events/100 PY; HR: 1.95 and 0.22, respectively; P = 0.05 and 0.004, respectively) [16].
Koifman, E. *et al.* (2016)	RCT (n = 212)	Watchman Device vs Warfarin Therapy	75 ± 8	14 studies with 246,005 patients were included in the analysis, among which 124,823 were treated with warfarin, 120,450 were treated with NOACs and 732 had Watchman implanted. Mean age was 72 ± 9 years, 53% were male, and mean CHADS2 score was 2.1 ± 1.6. Both NOACs and Watchman were superior to warfarin in hemorrhagic stroke prevention (OR = 0.46 [0.30 - 0.82] and OR = 0.21 [0.05 - 0.99], respectively). NOACs significantly reduced total stroke (OR = 0.78 [0.58 - 0.96]) and major bleeding (OR = 0.78 [0.65 - 0.91]) compared with warfarin. Indirect comparison between NOAC and Watchman revealed no significant differences in outcomes, though there was a trend toward higher rates of ischemic stroke with Watchman compared with NOAC (OR 2.60 [0.60 - 13.96]) with the opposite findings with hemorrhagic stroke (OR = 0.44 [0.09 - 2.14]) [17].

Continued

Pahlajani, Dev *et al.* (2016)	Meta Analysis (n = 2406)	Watchman Device vs Warfarin Therapy	71.2 + 9.42	With mean follow-up of 2.69 years, patients receiving LAAC with the Watchman device had significantly fewer hemorrhagic strokes (0.15 vs. 0.96 events/100 patient-years [PY]; hazard ratio [HR]: 0.22; P = 0.004), cardiovascular/unexplained death (1.1 vs. 2.3 events/100 PY; HR: 0.48; P = 0.006), and nonprocedural bleeding (6.0% vs. 11.3%; HR: 0.51; P = 0.006) compared with warfarin. All-cause stroke or systemic embolism was similar between both strategies (1.75 vs. 1.87 events/100 PY; HR: 1.02; 95% CI: 0.62 to 1.7; P = 0.94). There were more ischemic strokes in the device group (1.6 vs. 0.9 and 0.2 vs. 1.0 events/100 PY; HR: 1.95 and 0.22, respectively; P = 0.05 and 0.004, respectively). Both trials and registries identified similar event rates and consistent device effect in multiple subsets (refer to **Figure 5**) [16].
Secondary outcome sub analyses:				
Anticoagulant therapy and incidence of bleeding				
Patel, M. R. *et al.* (2011)	RCT (n = 14,264)	Rivaroxaban (Xarelto) 20mg or 15 mg daily for patients with a creatinine clearance of 30 to 49 mL per minute vs. dose adjusted (target international normalized ratio [INR], 2.0 to 3.0) Warfarin	71.2 + 9.42	Risk of major bleeding 1475 patients in the rivaroxaban group and 1449 patients in the warfarin group, respectively; hazard ratio in the rivaroxaban group, 1.03; 95% CI, 0.96 to 1.11; P = 0.442). Rates of major bleeding were similar in the rivaroxaban and warfarin groups (3.6% and 3.4%, respectively; P = 0.58) [18].
Rutherford O.C W. *et al.* (2020)	Randomized cohort trial (n = 20,504)	Dabigatranvsrivaroxaban	Dabigatran 70.9 + 10.95 Rivaroxaban 70.9 + 11.21	A major bleeding event occurred at a rate of 1.40/100 person-years in the dabigatran group, and 1.93 in the rivaroxaban group (HR 0.75; 95% CI 0.64 - 0.88).
	Randomized cohort trial (n = 27,298)	Rivaroxaban vs. apixaban	Rivaroxaban 72.7 + 11.08 Apixaban 72.7 + 11.66	The event rates of major bleeding were 1.76/100 person-years vs. 2.10/100 person-years in the apixaban- and rivaroxaban groups, respectively (HR 0.79; 95% CI 0.68 - 0.91) [13].

Continued

Li (2018)	Retrospective Cohort (n = 80,279)	Apixaban 2.5, 5 mg vs. warfarin respectively	Apixaban 5 mg 68.6 + 11 Apixaban 2.5 mg 82.5 + 9.5	Apixaban 5 mg BID associated with lower risk of major bleeding (HR: 0.59, 95% CI: 0.53 - 0.66). Apixaban 2.5 mg BID is also associated with a lower risk of major bleeding (HR: 0.59, 95% CI: 0.49 - 0.71) [14].
Siontis (2019)	Retrospective Cohort (n = 25,523)	NVAF and ESKD Apixaban vs. warfarin	68.22 + 11.89	Apixaban was associated with significantly less bleeding (HR 0.72, 95% CI 0.59 - 0.87; P < 0.001) [15]
Janssen Scientific Affairs, LLC (2016) PIONEER AF-PCI	RCT (n = 2,124)	Group 1: Rivaroxaban 15 mg daily plus P2Y12 Group 2: Rivaroxaban 2.5 mg twice daily followed by rivaroxaban 15 mg daily plus low-dose aspirin. Group 3: Warfarin plus DAPT followed by warfarin plus low-dose aspirin.	70.1 ± 8.97	Incidence of clinically significant bleeding: 16.8% of group 1 vs. 18.0% of group 2 vs. 26.7% of group 3 (HR 0.59, 95% CI 0.47 to 0.76; P < 0.001 for group 1 vs. 3; HR 0.63, 95% CI 0.5 to 0.8; P < 0.001 for group 2 vs. 3). Incidence of major bleeding (secondary outcome): 2.1% of group 1 vs. 1.9% of group 2 vs. 3.3% of group 3 (HR 0.66, 95% CI 0.33 to 1.31; P = 0.234 for group 1 vs. 3; HR 0.57, 95% CI 0.28 to 1.16; P = 0.114 for group 2 vs. 3)
Janssen Scientific Affairs, LLC (2010) NCT00403767	RCT (n = 14,269)	Rivaroxabanvswarfarin	71.2 ± 9.42	Composite event of major/non-major bleeding events of rivaroxaban vs. warfarin were similar: 0.21% vs. 0.20% (HR 1.03; 95% CI 0.96 to 1.11, P = 0.442).
Boehringer Ingelheim (2009) RE-LY NCT00262600	RCT (n = 5,883)	Group 1: Dabigatran 110 mg PO BID Group 2: Dabigatran 150 mg PO BID Group 3: Warfarin (INR 2 - 3)	71.5 ± 8.7	Major Bleeding: Group 1: 2.99%/YR (HR 0.80; 95% CI 0.70 to 0.93, P = 0.0026) Group 2: 3.55%/YR (HR 0.93; 95% CI 0.81 to 1.07, P = 0.3146) Group 3: 3.81%/YR.
Bristol-Myers Squibb (2011) ARISTOTLE NCT00412984	RCT (n = 18,201)	Apixaban (2.5, 5 mg) vs warfarin (INR 2 - 3)	69.1 ± 9.68	Rate of major bleeding for apixaban was 2.13%/yr compared to warfarin, 3.09% (HR 0.69; 95% CI 0.80 to 0.99, P < 0.001).
Bristol-Myers Squibb (2018) NCT02415400	RCT (n = 4,614)	Apixaban + ASA or placebo vs warfarin + ASA or placebo	69.9 ± 9.17	Major or clinically relevant bleeding: Apixaban 24.66%/yr demonstrated superiority vs warfarin 35.79%/yr (HR 0.69; 95% CI 0.58 to 0.82, P < 0.0001). ASA as adjuvant showed increase bleeding risk: 40.51%/yrvs placebo matching ASA 21.03% (HR 1.88; 95% CI 1.58 to 2.23, P < 0.0001).

Continued

Lip (2017)	Cohort (n = 14,020)	NOACs (apixaban, rivaroxaban, dabigatran) vs warfarin	66.5 (61.1 - 70.4)	No significant difference in stroke prevention. Bleeding events were significantly lower for treatment with apixaban ([HR], 0.35; 95% CI, 0.17 - 0.72) and dabigatran (HR, 0.48; 95% CI, 0.30 - 0.77) vs. warfarin. Bleeding event was not significantly different for treatment with rivaroxabanvs warfarin (HR, 0.84; 95% CI, 0.49 - 1.44).

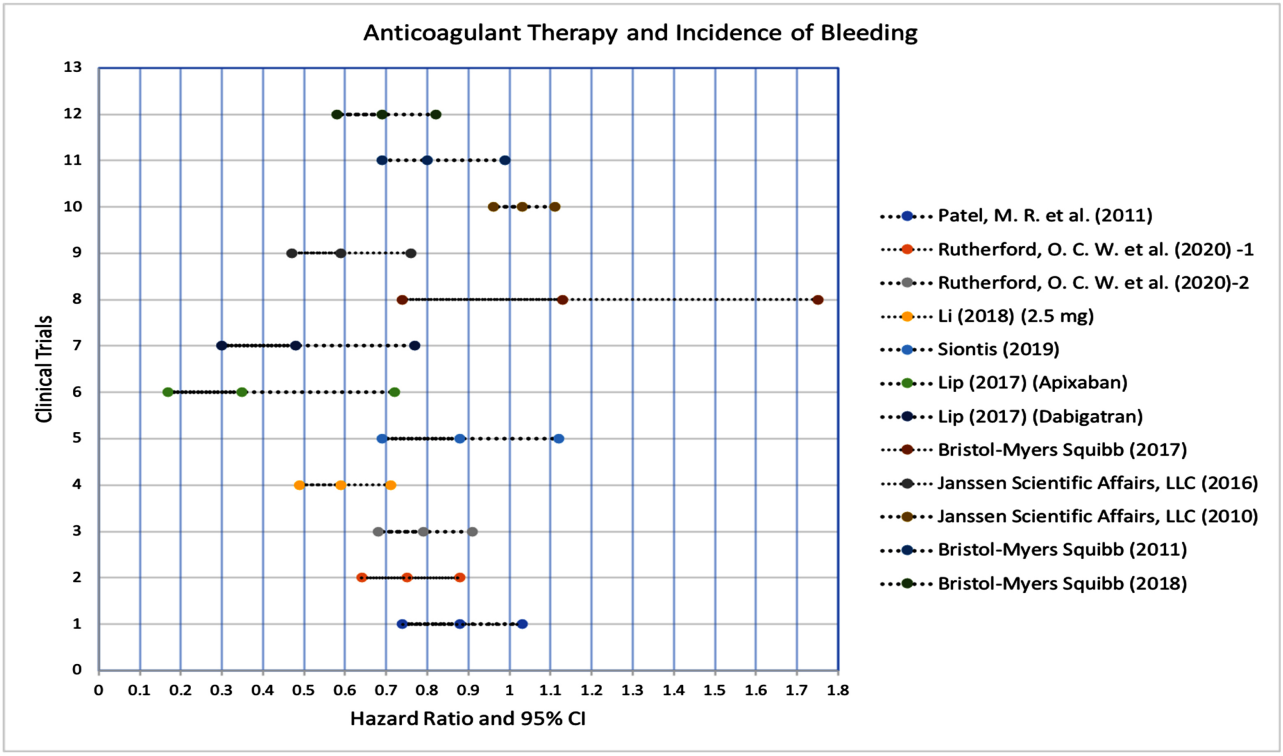

Figure 2. Anticoagulant therapy and their risks of stroke or systemic embolism based on trials.

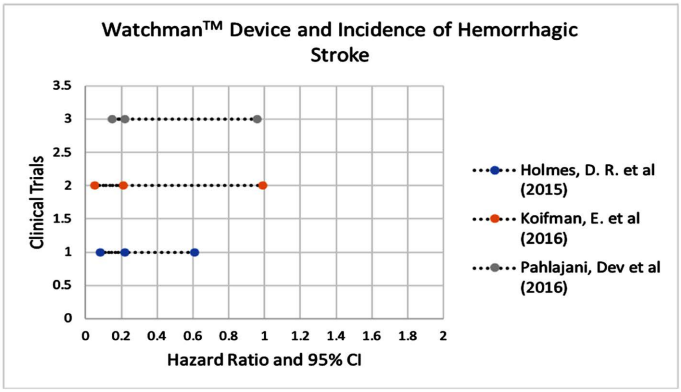

Figure 3. Anticoagulant therapy and their risks of bleeding based on trials.

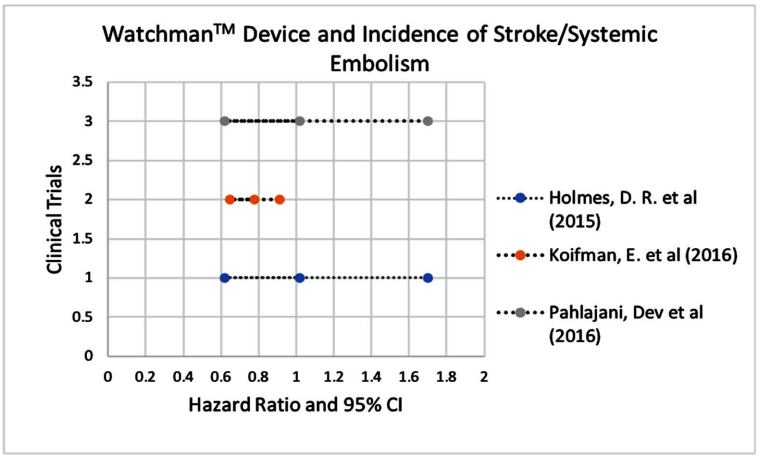

Figure 4. The risk of hemorrhagic stroke in the Watchman™ device.

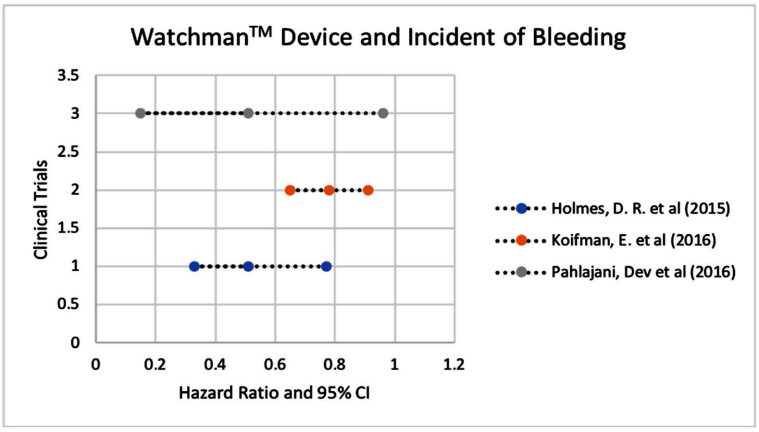

Figure 5. The risk of stroke/stroke embolism in the Watchman™ device.

3. Discussion

3.1. NOAC Use and the Risk of its Contributing Factors

Despite the fact statistically compelling connections were seen inclusive in the added studies, several of the looked at populations elected may have had numerous predisposing conditions. Predisposing characteristics include risk of bleeding, high blood pressure, age, discontinuing medications and cardiovascular diseases. According to Panaich & Holmes (2017), the incidence of atrial fibrillation increases in frequency with age, bleeding and stopping their anticoagulants during follow-ups [19].

The majority of the studies show a clear indication that the Watchman device was observed to be as safe and as effective in reducing the risk of stroke in patients with atrial fibrillation compared to other anticoagulants. As reported by Holmes, D. R. *et al.* (2015) [16], left atrial appendage closure (watchman device) resulted in improved rates of hemorrhagic stroke, cardiovascular/unexplained death, and nonprocedural bleeding compared to warfarin.

Watchman device had fewer hemorrhagic strokes (0.15 vs. 0.96 events/100 patient-years [PY]; hazard ratio [HR]: 0.22; 95% CI: 0.08 to 0.61; p 0.004), cardi-

ovascular/unexplained death (1.1 vs. 2.3 events/100 PY; HR: 0.48; 95% CI: 0.28 to 0.81; p = 0.006), and nonprocedural bleeding (6.0% vs. 11.3%; HR: 0.51; p = 0.006) compared with warfarin (refer to **Figure 6**) [20].

14 studies done by Koifman, E. *et al.* (2016) where 246,005 patients were included in the analysis, among which 124,823 were treated with warfarin, 120,450 were treated with NOACs and 732 had Watchman implanted. Both NOACs and Watchman were superior to warfarin in hemorrhagic stroke prevention (OR = 0.46 [0.30 - 0.82] and OR = 0.21 [0.05 - 0.99], respectively). NOACs significantly reduced total stroke (OR = 0.78 [0.58 - 0.96]) and major bleeding (OR = 0.78 [0.65 - 0.91]) compared with warfarin.

Indirect comparison between NOAC and Watchman revealed no significant differences in outcomes, though there was a trend toward higher rates of ischemic stroke with Watchman compared with NOAC (OR 2.60 [0.60 - 13.96]) with the opposite findings with hemorrhagic stroke (OR = 0.44 [0.09 - 2.14]). We also looked at anticoagulant therapy and incidence of stroke, and anticoagulant therapy and incidence of bleeding [17].

In one study regarding anticoagulant therapy and incidence of stroke, Rivaroxaban was noninferior to Warfarin. Stroke or systemic embolism occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (hazard ratio, 0.88; 95% CI, 0.74 to 1.03; P < 0.001 for noninferiority; P = 0.12 for superiority).

Risk of major bleeding 1475 patients in the rivaroxaban group and in 1449 patients in the warfarin group (14.9% and 14.5% per year, respectively; hazard ratio

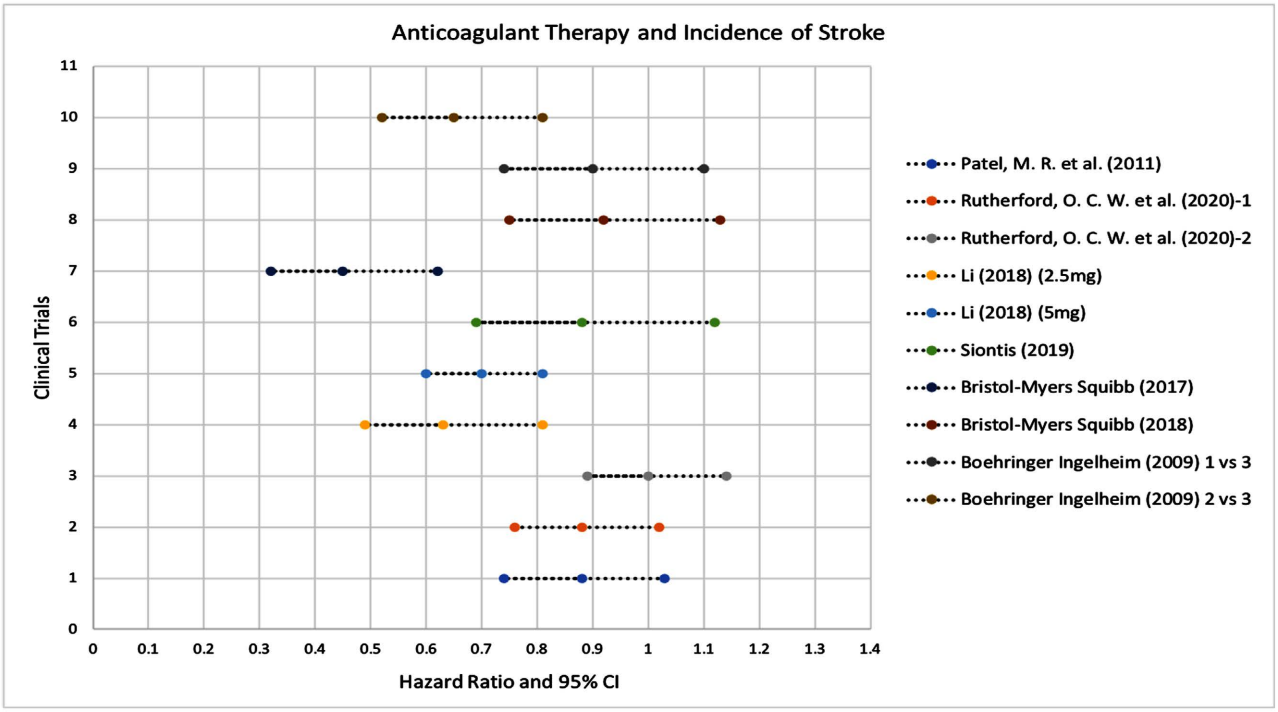

Figure 6. The risk of bleeding in the Watchman™ device.

in the rivaroxaban group, 1.03; 95% CI, 0.96 to 1.11; P = 0.442). Rates of major bleeding were similar in the rivaroxaban and warfarin groups (3.6% and 3.4%, respectively; P = 0.58) [18]. In another study looking at anticoagulant therapy and incidence of bleeding, rivaroxabanvs warfarin, incidence of major bleeding after cardiac ablation (4-week period): Warfarin was the only group with 1 major bleeding event, 0.4%.

The research also shows that bleeding events were significantly lower for treatment withapixaban ([HR], 0.35; 95% CI, 0.17 - 0.72) and dabigatran (HR, 0.48; 95% CI, 0.30 - 0.77) vs. warfarin. Bleeding events were not significantly different for treatment with rivaroxabanvs warfarin (HR, 0.84; 95% CI, 0.49 - 1.44). However, in a study done by Rutherford O.C.W. *et al.* (2020 a major bleeding event occurred at a rate of 1.40/100 person-years in the dabigatran group, and 1.93 in the rivaroxaban group (HR 0.75; 95% CI 0.64 - 0.88) [13].

3.2. Anticoagulation Classification

Differences between patients vary regarding the types of anticoagulants and the dosages that will be prescribed. Anticoagulants can be further classified into either vitamin K antagonist (*i.e.*, Warfarin), direct oral anticoagulants (*i.e.*, Pradaxa, Eliquis, Xarelto) and low molecular weight heparins (*i.e.*, dalteparin, enoxaparin). The majority of studies have shown that direct oral anticoagulants are associated with an increased efficacy compared to vitamin K antagonists like warfarin when comparing preventable device-related thrombosis and stroke prevention complications in initial closure with the Watchman Device. DOAC treatments were associated with a lower risk of stroke, intracranial hemorrhages, and death compared to vitamin K antagonists [21]. Warfarin tends to have a high adverse effect profile due to its association with being contradicted in pregnancy, patients with malignant hypertension, procedures with active bleeding and its hepatic metabolism and protein binding mechanisms that are common for its development of drug to drug interactions [22].

3.3. Anticoagulation Dosage

An additional key factor to take into consideration is the prescribed dosage of anticoagulant therapy. In medical practice, the use and prescribing of anticoagulants is very common and the dosages are important factors to determine the efficacy for the desired target populations. Patients that were being given doses higher than recommended were displaying considerable death and when given lower doses than suggested had additional hospital visits. There were also variations with age and the CHA_2DS_2-VASc score. According to FDA labels, the standard dose for rivaroxaban is 20 mg daily and 5mg for apixaban twice daily. For dabigatran, two doses were recommended based on the patient's age. Patients younger than 75 would benefit more with 150 mg twice daily and patients older than 80 were initially guided to 110 mg twice daily, but also with respect to if the patients were also on other medications [23] (refer to **Table 1**).

Table 1. Suggested anticoagulation for certain patient profiles (Farmakis *et al*., 2018) [23].

Labile INR, inability to check INR regularly	Dabigatran Rivaroxaban Apixaban Edoxaban
History or high risk of Intracranial hemorrhage	Dabigatran Rivaroxaban Apixaban Edoxaban
Stroke or systemic embolism while on Vitamin K antagonists	Dabigatran 150 mg BID Apixaban
Renal Function impairement eGFR < 15 ML/min/1.73m^2 eGFR 15 - 30 ML/min/1.73m^2 eGFR 30 - 50 ML/min/1.73m^2	Vitamin K antagonists Rivaroxaban 15 mg OD Apixaban 2.5 mg BID Edoxaban 30 mg OD Dabigatran 110 mg BID* Rivaroxaban 15 mg OD Apixaban Edoxaban 30 mg OD
History or high risk of bleeding	Dabigatran 110 mg BID Apixaban Edoxaban 30 mg OD
HAS-BLED score ≥ 3	Dabigatran 110 mg BID Apixaban Edoxaban 30 mg OD
Elderly > 80 years	Dabigatran 110 mg BID Rivaroxaban Apixaban
Nasogastric tube due to dysphagia	Rivaroxaban
Need for a reversal agent	Dabigatran

*150 mg BID if no other risk factors for bleeding; **150 mg BID not contraindicated; INR, internatinal normalized ratio; eGFR, estimated glomerular filtration rate; BID, twice daily; OD, once daily.

3.4. Mechanism of Action

Although there are various distinct mechanisms of action of anticoagulants that are FDA approved that are used for nonvalvular patients with AF, these specific anticoagulants pharmacological effects are of value consideration into the treatment of stroke prophylaxis and its efficacy as alternatives to the Watchman™ device.

Warfarin inhibits coagulation factors that require the presence of vitamin K. Vitamin K, in its active form, catalyzes the carboxylation of glutamic acid residues on factors II, VII, IX, and X. This reaction causes the reduction of vitamin K leading to an inactive form. This reaction requires the continual reactivation of via vitamin K epoxide reductase complex 1 (VKORC1). Warfarin inhibits the process of vitamin K reactivation by competitively inhibiting the VKORC1 com-

plex thereby reducing the activation of said clotting factors.

Rivaroxaban, also known by its brand name Xarelto, is classified as a direct factor Xa inhibitor. This drug is also useful in preventing deep vein thrombosis (DVT) and pulmonary embolisms (PE).

Factor Xa inhibitors such as apixaban and rivaroxaban are anticoagulants that directly inhibit both free and bound factor Xa (FXa) leading to the inhibition of fibrin formation and platelet activation. These FXa inhibitors are typically prescribed long-term and taken on a daily basis. Both medications are indicated for stroke prophylaxis in diagnosed non-valvularAFib patients.

Dabigatranetexilate is classified as a direct thrombin competitive inhibitor. This prodrug is rapidly hydrolyzed to its active form in which it gains its anticoagulant activity. By inhibiting both free and fibrin-bound thrombin, activation of factors V, VIII, XI, and XIII are inhibited along with thrombin induced platelet activation. Pradaxa is also indicated for stroke prophylaxis in patients diagnosed with nonvalvularAFib and has shown a decrease in stroke-related events.

The Watchman device is a dome-shaped device that comes in five sizes: 21, 24, 27, 30, and 33 mm. The procedure requires access to the femoral artery in which, under fluoroscopic guidance, the catheter is advanced by the surgeon into the LAA. Once the device has been deployed, fluoroscopy and Transesophageal Echocardiogram (TEE) are used to confirm position, anchor, size, and seal of the device. Preclinical studies completed on the Watchman™ implant indicate endothelial tissue covers the device in approximately 45 days. Oral anticoagulation is given post-surgery until closure of the LAA can be confirmed. Prospective studies utilized warfarin anticoagulation for a period of 45 days followed by dual antiplatelet therapy (DAPT) for a period of six months.

3.5. Mechanism of Action

The information presented in this paper affirms there is in fact solid evidence that The Watchman Device does have its barriers as well. According to Panaich & Holmes (2017), there are limitations to the LAA closure such as technical skills, risk of complications, not enough evidence against NOACs, and the matter of prices. It is important to consider the effectiveness of the Watchman device not only in terms of stroke reduction, but with regard to technical skill, long-term safety, and procedural success. Experience with the Watchman Device is also improving, and the complication rates are lowering with better technology and new arrangers with better and more experience. Further research upon more of its considerations will be more obtainable as more trials and research are available.

4. Conclusions

From the presented data, it may be considered that the Watchman™ device is a viable and effective alternative for stroke prophylaxis in certain patient populations. Compared to traditional anticoagulant therapies for non-valvular atrial fi-

brillation, these studies suggest that the Watchman™ device can reduce bleeding time and, in most cases, the risk of stroke is less than or equal to traditional anti-coagulants. As presented in graph 3, the Watchman™ device demonstrates significant reduction in risks of hemorrhagic strokes. In contrast, in graphs 1, 2 and 5, there is no remarkable difference between the Watchman™ and Warfarin, Rivaroxaban, Apixaban or Dabigatran. Furthermore, through reviewing these trials, especially PROTECT AF and PREVAIL trials demonstrated that left atrial appendage closure with Watchman device provides stroke prophylaxis for non-valvular atrial fibrillation to a similar degree to oral anticoagulant with warfarin.

Although the Watchman™ device may improve in some areas and can be somewhat comparable to the traditional oral anticoagulants, it is not perfect. This device had a higher rate of ischemic strokes. The risks caused by this device may decrease significantly if taken with NOAC compared to warfarin, preliminary data have shown that NOACs have a lower risk of stroke.

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5.1. Reviewer 1

Dr. MirjanaMilutinovic is an accomplished medical professional specializing in internal medicine, ophthalmology, and biomedical engineering. She obtained her Medical Doctor degree from Belgrade University in 1977 and pursued a Master's degree in Biomedical Engineering. With extensive clinical experience, she excelled as a general practitioner in the Emergency Department and further specialized in ophthalmology at the renowned University Eye Clinic in Belgrade. Dr. Milutinovic held esteemed positions, including Deputy Director and Ophthalmologist at the Railway Health Center of Serbia. She has contributed significantly to medical research with about 40 publications and presentations. Since 2011, she has been an active educator at Saint James School of Medicine, focusing on Neuroscience and Physical Diagnosis. Dr. Milutinovic's expertise and multidisciplinary background make her a highly qualified reviewer in the field of internal medicine.

5.2. Reviewer 2

Dr. Alexander Dusic is currently serving as an Associate Professor at St. James School of Medicine since August 2008. He possesses a diverse educational background, including a Masters in Oncology Epidemiology from the University of Belgrade, where he also completed an Oncology Research Fellowship at Bezanijska Kosa Medical Center. Dr. Dusic's journey began with a Doctor of Medi-

cine degree from the University of Belgrade in 1991, solidifying their foundation in medicine. Holding certifications such as USMLE Steps 1, 2, and 3, along with licenses to practice in Serbia and an ECFMG accreditation, they exhibit a commitment to professional growth and international standards. Notably, they have excelled in teaching Physiology, Microbiology, Histology, Embryology, Medical Ethics, and more, and currently instruct BSRC (MD5) and Behavioral Science at the Anguilla campus. Their involvement extends beyond academia, actively mentoring medical student teams in research and statistical analysis, engaging in community volunteer work, and serving as Chairman of the Curriculum Subcommittee and School-wide Committee. Collectively, their qualifications reflect a dedication to education, research, and community enrichment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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