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Comparison of Watchman device with new oral anti-coagulants in patients with atrial fibrillation: A network meta-analysis☆

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ABSTRACT

Background: New oral anticoagulants (NOAC) and the Watchman device represent an alternative to warfarin for stroke prophylaxis in atrial fibrillation (AF) patients. However, no studies compare these new treatments. We performed a network meta-analysis to indirectly compare Watchman and NOACs among AF patients.
Methods: We performed a MEDLINE search for studies comparing warfarin with NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) or Watchman in AF patients with reported clinical outcomes. Mixed treatment comparison model generation was performed to directly and indirectly compare NOACs, warfarin and Watchman.
Results: 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]).
Conclusions: NOAC therapy was superior to warfarin for multiple outcomes while Watchman reduced hemorrhagic stroke. Further studies are needed to assess Watchman versus NOAC to optimize therapy for stroke prevention in AF patients.

1. Introduction

Vitamin K antagonists, such as warfarin, have traditionally been prescribed for stroke prophylaxis in high-risk patients with atrial fibrillation (AF) [1,2]. However, warfarin is limited by a narrow therapeutic range and an increased risk of bleeding [3], leading to high rates of drug discontinuation and under-treatment [4]. In recent years, the introduction of new oral anticoagulants (NOACs) marked a major change in therapy for patients with AF. Large multicenter randomized controlled trials (RCT) demonstrated NOACs to be non-inferior or even superior to warfarin in stroke and systemic embolism prevention with reduced bleeding rates [5–8]. These data led the major societies to endorse NOACs as an alternative to warfarin in patients with AF [9,10] and led to their approval by the Food and Drug Administration (FDA) for the treatment of non-valvular AF. An alternative strategy to prevent stroke and systemic embolism in patients with AF is to exclude the left atrial appendage, which is a common source of embolism [11,12]. While this has previously been accomplished through surgical means, interventions targeting the left atrial appendage were developed in order to minimize the long-term bleeding risk with warfarin [13–16]. The FDA recently approved the Watchman device for treatment of AF patients with high risk for stroke and systemic embolism based on studies comparing the device to warfarin therapy. To date, there is no data comparing the risk of bleeding and stroke for patients with AF treated with the Watchman device and NOACs. Therefore, we performed a network meta-analysis to compare the efficacy and safety of NOACs and the Watchman device in patients with AF.

2. Methods

The primary objective of this network meta-analysis was to compare safety and efficacy of the Watchman device versus NOACs in patients

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with AF in terms of stroke prevention, hemorrhagic complication, and all-cause mortality. Two independent reviewers (EK and MJL) systematically searched (July 2015) MEDLINE/PubMed applying the search terms "Watchman" OR "Dabigatran" OR "Rivaroxaban" OR "Apixaban" OR "Edoxaban". Studies included in the meta-analysis were phase 3 or post-marketing and had to provide comparison of either NOACs or the Watchman device with warfarin therapy in patients with AF and report clinical outcomes. We excluded any study that: had a different control arm (such as aspirin or dual antiplatelet therapy), had inadequate data to abstract clinical outcomes, had duplication of data, or were available only in an abstract form. Data were abstracted by the same two investigators (EK and MJL) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [17,18]. Baseline characteristics were collected when available. Outcomes data for all-cause mortality, ischemic stroke, hemorrhagic stroke, total stroke, and major bleeding events were recorded. We accepted the study definitions for adverse events.

Dichotomous variables are reported as percentages while continuous variables were reported as mean ± standard deviation or median (interquartile range). Mixed treatment comparison model generation was performed to directly and indirectly compare outcomes for the Watchman device, NOACs, and warfarin using GeMTC 0.14.3 software (GeMTC, http://drugis.org/mtc). Bayesian hierarchical random-effects model with directed acyclic graph model for general-purpose Markov chain Monte Carlo analysis was performed with 50,000 tuning iterations and 100,000 simulation iterations. Data are presented as odd ratios (OR) [95% credible intervals (CI)]. Convergence was appraised graphically according to Gelman and Rubin [19]. Data from a consistency model are presented and direction of findings was confirmed with an inconsistency model to serve as a sensitivity analysis. Additional sensitivity analysis was performed with removal of one study at a time to confirm directionality and magnitude of findings. Statistical significance was defined as a p-value <0.05. Subgroup analysis was also performed to compare outcomes only among RCTs.

3. Results

We identified 3208 MEDLINE citations using the previously defined search terms. Implementing our inclusion/exclusion criteria, we evaluated 122 abstract and 42 full-text publications and included 14 studies [5–8,20–30] of 246,005 patients with AF in this network meta-analysis (Fig. 1). There were 124,823 patients treated with warfarin, 120,450 patients treated with NOACs, and 732 patients had a Watchman device implanted. Twelve studies with 244,891 patients compared NOACs with warfarin, among which 5 were RCTs. Two studies with 1114 patients compared the Watchman device with warfarin therapy, both of which were RCTs (Table 1). The patients included in these studies had a mean age of 72 ± 9 years; 53% were male; and mean CHADS2 score was 2.1 ± 1.6. Patient characteristics are shown in Table 2.

Overall, NOACs were associated with a significant reduction in total stroke compared with warfarin (OR = 0.78, 95% CI [0.58–0.96]). Though there was a trend toward reduction in total stroke, the Watchman device did not significantly reduce the risk of total stroke compared with warfarin (OR = 0.67 95% CI [0.29–1.52]). Both NOACs (OR 0.46, 95% CI [0.30–0.82]) and the Watchman device (OR 0.21, 95% CI [0.05–0.99]) significantly decreased the risk of hemorrhagic stroke compared with warfarin. However, the Watchman device did not significantly reduce the risk of hemorrhagic stroke compared with NOACs (OR 0.44, 95% CI [0.09–2.14]). While there was a trend toward reduction in ischemic stroke with NOACs compared with warfarin (OR 0.63, 95% CI [0.35–1.03]), there was an interesting trend toward increased risk of ischemic stroke with the Watchman device compared with warfarin (OR 1.64, 95% CI [0.41–7.70]) and compared with NOACs (OR 2.60, 95% CI [0.60–13.96]).

Major bleeding events were significantly reduced with NOACs compared with warfarin (OR = 0.78, 95% CI [0.65–0.91]). While it did not reach statistical significance, there was a trend toward a reduction in major bleeding with Watchman device compared with warfarin (OR = 0.62, 95% CI [0.29–1.39]). There was no difference in major bleeding for NOACs compared with the Watchman device (OR 1.25, 95% CI [0.55–2.76]).

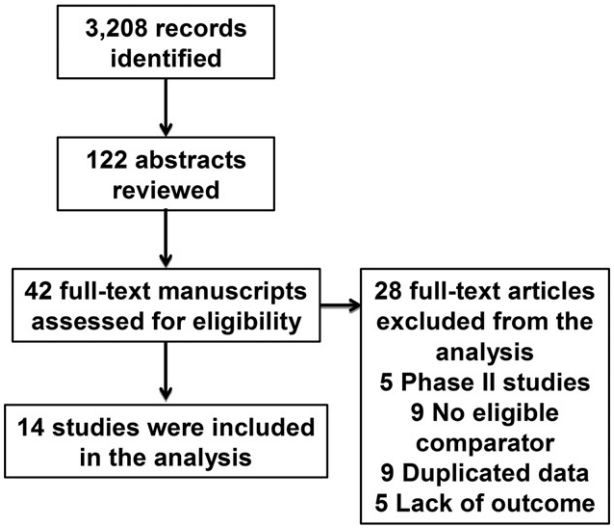

Fig. 1. Study flow-chart.

There was a trend toward reduction in all-cause mortality for NOACs (OR = 0.66, 95% CI [0.40–1.02]) and a weaker trend for Watchman (OR = 0.79, 95% CI [0.27–2.49]) when compared with warfarin. These results are summarized in Fig. 2. Use of an inconsistency model as well as use of different priors confirmed the direction of our findings. These findings were further supported with rank probability estimates for the different therapies (Supplemental Fig. 1). For example, warfarin therapy was associated with the greatest risk of hemorrhagic stroke, while the Watchman device had the lowest risk of hemorrhagic stroke. Alternatively, NOACs were least likely associated with ischemic stroke, while the Watchman device had the greatest risk of ischemic stroke.

When limiting the included studies to RCTs, there was again no significant difference between the Watchman device and NOACs in regard to any outcomes. Compared with warfarin, NOACs led to a significant reduction in all-cause mortality (OR 0.89, [0.80–0.97]), significant reduction in hemorrhagic stroke (OR 0.45, [0.28–0.75]), and a trend toward reduction in total stroke (OR 0.84, [0.62–1.03]) and major bleeding (OR 0.79, [0.61–1.03]) when limiting the included studies to RCTs. Compared with warfarin, the Watchman device led to a significant reduction in hemorrhagic stroke (OR 0.19, [0.05, 0.94]) and a trend toward reduction in all-cause mortality (OR 0.68, [0.45–1.04]). These data on RCTS are demonstrated in Fig. 3.

4. Discussion

The present study confirms that both NOACs and Watchman device significantly reduce the risk of hemorrhagic stroke compared with warfarin in patients with AF. NOACs also reduce major bleeding events and the risk of total stroke and had a trend toward reduction in ischemic stroke and improved survival when compared with warfarin. Atrial fibrillation patients treated with the Watchman device had a trend toward reduction in major bleeding events, total stroke, and all-cause mortality when compared with warfarin. Interestingly, the Watchman device had a trend toward greater risk of ischemic stroke compared with warfarin. When comparing NOACs and Watchman, there was more than a two-fold increase in the risk for hemorrhagic stroke in the NOACs compared with the Watchman device. This difference, though not statistically significant, makes sense given the nature of