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Review Article

Clinical and Safety Outcomes of Oral Antithrombotics for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Network Meta-analysis

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A B S T R A C T

Introduction: Novel oral anticoagulants (NOACs) expanded the options for stroke prevention in atrial fibrillation (AF). Earlier studies comparing their relative effectiveness and safety typically do not incorporate age-related differences or postmarketing studies. This study aimed to summarize and compare clinical and safety outcomes of oral antithrombotics for stroke prevention in AF in younger (65–74 years) and older (≥75 years) elderly.

Methods: We searched PubMed, Embase, and The Cochrane Library from inception through May 1, 2015, for randomized and nonrandomized studies comparing NOACs, warfarin, and aspirin in elderly with AF. Stroke and systemic embolism (SSE) and major bleeding (MB) are the main outcomes. We also studied secondary outcomes of ischemic stroke, all-cause mortality, intracranial bleeding, and gastrointestinal bleeding.

Results: Of 5255 publications identified, 25 randomized controlled trials and 24 nonrandomized studies of 897,748 patients were included. NOACs reduced the risk of SSE compared with warfarin (rate ratios [RRs] range from 0.78–0.82). Relative to SSE, NOACs demonstrated a smaller benefit for ischemic stroke (dabigatran 110 mg, RR 1.08; edoxaban, 1.00; apixaban, 0.99). On the contrary, aspirin was associated with a significantly higher risk of SSE, ischemic stroke, and mortality than warfarin or NOACs (RR > 1), particularly in older elderly. Regarding safety, medium-dose aspirin (100–300 mg daily) and aspirin/clopidogrel combination showed an increased risk of MB compared with warfarin (RR 1.17 and 1.15, respectively), as per dabigatran 150 mg and rivaroxaban in older elderly (RR 1.17 and 1.12, respectively). Among the NOACs, dabigatran 150 mg conferred greater gastrointestinal bleeding risk compared with warfarin (RR 1.51), whereas rivaroxaban (RR 0.73) demonstrated less benefit of reduced intracranial bleeding than other NOACs (RRs range 0.39–0.46).

Conclusions: Lower rates of SSE and intracranial bleeding were observed with the NOACs compared with warfarin. Dabigatran 150 mg and rivaroxaban were associated with higher rates of MB in older elderly.

Atrial fibrillation (AF) is the most common type of cardiac rhythm disorder and its prevalence increases with age, affecting approximately 10% of those aged 80 years and older. Patients with AF are at 2 to 17 times increased risk of stroke than the general population, and the risk of stroke also increases with age.[1] To prevent stroke and systemic embolism (SSE) in patients with AF, oral antithrombotics are commonly prescribed, including anticoagulant and antiplatelet drugs. Although warfarin has been the mainstay oral anticoagulant for

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decades, limitations include variable effects, narrow therapeutic index requiring monitoring, and multiple drug-drug and drug-food interactions.[2] In this regard, the novel oral anticoagulants (NOACs), apixaban, dabigatran, edoxaban, and rivaroxaban, offer an attractive alternative. These newer agents exhibit a predictable dose effect and do not require routine coagulation monitoring. They have similar or better efficacy in preventing SSE compared with warfarin, and may have reduced major bleeding (MB) risks.[3,4] However, they present other challenges, such as lack of reversal agents during bleeding emergencies.[5]

Despite consistent evidence of the superiority of anticoagulant over antiplatelet agents in preventing stroke in AF, many clinicians still prescribe aspirin in real-world practice, either alone or in combination with clopidogrel, due to concerns about the risk of bleeding, especially in the elderly.[6] Of particular interest is the age group 75 years and older (popularly termed the "older elderly"), who represents a population at greater need for preventive treatment due to increased risk of SSE, yet also presents greater risk of bleeding and its deleterious consequences compared with the younger elderly aged 65 to 74 years. New data from subgroup analyses of pivotal outcomes trials of the NOACs further suggest a difference in treatment effects (in particular, increased risk of bleeding) between the 2 age groups.[7,8] Taking into consideration these potential age-related differences in treatment effects, there is little guidance on the comparative efficacy and safety of the different treatment options in the elderly population.

This provided the impetus for our current study, which aims to summarize and compare the clinical and safety outcomes of oral antithrombotics for stroke prevention in AF using a systematic review and network meta-analysis that incorporates both younger and older elderly. We supplemented data from randomized controlled trials (RCTs) with real-world information from postmarketing nonrandomized studies (NRSs) to better reflect the true harm in real-world prescribing.[9] Specifically, postmarketing NRSs have consistently reported an increase in gastrointestinal bleeding with NOACs[10–12]; there also may be an increased risk of myocardial infarction (MI) with dabigatran.[13] We build on previous work by expanding the evidence base beyond RCTs to improve generalizability of the results to real-world patients.

Methods

Data Sources and Searches

We searched PubMed, Embase, and The Cochrane Library for studies from inception through May 1, 2015. Search terms included atrial fibrillation, anticoagulant, antiplatelet, apixaban, dabigatran, edoxaban, rivaroxaban, warfarin, and aspirin. The search was limited to English-language articles involving human subjects (eTable 1).

Study Selection

Three reviewers (LL, HJZ, ALK) screened potentially relevant articles for eligible studies that compared NOACs, warfarin, or aspirin (±clopidogrel) with each other or no treatment for stroke prevention in elderly (≥65 years) with AF. To reflect current prescribing practice, we excluded studies or study arms that administered warfarin at nonstandard doses (eg, low-dose warfarin). We excluded studies of triple therapy (warfarin, aspirin, and clopidogrel) due to significant heterogeneity in target patient population. We included phase 2 or 3 RCTs, as well as NRSs comprising prospective cohort studies and retrospective study designs. We also included unpublished studies if the abstracts contained sufficient information regarding patient characteristics, follow-up duration, and main results. To assess the agreement between reviewers for study selection, we used the kappa statistic, which measures agreement beyond chance.[14]

Data Extraction and Quality Assessment

Two reviewers (LL and ALK) extracted trial-level data. For trials reported in more than one publication, we extracted data from the most complete publication and used other publications to supplement data for the elderly subgroups. We contacted 13 study authors to request additional subgroup data. Eight (62%) of 13 responded, of whom 2 provided unpublished subgroup data.

Two reviewers (LL and ALK) performed quality assessment using the Cochrane Risk of Bias Tool for RCTs and ACROBAT-NRSI (A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions).[15,16] RCTs with high or unclear risk of bias for any of the 6 domains were classified as high risk of bias. NRSs with any of the 7 domains at serious risk of bias were classified as high risk of bias. As it is unlikely that NRSs have low risk of bias due to confounding, the rest were deemed to have moderate risk of bias.

Data Synthesis and Analysis

We performed an extension of frequentist random-effects network meta-analysis using the *mvmeta* routine in STATA 13 statistical software (StataCorp, College Station, TX).[17] In network meta-analysis, for any given comparison between 2 treatments, direct evidence from head-to-head studies and indirect evidence from studies with a shared comparator can be synthesized into a single effect size. This allows integration of evidence for all treatments to increase precision of effect estimates, based on the assumption that included trials were conducted under comparable conditions.[18]

We focused on 2 primary clinical and safety outcomes: stroke (ischemic and hemorrhagic) and systemic embolism, and MB. We used trial-specific definitions of MB (eTable 2). We also studied 5 secondary outcomes of ischemic stroke, all-cause mortality, intracranial bleeding, gastrointestinal bleeding, and MI. We used the rate of outcome per 100 patient-years to obtain the rate ratios (RR) of one treatment compared with another. A result was considered significant if the 95% confidence interval did not include 1. We calculated Surface Under the Cumulative RAnking curve (SUCRA)[18] values expressed as percentages for primary outcomes. SUCRA provides a composite measure that incorporates ranking and uncertainty to reflect the relative probability of a treatment being among the best option.

We assessed potential network inconsistency by *P* value generated from design-by-treatment model.[19] We calculated the difference between direct and indirect evidence to identify inconsistent loops in the network (95% confidence interval excludes 1). A loop of evidence is a collection of studies that links treatments to allow for indirect comparisons; the simplest loop is a triangle formed by 3 direct comparison studies with shared comparators.[18] We assessed the extent of publication bias through visual inspection of funnel plots. Results were reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions.[20]

Subgroup and Sensitivity Analyses

We defined a priori subgroup analyses by age (65–74 years versus ≥75 years) and study design (RCT versus NRS). We conducted sensitivity analyses restricting to studies with low or moderate risk of bias.

Results

Of 5255 citations identified, we excluded 5168 after screening the title and abstract, and another 38 after full-text assessment (Figure 1 and eTable 3). Interrater agreement for study selection was reliable