Mixed Comparison of Stroke Prevention Treatments in Individuals With Nonrheumatic Atrial Fibrillation

Nicola J. Cooper, PhD; Alexander J. Sutton, PhD; Guobing Lu, MSc; Kamlesh Khunti, MD

Background: We aimed to identify different stroke prevention treatments for atrial fibrillation assessed in randomized controlled trials and to compare them within a single evidence synthesis framework.

Methods: We updated the Cochrane review on anticoagulants and antiplatelet therapy for nonrheumatic atrial fibrillation to include randomized controlled trials published between January 2000 and March 2005 identified via the CENTRAL database and MEDLINE. A mixed-treatment comparison method was used to combine direct within-trial, between-treatment comparisons with indirect trial evidence while maintaining randomization.

Results: Data were combined from 19 clinical trials that included 17,833 patients randomized to 9 treatment strategies, including placebo. For prevention of ischemic stroke, adjusted standard-dose warfarin sodium (relative rate [RR], 0.35; 95% credible interval [CrI], 0.24 to 0.52), adjusted low-dose warfarin (RR, 0.35; 95% CrI, 0.19 to 0.60), ximelagatran (RR, 0.34; 95% CrI, 0.18 to 0.61), and aspirin (RR, 0.64; 95% CrI, 0.44 to 0.88) were all associated with a significantly lower rate of ischemic stroke compared with placebo. For major and fatal bleeding episodes, there was some evidence of an increased risk for all treatments but none were statistically significant. Assuming a baseline risk of 51 ischemic stroke events per 1000 person-years, it can be estimated that adjusted standard-dose warfarin could prevent 28 (95% CrI, −37 to −19) ischemic strokes at the expense of 11 (95% CrI, −1 to +39) major or fatal bleeding episodes. In comparison, aspirin could prevent 16 (95% CrI, −26 to −5) ischemic strokes at the expense of 6 (95% CrI, −3 to +27) major or fatal bleeding episodes.

Conclusions: A lower rate of ischemic stroke and a higher rate of major bleeding episodes were found to be associated with oral anticoagulants compared with aspirin, and both anticoagulants and aspirin were found to be associated with a reduction in the rate of stroke compared with placebo.

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objectives of this article are to synthesize the available evidence from RCTs within a single analysis using a mixed-(multiple-) treatment comparison method,\textsuperscript{12,13} also known as a network meta-analysis technique,\textsuperscript{14,15} and to compare the different treatment options with one another, thus allowing comparisons of agents not addressed within any of the individual primary trials.

\section*{METHODS}

A number of different stroke prevention treatments are available for individuals with nonrheumatic atrial fibrillation. The review focused on trials that assessed the long-term use of treatments (ie, at least 12 months). The outcome measures of interest in this analysis were ischemic strokes and major or fatal bleeding episodes per 1000 person-years of follow-up.

\section*{LITERATURE SEARCH}

We used the Cochrane review on anticoagulants or antiplatelet therapy for nonrheumatic atrial fibrillation\textsuperscript{7} and updated it to include RCTs published between January 2000 and March 2005. The primary source of literature for this review was the CENTRAL database of the Cochrane Collaboration. As a secondary source, MEDLINE was searched using the terms atrial fibrillation, stroke, and prevention combined with an RCT filter.\textsuperscript{16} The RCTs were eligible for inclusion in the review if the follow-up period was at least 12 months.

\section*{STATISTICAL METHODS}

Mixed-treatment comparison methods\textsuperscript{12,13} were used to compare the different treatment regimens for stroke prevention in patients with atrial fibrillation. These methods are a generalization of meta-analysis methods because they allow comparisons of agents not addressed within any of the individual primary trials. In addition to analyzing the direct within-trial comparisons between 2 treatments (eg, A vs C), the mixed-treatment comparison framework enabled us to incorporate the indirect comparisons constructed from 2 trials that have 1 treatment in common (eg, A vs B, B vs C).\textsuperscript{12,14} Such methods can only be applied to connected networks of RCTs.\textsuperscript{13} For example, a comparison of treatments A, B, C, and D could be achieved using trials that contained the following pairwise comparisons: A vs B, B vs C, or C vs D; if only trials of A vs B and C vs D existed, then the network would be disconnected. This type of analysis preserves the within-trial randomized treatment comparison of each trial while combining all available comparisons between treatments.

A random-effects Poisson regression model was fitted,\textsuperscript{17} taking into account the correlation structure induced by the multi-arm trials. The analysis used the rate of stroke and the rate of major or fatal bleeding episodes per 1000 person-years to obtain the log rate ratios of one treatment relative to another treatment. Rates, rather than number of events, were considered the most appropriate outcome for this analysis because they incorporate the duration of the trials and also allow for multiple events within individual patients. The assumptions of a mixed-treatment comparison analysis are that (1) study-specific treatment effects are drawn from a common population (exchangeable) and (2) heterogeneity is constant between the different comparisons.

The goodness of fit of the model to the data was measured by calculating the residual deviance defined as the difference between the deviance for the fitted model and the deviance for the saturated model, where the deviance measures the fit of the model to the data points using the likelihood function. Under the null hypothesis that the model provides an adequate fit to the data, it is expected that residual deviance would have a mean equal to the number of unconstrained data points.\textsuperscript{18,19}

All analyses were conducted using a Bayesian Markov chain Monte Carlo method\textsuperscript{20} and fitted in the freely available Bayesian software, WinBUGS.\textsuperscript{20} Further technical details of the analysis together with the WinBUGS code are available at http://www.hs.le.ac.uk/personal/ajs22/mtc/supplement.htm.

\section*{RESULTS}

We identified 6 RCTs,\textsuperscript{21-26} which had all been published since December 1999, to add to the 14 RCTs\textsuperscript{27-40} identified in the original Cochrane review to provide us with a total of 20 RCTs that consisted of 11 different treatment strategies. One of the newly identified trials\textsuperscript{25} failed to fit into the network framework of the RCT (Figure 1) because of its chosen treatment comparators (ie, triflusal and acenocoumarol), which were not considered by any of the other identified trials; therefore, this trial was excluded from the analysis. Two further trials were also excluded from the analyses because of short follow-up (ie, <12 months).\textsuperscript{26,37} Two\textsuperscript{33,35} of the remaining 17 RCTs separated participants into warfarin-eligible and warfarin-ineligible groups based on clinical features or patient preference\textsuperscript{31,32,35} or into groups based on age of 75 years or younger and age older than 75 years.\textsuperscript{33}

In both RCTs, the different patient groups were originally analyzed separately; thus, we have done likewise, increasing the total number of trials to 19. Note that, for 2 of the trials included in the analysis, the comparator to the active treatment was no treatment rather than placebo.\textsuperscript{23,27} These trials were included in the initial analysis as being equivalent to placebo but excluded in a sensitivity analysis to assess their influence on the overall results.
The data extracted from the trial publications are presented in the Table and include the number of ischemic strokes and major or fatal bleeding episodes, as well as the number of individuals in each of the trials and total number of person-years of observation.

The trials identified were from Asia, Australia, Canada, Denmark, Italy, Japan, the Netherlands, Spain, Sweden, and...
the United States, included a total of 17,833 patients followed up for an average of 1.8 years, and considered 9 different treatment regimens. Treatment strategies are displayed as a network meta-analysis diagram in Figure 1, where the different treatment strategies are represented as nodes in the network and the links between the nodes represent pairwise treatment comparisons extracted from the RCTs identified (eg, if an RCT compared adjusted standard-dose warfarin vs aspirin vs placebo, this is represented in the diagram as 3 pairwise comparisons: adjusted standard-dose warfarin vs aspirin, adjusted standard-dose warfarin vs placebo, and aspirin vs placebo). No trial evidence was identified that compared all of the 9 treatment regimens directly (ie, within 1 RCT). However, as can be observed from Figure 1, the 19 trials identified formed a connected network, which is essential when applying mixed-treatment comparisons, and included 13 two-arm trials, 5 three-arm trials, and 1 four-arm trial, resulting in a total of 45 trial arms. Note that warfarin has been classified into 3 categories as defined in the published trial reports: (1) adjusted standard-dose warfarin (international normalized ratio [INR], 2.0-4.5), (2) adjusted low-dose warfarin (INR, 1.1-2.8), and (3) fixed low-dose warfarin sodium (1.25 mg/d).

**PREVENTION OF STROKE**

Figure 2A displays a caterpillar plot of the relative rate (RR) of stroke for all the possible pairwise comparisons of the different treatments. For prevention of stroke, adjusted standard-dose warfarin (RR, 0.35; 95% credible interval [CrI], 0.24-0.52), adjusted low-dose warfarin (RR, 0.35; 95% CrI, 0.19-0.60), ximelagatran (RR, 0.34; 95% CrI, 0.18-0.61), and aspirin (RR, 0.64; 95% CrI, 0.44-0.88) were associated with a statistically significant lower rate of stroke compared with placebo (at the .05 level). Fixed low-dose warfarin (RR, 3.21; 95% CrI, 1.06-7.37), aspirin (RR, 1.85; 95% CrI, 1.25-2.88), and fixed low-dose warfarin plus aspirin (RR, 3.10; 95% CrI, 1.74-5.12) were associated with a statistically significant higher rate of stroke compared with adjusted standard-dose warfarin. The residual deviance was calculated to be 45.22.
This was equal to the number of unconstrained data points (45) of the model, thus demonstrating a good fit of the model to the data.

**ADVERSE EVENTS: MAJOR OR FATAL BLEEDING EPISODES**

Figure 2B displays a caterpillar plot of the RR of major or fatal bleeding episodes for all the possible pairwise comparisons of the 8 different treatments. (No data are available on major or fatal bleeding episodes for alternate-day aspirin.) When compared with placebo, there is evidence of an increased risk in major or fatal bleeding episodes for all treatments, but none are statistically significant at the .05 level (ie, all CrIs contain 1.0). The residual deviance was calculated to be 38.59. This was similar to the number of unconstrained data points (37) of the model, thus demonstrating a good fit of the model to the data.

In a sensitivity analysis, the trials that included control arms rather than placebo arms were removed and the data reanalyzed. The omission of these trials changed the results slightly but did not affect the overall conclusions of the analysis. In a second sensitivity analysis, the National Study for Prevention of Embolism in Atrial Fibrillation trial data, originally excluded because it failed to fit into the network, were included in the analysis by grouping acenocoumarol (a vitamin K antagonist of the coumarin class) with adjusted standard-dose warfarin because it shares a common mechanism of action. Some evidence indicated that trifusals is associated with a higher rate of ischemic stroke than other active treatments, but none were statistically significant at the .05 level.

In this mixed-treatment comparison analysis, we were able to compare the 9 different treatment strategies for stroke prevention in individuals with nonrheumatic atrial fibrillation with one another, thus allowing comparisons of agents not addressed within any of the individual primary trials. Although our results are not directly comparable with most previous meta-analyses because of the use of rates rather than odds ratios, overall they agree with previous pairwise meta-analyses; that is, lower odds of ischemic stroke and higher odds of major bleeding episodes were found to be associated with oral anticoagulants compared with aspirin, and both anticoagulants and aspirin were found to be associated with a reduction in the odds of stroke compared with placebo. A systematic review by Reynolds et al examined the relationship between the INR and the outcomes of stroke and bleeding in patients with atrial fibrillation who were receiving anticoagulation with warfarin. They found that the 1.5 to 2.0 INR stratum was associated with significantly higher rates of stroke compared with the 2 to 3 INR stratum (odds ratio, 2.11; 95% CrI, 1.06-4.19), but a comparison of an INR of 2 to 3 with an INR of less than 1.5 and an INR of more than 3 was not statistically significant, but caution is required when interpreting their results because of the inclusion of observational study data and RCTs and the potential biases associated with it.

To put the results of our analyses into perspective, if the baseline risk in people with nonrheumatic atrial fibrillation is 51 ischemic stroke events per 1000 person-years (ie, the average rate in the placebo or control arms of the trials), adjusted standard-dose warfarin compared with placebo could prevent 28 (95% CrI, −37 to −19) strokes at the expense of 11 (95% CrI, −1 to +39) major or fatal bleeding episodes, aspirin could prevent 16 (95% CrI, −26 to −5) strokes at the expense of 6 (95% CrI, −3 to +27) major or fatal bleeding episodes, indobufen could prevent 33 (95% CrI, −49 to +3) strokes at the expense of 22 (95% CrI, −8 to +181) major or fatal bleeding episodes, and ximelagatran could prevent 29 (95% CrI, −39 to 16) strokes at the expense of 10 (95% CrI, −5 to +60) major or fatal bleeding episodes. Alternate-day aspirin could prevent 23 (95% CrI, −38 to +5) strokes, but we have no data on the number of major or fatal bleeding episodes; however, we would not expect it to exceed that estimated for daily aspirin (ie, 6 [95% CrI, −3 to +27]). Note that, in the Low-dose Aspirin, Stroke, and Atrial Fibrillation (LASAF) trial, which compared alternate-day aspirin with aspirin and placebo, recruitment was stopped early because of the publication of other trials that showed adjusted standard-dose warfarin to be a superior treatment to aspirin. For this reason, the LASAF trial was underpowered, resulting in large uncertainty in the rate ratio estimates that contained alternate-day aspirin. Other limitations with the trial data that should be highlighted are that most trials, including adjusted-standard- or low-dose warfarin, were open-label (unblinded) trials because of the necessity to adjust the dose, and 3 trials allowed the concurrent use of aspirin.

As observed by Taylor and Ebrahim, marked clinical heterogeneity exists in risk among patients included in the different trials. Although all trials were designed to examine the effects of treatment in nonrheumatic atrial fibrillation, most included a proportion of patients who had histories of stroke or transient ischemic attack (ranging from 0% to 100% of patients, Table). Like standard pairwise meta-analysis, mixed-treatment comparisons assume that there is no baseline risk by treatment interactions across studies. The goodness of fit of the models to the data, measured by the residual deviance, was found to be good (ie, residual deviance approximately equal to the number of unconstrained data points), thus providing little evidence to suggest that treatment effect is not reasonably consistent across risk groups.

To examine the effects of treatment in nonrheumatic atrial fibrillation, most included a proportion of patients who had histories of stroke or transient ischemic attack (ranging from 0% to 100% of patients, Table). Like standard pairwise meta-analysis, mixed-treatment comparisons assume that there is no baseline risk by treatment interactions across studies. The goodness of fit of the models to the data, measured by the residual deviance, was found to be good (ie, residual deviance approximately equal to the number of unconstrained data points), thus providing little evidence to suggest that treatment effect is not reasonably consistent across risk groups.

The key assumption of a random-effects mixed-treatment comparison model is that the treatment effects in each trial are different but from a common distribution. This assumption is similar to that underlying standard pairwise meta-analysis but with the additional assumption that this common distribution is the same across the entire set of trials irrespective of which treatments were evaluated in the primary trials. Another assumption is that the treatment effects are additive; that is, the relative effect of treatment A vs C is estimable from the effects of A vs B and B vs C. The assessment of publication bias is more complex in a mixed-treatment comparison framework and is an area that requires further research. However, funnel plots (not shown) were plotted for adjusted standard-dose warfarin vs aspirin...
where there were 7 trials available, but the results were inconclusive because of the small number of trials.

Notably, RCTs are not specifically designed or powered to investigate adverse events such as bleeding episodes; therefore, further work may include the incorporation of evidence from relevant large observational studies while being fully aware of the potential biases associated with such study designs.45-46

Also important to consider is the issue of convenience of the treatment regimen to both the patient and the physician, which may affect compliance in routine practice. For instance, because of its narrow therapeutic window and known drug and food interactions, warfarin needs regular monitoring, which can be inconvenient to both the patient and physician.3 However, anticoagulation clinics have improved the quality of anticoagulation within the community, and schemes for self-monitoring of INR at home may improve the convenience and quality of anticoagulation monitoring in the future.

Although the 2 trials of ximelagatran compared with adjusted standard-dose warfarin found the 2 agents to be broadly similar, the foreseen advantage of ximelagatran was the ability to use the drug in a standard dosage without needing to perform frequent blood tests and dosage adjustments. Unfortunately, concern has been raised regarding the high risk of toxic effects to the liver in the long-term indications; thus, it would seem sensible that liver function would need to be monitored, although no formal guidance on this has been given.3 Ximelagatran has not yet received the US Food and Drug Administration’s or European regulatory authorities’ approval for long-term clinical use for the prevention of strokes in patients with atrial fibrillation. Compared with warfarin and ximelagatran (which may need monitoring for liver function), aspirin does not require routine monitoring.

This analysis was based on evidence from RCTs. Concerns exist regarding whether results of RCTs on anticoagulation in patients with atrial fibrillation are generalizable to clinical practice. Evans and Kalra47 conducted a systematic review of the published medical literature to identify studies of patients with atrial fibrillation who were treated with warfarin in clinical practice. They found that, although the patients in clinical practice tended to be older and had more comorbid conditions compared with participants in RCTs, the stroke and major bleeding rates were similar. However, a higher rate of minor bleeding was observed in clinical practice than in trials, which may require more intensive monitoring and thus have important implications for cost of care.

An expected increase in the prevalence of atrial fibrillation due to the increasing age of the population means that optimal stroke prevention strategies are required. In this analysis, we applied a mixed-treatment comparison method to go beyond the pairwise comparisons reported in previous systematic reviews, including meta-analyses,5-11 to a comparison of all candidate treatments simultaneously. To inform health care policy decisions, the results from this type of analysis could be fed directly into a clinical or economic decision model that assesses both the benefits and harms of the various interventions for the prevention of stroke in patients with atrial fibrillation.

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Correspondence: Alexander J. Sutton, PhD, Centre for Biostatistics and Genetic Epidemiology, Department of Health Sciences, University of Leicester, 22-28 Princess Rd W, Leicester LE1 6TP, England (ajs22@le.ac.uk).

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