Nonvitamin-K-Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Previous Stroke or Transient Ischemic Attack
A Systematic Review and Meta-Analysis of Randomized Controlled Trials

George Ntaios, MD; Vasileios Papavasileiou, MD; Hans-Christoph Diener, MD; Konstantinos Makaritsis, MD; Patrik Michel, MD

Background and Purpose—To assess whether the combined analysis of all phase III trials of nonvitamin-K-antagonist (non-VKA) oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack shows a significant difference in efficacy or safety compared with warfarin.

Methods—We searched PubMed until May 31, 2012, for randomized clinical trials using the following search items: atrial fibrillation, anticoagulation, warfarin, and previous stroke or transient ischemic attack. Studies had to be phase III trials in atrial fibrillation patients comparing warfarin with a non-VKA currently on the market or with the intention to be brought to the market in North America or Europe. Analysis was performed on intention-to-treat basis. A fixed-effects model was used as more appropriate than a random-effects model when combining a small number of studies.

Results—Among 47 potentially eligible articles, 3 were included in the meta-analysis. In 14,527 patients, non-VKAs were associated with a significant reduction of stroke/systemic embolism (odds ratios, 0.85 [95% CI, 0.74–0.99]; relative risk reduction, 14%; absolute risk reduction, 0.7%; number needed to treat, 134 over 1.8–2.0 years) compared with warfarin. Non-VKAs were also associated with a significant reduction of major bleeding compared with warfarin (odds ratios, 0.86 [95% CI, 0.75–0.99]; relative risk reduction, 13%; absolute risk reduction, 0.8%; number needed to treat, 125), mainly driven by the significant reduction of hemorrhagic stroke (odds ratios, 0.44 [95% CI, 0.32–0.62]; relative risk reduction, 57.9%; absolute risk reduction, 0.7%; number needed to treat, 139).

Conclusions—In the context of the significant limitations of combining the results of disparate trials of different agents, non-VKAs seem to be associated with a significant reduction in rates of stroke or systemic embolism, hemorrhagic stroke, and major bleeding when compared with warfarin in patients with previous stroke or transient ischemic attack. (Stroke. 2012;43:000-000.)

Key Words: anticoagulants ■ apixaban ■ atrial fibrillation ■ dabigatran ■ rivaroxaban ■ stroke ■ transient ischemic attack ■ warfarin

Three nonvitamin-K-antagonist (non-VKA) oral anticoagulants were recently shown noninferior or superior to warfarin in patients with atrial fibrillation (AF). In particular, the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE),1 the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY),2 and the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)3 trials assessed the relative efficacy and safety of apixaban, dabigatran, and rivaroxaban, respectively, compared with warfarin. The subgroup analyses of these trials for patients with a previous stroke or transient ischemic attack (TIA) were recently published.4–6 In these subgroup analyses, no significant interaction was identified between previous stroke or TIA and the effects on the primary efficacy outcome of stroke or systemic embolism, a finding which shows that the treatment effect in this specific subgroup did not differ from the overall population. However, reductions of the primary outcome in the non-VKA arms and adverse effects compared with the warfarin arms were not statistically significant, probably due to inadequate power of the subgroup analyses. The tests of interaction performed in these subgroup analyses are quite insensitive and may have missed subtle differences in the effects of these drugs in patients with and without previous stroke or TIA. Pooling the results of all 3 studies is a helpful way to overpass the inadequate power of the subgroup analyses.
In this study, we aimed to assess whether the meta-analysis of all phase III trials of non-VKA in patients with AF and previous stroke or TIA shows a significant difference in efficacy or safety when compared with warfarin.

Methods

Search Strategy and Inclusion Criteria
We searched PubMed until May 31, 2012. The search items were AF, anticoagulation, warfarin, and previous stroke or TIA. Also, we searched the references of related letters, reviews, and editorials to identify potentially eligible studies. To be eligible for the present analysis, the studies had to be phase III trials in patients with AF and previous stroke or TIA comparing a VKA with a more recently developed oral anticoagulant currently on the market or with the intention to be brought to the market in North America or Europe.

Data Extraction
The extraction of the data was performed independently by 2 reviewers (G.N. and V.P.). For each outcome, the number of patients who were originally randomized to each treatment arm was extracted to allow for an intention-to-treat analysis. Data unavailable in the current publications were obtained by direct contact with and authorization of the study steering committees. Any discrepancy or uncertainty was resolved by consensus or discussion with the other authors.

The primary efficacy outcome was stroke or systemic embolism. Secondary efficacy outcome included stroke of any type, ischemic or unknown stroke, disabling or fatal stroke, hemorrhagic stroke, cardiovascular death, death from any cause, and myocardial infarction. The primary safety outcome was major bleeding. Additional safety outcomes included intracranial bleeding and gastrointestinal bleeding.

Statistical Analysis
Data were analyzed in an intention-to-treat basis. Odds ratios and 95% CIs were calculated for each outcome using the Peto fixed-effects method. Although a random-effects model provides a larger scope of inference and would be more appropriate when combining trials with different treatments, random-effects models are not statistically sound for combining a very small number of studies. Heterogeneity between trials was assessed by the I² index, which measures the percentage of the variability in effect estimates that is attributable to heterogeneity. Absolute risk reduction (ARR) was calculated as

\[
\text{ARR} = \frac{(\text{WE}/\text{WS}) - (\text{NE}/\text{NS})}{(\text{WE}/\text{WS})}
\]

Relative risk reduction (RRR) was calculated as

\[
\text{RRR} = \frac{(\text{WE}/\text{WS}) - (\text{NE}/\text{NS})}{(\text{WE}/\text{WS})}
\]

Number needed to treat (NNT) to prevent 1 event was calculated as

\[
\text{NNT} = \frac{1}{(\text{WE}/\text{WS}) - (\text{NE}/\text{NS})}
\]

All analyses were performed with the Review Manager (RevMan) version 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

Results
Among 47 potentially eligible articles that were identified in the literature, 3 fulfilled our criteria and were included in the analysis (Figure 1). Two trials of ximelagatran were excluded (WE/WS)–(NE/NS), where WE is the number of events in the warfarin group, WS the number of patients randomized to warfarin, NE the number of events in the non-VKA group, and NS the number of patients randomized to non-VKA. Relative risk reduction (RRR) was calculated as \([(\text{WE}/\text{WS})−(\text{NE}/\text{NS})]/(\text{WE}/\text{WS})\]. Number needed to treat (NNT) to prevent 1 event was calculated as \(1/(\text{WE}/\text{WS})−(\text{NE}/\text{NS})\). ARR, RRR, and NNT were calculated for the median follow-up of the trials which ranged between 1.8 and 2.0 years.

Table. Characteristics of the Populations With Previous Stroke or Transient Ischemic Attack Included in the Meta-Analysis

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>3623</td>
<td>7468</td>
<td>3436</td>
</tr>
<tr>
<td>Allocated to non-VKA/warfarin</td>
<td>2428/1195</td>
<td>3754/3714</td>
<td>1694/1742</td>
</tr>
<tr>
<td>Period in the therapeutic INR range (for patients allocated to warfarin)</td>
<td>63%</td>
<td>57.1%</td>
<td>65.0%</td>
</tr>
<tr>
<td>Duration of follow-up, median (IQR)</td>
<td>2.0 (1.14–2.86) y</td>
<td>676 (510–845) d</td>
<td>1.8 (1.4–2.3) y</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>2279 (62.9)</td>
<td>4538 (60.8)</td>
<td>2152 (62.6)</td>
</tr>
<tr>
<td>CHADS2 score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>0 (0)</td>
<td>Not described</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>377 (10.4)</td>
<td>Not described</td>
<td>268 (8)</td>
</tr>
<tr>
<td>≥3</td>
<td>3246 (89.6)</td>
<td>Not described</td>
<td>3168 (92)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2783 (76.8)</td>
<td>6343 (84.9)</td>
<td>2858 (83)</td>
</tr>
<tr>
<td>On aspirin at randomization, n (%)</td>
<td>1444 (39.9)</td>
<td>2808 (37.6)*</td>
<td>1067 (31.1)</td>
</tr>
<tr>
<td>VKA naive, n (%)</td>
<td>1614 (44.5)</td>
<td>3039 (40.7)</td>
<td>1354 (39.4)</td>
</tr>
</tbody>
</table>

ARISTOTLE indicates the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; INR, international normalized ratio; IQR, interquartile range; RE-LY, the Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; and VKA, vitamin K antagonists.

*Data corresponds with patients previously on ASA, but not necessarily at randomization.
from the meta-analysis because the drug was withdrawn after reports about hepatotoxicity. A trial of idraparinux was excluded because this agent was not brought to market due to increased bleeding complications. The main characteristics of the trials included in the analysis are summarized in the Table.

Among 14,527 patients with AF and previous stroke or TIA in these 3 trials, 7,876 patients were allocated to a non-VKA and 6,651 to warfarin. The median follow-up ranged between 1.8 and 2.0 years. The mean proportion of center based time in therapeutic international normalized ratio ranged between 57.1% and 65.0%.

### Efficacy Outcomes

In the analysis of the primary efficacy outcome, non-VKAs were associated with a significant reduction of stroke or systemic embolism compared with warfarin (RRR, 14%; ARR, 0.7%; NNT to prevent 1 stroke or systemic embolism, 134; Figure 2).

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Forest plot of the effects of nonvitamin-K-antagonists (non-VKAs) vs warfarin on efficacy outcomes (stroke or systemic embolism; stroke; ischemic or unknown stroke; disabling or fatal stroke) in patients with atrial fibrillation (AF) and previous stroke or transient ischemic attack. ARISTOTLE indicates the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; df, degree of freedom; RE-LY indicates the Randomized Evaluation of Long-Term Anticoagulation Therapy; and ROCKET AF, the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.
Non-VKAs were also associated with a significant reduction of hemorrhagic stroke compared with warfarin (RRR, 57.9%; ARR, 0.7%; NNT to prevent 1 hemorrhagic stroke, 139; Figure 3). There was also a 13% reduction in any stroke that was not significant. A trend was identified toward less disabling or fatal strokes (Figure 2) and lower any-cause mortality in favor of non-VKAs (Figure 3). There was a trend toward more myocardial infarctions in patients allocated to dabigatran or rivaroxaban compared with warfarin (data about myocardial infarction were not available for patients allocated to apixaban; Figure 3). Finally, no statistically significant difference between non-VKAs and warfarin was identified for the outcomes of ischemic/unknown stroke (Figure 2) and cardiovascular death (Figure 3).

**Safety Outcomes**

In all 3 trials, major bleeding was defined according to the International Society on Thrombosis and Haemostasis. In the analysis of the primary safety outcome, non-VKAs

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**Figure 3.** Forest plot of the effects of nonvitamin-K-antagonists (non-VKAs) vs warfarin on efficacy outcomes (hemorrhagic stroke; cardiovascular death; death from any cause; myocardial infarction) in patients with atrial fibrillation (AF) and previous stroke or transient ischemic attack. ARISTOTLE indicates the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; df, degree of freedom; RE-LY indicates the Randomized Evaluation of Long-Term Anticoagulation Therapy; and ROCKET AF, the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.
were associated with a 14% significant reduction of major bleeding compared with warfarin (RRR, 13%; ARR, 0.8%; NNT to prevent 1 major bleeding, 125; Figure 4). This was mainly driven by a significant reduction of intracranial bleeding (RRR, 53.9%; ARR, 1.0%; NNT to prevent 1 intracranial bleeding, 98) in patients allocated to non-VKAs compared with warfarin (Figure 4). There was a trend of more gastrointestinal major bleedings in patients allocated to apixaban or dabigatran compared with warfarin, which was mainly driven by the effect of the high-dose dabigatran (data about gastrointestinal major bleeding were not available for patients allocated to rivaroxaban; Figure 4). There was a trend of increased heterogeneity in all safety outcomes, which however did not reach statistical significance (Figure 4).

**Discussion**

In this meta-analysis, we aimed to assess the efficacy and safety of non-VKAs compared with warfarin in patients with AF and previous stroke or TIA. The results show that compared with warfarin, non-VKAs seem to be associated with a significant reduction in the rates of stroke or systemic embolism, major bleeding, and hemorrhagic stroke in a median follow-up of 1.8 to 2.0 years.

Recently, the ARISTOTLE, RE-LY, and ROCKET AF trials showed that apixaban, dabigatran, and rivaroxaban (the latter only in the per-protocol analysis, but not in the intention-to-treat analysis) are associated with a lower rate of stroke or systemic embolism in the overall population of patients with AF. However, in the 3 subgroup analyses of these trials in patients with previous stroke or TIA, the proportion of patients who reached the primary end point was not significantly different between non-VKA and warfarin. The most plausible explanation is the fact that the subgroup analyses were not sufficiently large to detect such an effect, especially taken into consideration that there was no interaction in these analyses between previous stroke or TIA and the effects on primary outcome. The present meta-analysis of these 3 trials including 14,527 patients allows for more powered analysis and adds

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**Figure 4.** Forest plot of the effects of nonvitamin-K-antagonists (non-VKAs) vs warfarin on safety outcomes in patients with atrial fibrillation (AF) and previous stroke or transient ischemic attack. ARISTOTLE indicates the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; df, degree of freedom; RE-LY indicates the Randomized Evaluation of Long-Term Anticoagulation Therapy; and ROCKET AF, the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.
further evidence that non-VKAs seem to be associated with a 15% reduction of stroke or systemic embolism compared with warfarin in patients with previous stroke or TIA. Taken into account that international normalized ratio measurement, dose adjustment, and dietary restrictions are not required for patients who receive non-VKAs, they offer a significant advantage over VKAs. In contrast, one needs to keep in mind that less frequent physician contact may decrease compliance in cerebrovascular patients and that non-VKAs have a shorter half-life, which may potentially increase the risk of thromboembolic events in less compliant patients. Furthermore, at present there is no specific antidote for patients who require an immediate reversal of their effect, but for dabigatran and apixaban antidotes are in development. Also, non-VKAs have a significantly higher cost than warfarin; however, several studies have shown that they are cost-effective not only for primary stroke prevention but also for secondary stroke prevention. Finally, non-VKAs are mainly excreted via kidneys and therefore their use should be cautious in patients with renal insufficiency.

The major weakness of this meta-analysis is the disparity of the agents: it combines different drugs that elaborate different mechanisms, that is, 2 Xa antagonists (apixaban and rivaroxaban) and 1 direct thrombin antagonist (dabigatran). In this context, the different efficacy and safety profiles of the 3 agents is a significant limitation and needs to be kept in mind; on the contrary, all 3 included studies investigated similar target populations, used similar end points, and had similar follow-ups. In addition, the present study is limited by the inherent shortcomings of most meta-analyses: differences in the selection criteria among trials, variations in the definitions of comorbidities and outcomes used in the trials, and differences in the length of follow-up among trials. Also, it needs to be emphasized that the proportion of time of patients treated with warfarin within therapeutic international normalized ratio range varied among trials.

In conclusion, the present meta-analysis shows that non-VKAs seem to be more efficacious and safer to prevent stroke or systemic embolism compared with warfarin in patients with AF and previous stroke or TIA. The ongoing trials of other non-VKAs like edoxaban and AZD0837 are anticipated to show whether the therapeutic options for stroke prevention in patients with AF can increase further.

Disclosures

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References


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