

# Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial



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## Summary

**Background** In the ARISTOTLE trial, the rate of stroke or systemic embolism was reduced by apixaban compared with warfarin in patients with atrial fibrillation (AF). Patients with AF and previous stroke or transient ischaemic attack (TIA) have a high risk of stroke. We therefore aimed to assess the efficacy and safety of apixaban compared with warfarin in prespecified subgroups of patients with and without previous stroke or TIA.

**Methods** Between Dec 19, 2006, and April 2, 2010, patients were enrolled in the ARISTOTLE trial at 1034 clinical sites in 39 countries. 18 201 patients with AF or atrial flutter were randomly assigned to receive apixaban 5 mg twice daily or warfarin (target international normalised ratio 2.0–3.0). The median duration of follow-up was 1.8 years (IQR 1.4–2.3). The primary efficacy outcome was stroke or systemic embolism, analysed by intention to treat. The primary safety outcome was major bleeding in the on-treatment population. All participants, investigators, and sponsors were masked to treatment assignments. In this subgroup analysis, we estimated event rates and used Cox models to compare outcomes in patients with and without previous stroke or TIA. The ARISTOTLE trial is registered with ClinicalTrials.gov, number NTC00412984.

**Findings** Of the trial population, 3436 (19%) had a previous stroke or TIA. In the subgroup of patients with previous stroke or TIA, the rate of stroke or systemic embolism was 2.46 per 100 patient-years of follow-up in the apixaban group and 3.24 in the warfarin group (hazard ratio [HR] 0.76, 95% CI 0.56 to 1.03); in the subgroup of patients without previous stroke or TIA, the rate of stroke or systemic embolism was 1.01 per 100 patient-years of follow-up with apixaban and 1.23 with warfarin (HR 0.82, 95% CI 0.65 to 1.03; *p* for interaction=0.71). The absolute reduction in the rate of stroke and systemic embolism with apixaban versus warfarin was 0.77 per 100 patient-years of follow-up (95% CI –0.08 to 1.63) in patients with and 0.22 (–0.03 to 0.47) in those without previous stroke or TIA. The difference in major bleeding with apixaban compared with warfarin was 1.07 per 100 patient-years (95% CI 0.09–2.04) in patients with and 0.93 (0.54–1.32) in those without previous stroke or TIA.

**Interpretation** The effects of apixaban versus warfarin were consistent in patients with AF with and without previous stroke or TIA. Owing to the higher risk of these outcomes in patients with previous stroke or TIA, the absolute benefits of apixaban might be greater in this population.

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## Introduction

Patients with atrial fibrillation (AF) are at increased risk of stroke, particularly if they have already had an ischaemic stroke or a transient ischaemic attack (TIA).<sup>1,2</sup> Warfarin and other vitamin K antagonists are effective treatments, reducing the risk of stroke by about two-thirds, but their use is limited by a narrow therapeutic range, drug and food interactions, the need for coagulation monitoring, and the risk of bleeding.<sup>3</sup> Before the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial was completed,<sup>4</sup> findings from two trials showed that two oral anticoagulants, dabigatran and rivaroxaban, were equivalent or superior to warfarin in prevention of stroke or systemic embolism in patients with AF.<sup>5,6</sup>

Apixaban is an oral direct factor Xa inhibitor with rapid absorption, a 12 h half-life, and 25% renal excretion.<sup>7</sup> It is given in a fixed dose twice daily and, unlike oral vitamin K antagonists, does not need routine coagulation monitoring. In the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients who have Failed or are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial,<sup>8</sup> apixaban reduced the rate of stroke or systemic embolism by 55% compared with aspirin without increasing the risk of major bleeding. In the ARISTOTLE trial,<sup>9</sup> apixaban was compared with adjusted-dose warfarin for the prevention of stroke or systemic embolism in patients with AF and at least one additional risk factor for stroke. The trial design and results have been reported.<sup>4,9</sup> The rate of the primary outcome (stroke

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See Online for appendix

or systemic embolism) was significantly reduced by apixaban compared with warfarin, as were the rates of major bleeding and death from any cause. The rate of haemorrhagic stroke in the apixaban group was about half the rate in the warfarin group.

In this prespecified subgroup analysis of the ARISTOTLE trial,<sup>4,9</sup> we investigated the efficacy and safety of apixaban compared with warfarin in subgroups of patients with and without previous stroke or TIA. This assessment is important because patients with previous stroke or TIA are at high risk of recurrent stroke<sup>2</sup> and of bleeding from anticoagulation therapy, particularly cerebral haemorrhage.<sup>10,11</sup>

## Methods

### Patients

In the randomised, double-blind ARISTOTLE trial, patients with AF or atrial flutter were randomly assigned to apixaban and warfarin placebo or to dose-adjusted warfarin (target international normalised ratio 2.0–3.0) and apixaban placebo. The dose was 5 mg twice daily, or 2.5 mg twice daily for patients with two or more of the following factors: age 80 years or older, bodyweight 60 kg or less, and serum creatinine 133 µmol/L or greater. Patients were enrolled at 1034 clinical sites in 39 countries between Dec 19, 2006, and April 2, 2010. The median duration of follow-up was 1.8 years (IQR 1.4–2.3).<sup>9</sup> Patients with a previous intracranial haemorrhage (ICH) or any stroke within 7 days before random assignment were excluded. Concomitant use of aspirin (≤165 mg/day) was allowed, but dual antiplatelet therapy with aspirin plus clopidogrel was not. Information about previous stroke or TIA was assessed by the investigators and reported on the case report form at the time of enrolment. Renal function was classified into four categories (normal, mild impairment, moderate impairment, and severe impairment) according to the study design.<sup>4</sup> Severity of stroke deficit (defined as none, minor, moderate, or severe) was also assessed by the investigators and reported on the case report form.

All appropriate national regulatory authorities and ethics committees of the participating centres approved the ARISTOTLE trial. All patients gave written informed consent for participation in the trial before enrolment.

### Randomisation and masking

Patients were randomly assigned (1:1) to apixaban or warfarin by a 24 h central computerised and interactive voice-response system. Randomisation was stratified according to whether patients had received warfarin previously and according to clinical site, but not by previous stroke or TIA. Participants, investigators, members of all committees, and the sponsor staff undertaking the study were masked to individual participant treatment assignments.

### Procedures

The primary efficacy outcome was stroke or systemic embolism. The key secondary efficacy outcome was death from any cause. The primary and secondary efficacy analyses included all patients who were randomly assigned (intention-to-treat population). Additional outcomes were any stroke, haemorrhagic and ischaemic or uncertain type of stroke, disabling or fatal stroke, and cardiovascular death. The primary safety outcome was major bleeding, as defined by the International Society on Thrombosis and Haemostasis criteria.<sup>12</sup> Other secondary safety outcomes were intracranial, gastrointestinal, and total bleeding. A clinical events committee, the members of which were

	Previous stroke or TIA (n=3436)	No previous stroke or TIA (n=14765)	p value
Age (years)	70.1 (9.5)	68.8 (9.7)	<0.0001
Age ≥75 years	1205 (35%)	4473 (30%)	<0.0001
Women	1284 (37%)	5132 (35%)	0.004
Systolic blood pressure (mm Hg)*	131.4 (16.4)	131.0 (16.4)	0.15
Diastolic blood pressure (mm Hg)*	78.6 (10.5)	79.3 (10.5)	0.0005
Weight (kg)†	79.2 (19.1)	85.2 (20.9)	<0.0001
Previous myocardial infarction	587 (17%)	1998 (14%)	<0.0001
Congestive heart failure within 3 months	939 (27%)	4602 (31%)	<0.0001
Diabetes	902 (26%)	3645 (25%)	0.057
Hypertension	2858 (83%)	13 058 (88%)	<0.0001
Previous clinically relevant or spontaneous bleeding	676 (20%)	2364 (16%)	<0.0001
History of fall within previous year	210 (6%)	543 (4%)	<0.0001
Vitamin K antagonist naive	1354 (39%)	6446 (44%)	<0.0001
CHADS <sub>2</sub> score	3.7 (0.9)	1.7 (0.8)	<0.0001
≤1	0 (0%)	6183 (42%)	<0.0001
2	268 (8%)	6248 (42%)	..
≥3	3168 (92%)	2334 (16%)	..
Renal function‡			
Normal (>80 mL/min)	1093 (32%)	6425 (44%)	<0.0001
Mild impairment (>50–80 mL/min)	1590 (46%)	5997 (41%)	..
Moderate impairment (>30–50 mL/min)	668 (20%)	2079 (14%)	..
Severe impairment (≤30 mL/min)	69 (2%)	201 (1%)	..
Drugs at time of randomisation			
ACE inhibitors	1566 (46%)	7319 (50%)	<0.0001
ARBs	797 (23%)	3515 (24%)	0.46
ACE inhibitors or ARBs	2298 (67%)	10 534 (71%)	<0.0001
β blockers	2034 (59%)	9448 (64%)	<0.0001
Calcium channel blockers	1112 (32%)	4455 (30%)	<0.0001
Aspirin	1067 (31%)	4565 (31%)	0.89
Clopidogrel	101 (3%)	237 (2%)	<0.0001
Statins	1659 (48%)	5814 (39%)	<0.0001
Non-steroidal anti-inflammatory drugs	288 (8%)	1232 (8%)	0.95
Gastric acid drugs	698 (20%)	2652 (18%)	0.0015

Data are mean (SD) or number (%). ACE=angiotensin-converting enzyme. ARB= angiotensin receptor blocker. TIA=transient ischaemic attack. \*Blood pressure data missing for nine patients with previous stroke or TIA and 30 patients without. †Weight data missing for nine patients with previous stroke or TIA and 53 patients without. ‡Renal function data missing for 16 patients with previous stroke or TIA and 63 patients without.

**Table: Baseline demographics and clinical characteristics**

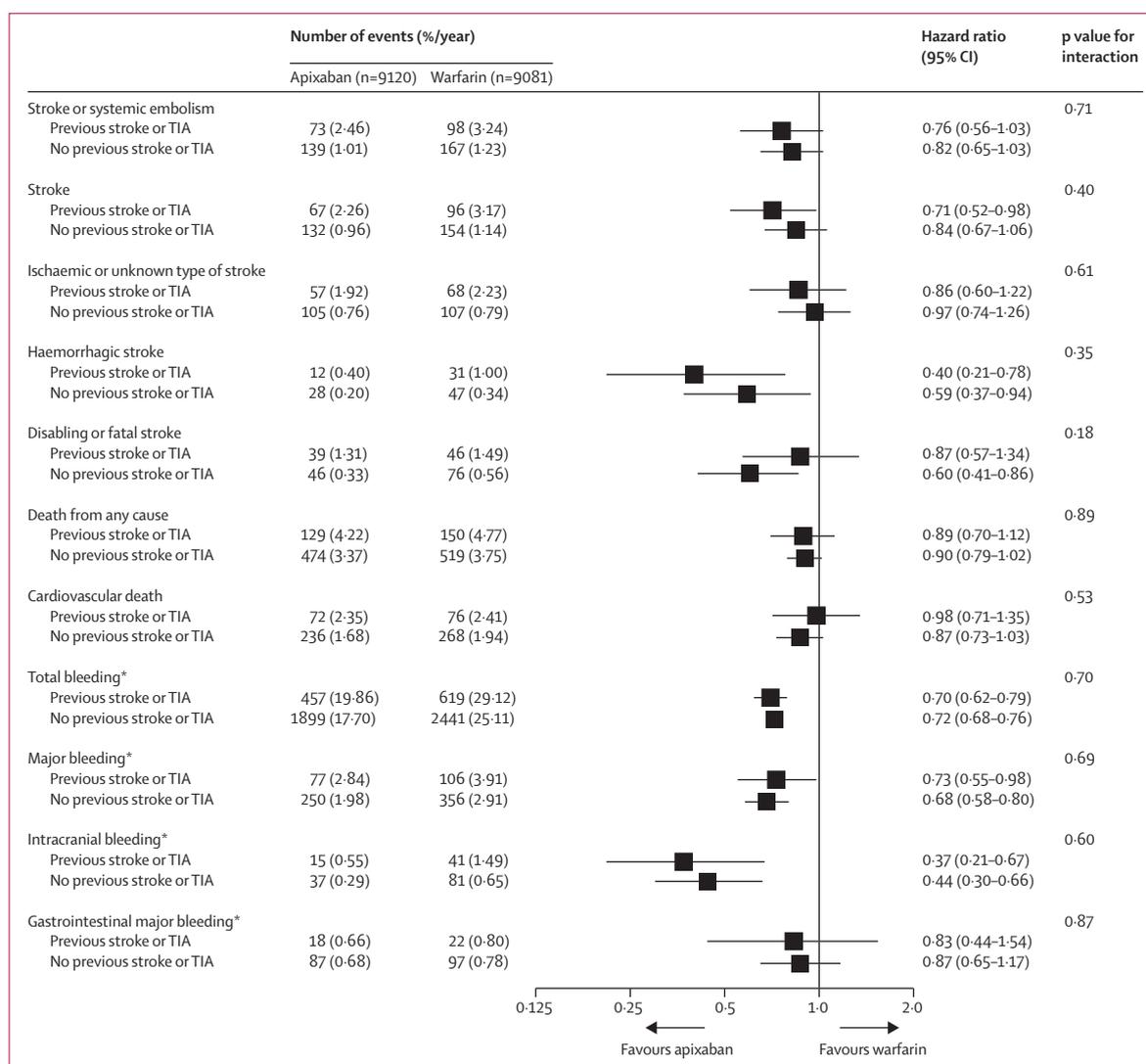
not aware of study group assignments, adjudicated the primary and secondary efficacy and safety outcomes on the basis of prespecified criteria.<sup>4</sup>

### Statistical analysis

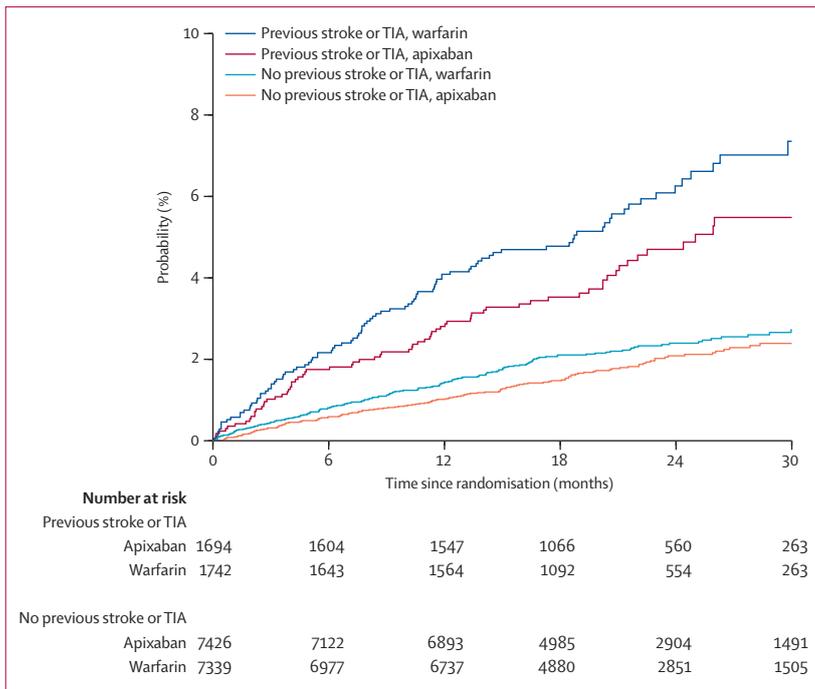
Demographics and clinical characteristics were summarised by history of stroke or TIA with means and SDs for continuous variables and frequencies and percentages for categorical variables. Statistical differences between the two groups were assessed with Student's *t* tests and Fisher's exact tests. Ordinal variables were compared by trend tests. Primary and key secondary outcomes were summarised by randomised treatment and previous stroke or TIA status by rates per 100 patient-years of follow-up. The primary efficacy and safety endpoints were presented graphically with Kaplan-Meier estimates of the event rates by subgroup and randomised treatment.

Cox models, including the randomised treatment, previous stroke or TIA status, and their interaction, were used to test the interaction between treatment and subgroup and to derive hazard ratios (HRs) for the treatment effect for patients with and without previous stroke or TIA.

By the same statistical methods described earlier, we did a post-hoc analysis comparing patients with previous stroke or TIA within 30 days before random allocation with patients with previous stroke or TIA more than 30 days before random allocation. A 30-day cutoff was chosen because the first few weeks after a cerebral ischaemic event are a high-risk period for further events and for haemorrhagic transformation of infarcts.<sup>13-15</sup> Additionally, because patients with previous stroke within 7 days before random allocation were excluded from the ARISTOTLE trial, we further



**Figure 1: Major study outcomes in patients with (n=3436) and without (n=14765) previous stroke or TIA**  
TIA=transient ischaemic attack. \*49088 patients in the apixaban group and 9052 in the warfarin group.



**Figure 2: Time to stroke or systemic embolism in patients with and without previous stroke or TIA**  
TIA=transient ischaemic attack. Plot shows the Kaplan-Meier estimated probability of an event.

analysed ischaemic and haemorrhagic events for patients with previous stroke or TIA within the first 14 days before random allocation. In this subacute phase, the risk for subsequent events can be even higher than after this period.<sup>13,14</sup>

The proportional hazard assumption was assessed by methods that are based on the cumulative sums of martingale residuals.<sup>16</sup> The proportional hazard assumption was valid for all outcomes presented in the Results section. Numbers needed to treat and their confidence intervals for major bleeding were derived from the survival probabilities in the warfarin group and the HR comparing apixaban with warfarin.<sup>17</sup>

ARISTOTLE is registered with ClinicalTrials.gov, number NCT00412984.

#### Role of the funding source

Bristol-Myers Squibb and Pfizer funded the study, and the primary analyses were done at both Bristol-Myers Squibb and the Duke Clinical Research Institute (Durham, NC, USA). MH and PM are employees of Bristol-Myers Squibb and participated with the other authors in the study design and in the collection, analysis, and interpretation of the data, and writing of the report. The sponsor played no part in the decision to submit for publication. The corresponding author had full access to all the data in the study through the Duke Clinical Research Institute. The coauthors and steering committee members had final responsibility for the decision to submit for publication.

## Results

Of the 18 201 patients enrolled in ARISTOTLE, 3436 (19%) had a previous stroke or a TIA. Of the patients with previous stroke or TIA, 956 (28%) had TIA only and 1826 (53%) had stroke only; the remainder had both (301 [9%]) or their type of previous ischaemia was unknown (353 [10%]). Of the 3035 previous events for which the timing of the event was known, 1016 (33%) occurred within the 1 year before enrolment. 1784 (84%) of 2124 patients with previous stroke of known severity had no or minor sequelae, 31 (1%) had experienced severe sequelae, and 309 (15%) had a previous stroke of moderate severity. Severity data were missing for three patients with stroke. The table shows the baseline demographics and clinical characteristics of patients with and without previous stroke or TIA. Patients with a previous stroke or a TIA were older and seemed slightly more likely to have diabetes but less likely to have hypertension and history of congestive heart failure. Accordingly, patients with a previous stroke or a TIA had higher CHADS<sub>2</sub> scores (a measure of the risk of stroke, in which congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus are each assigned 1 point and previous stroke or TIA is assigned 2 points), with a score of 3 or more in 92% of patients with previous stroke or TIA compared with 16% of those without.

Of 1694 patients with previous stroke or TIA randomly assigned apixaban, 112 (7%) received the reduced dose (2.5 mg twice daily) and 1582 (93%) received the normal dose (5 mg twice daily). Of 7426 patients without previous stroke or TIA randomly assigned to apixaban, 316 (4%) received the reduced dose and 7110 (96%) received the normal dose.

In the group of patients with previous stroke or TIA, study drug discontinuation rates per 100 patient-years of follow-up were 13.9 (383 patients) in the apixaban group and 16.8 (463 patients) in the warfarin group. For patients without previous stroke or TIA, the rates were 12.2 per 100 patient-years (1557 patients) for apixaban and 13.2 per 100 patient-years (1643 patients) for warfarin (p for interaction=0.18). In the warfarin group, the median time in the target range of the international normalised ratio was 65% (IQR 51–76%) in patients with previous stroke or TIA and 66% (53–77%) in those without (p=0.022).

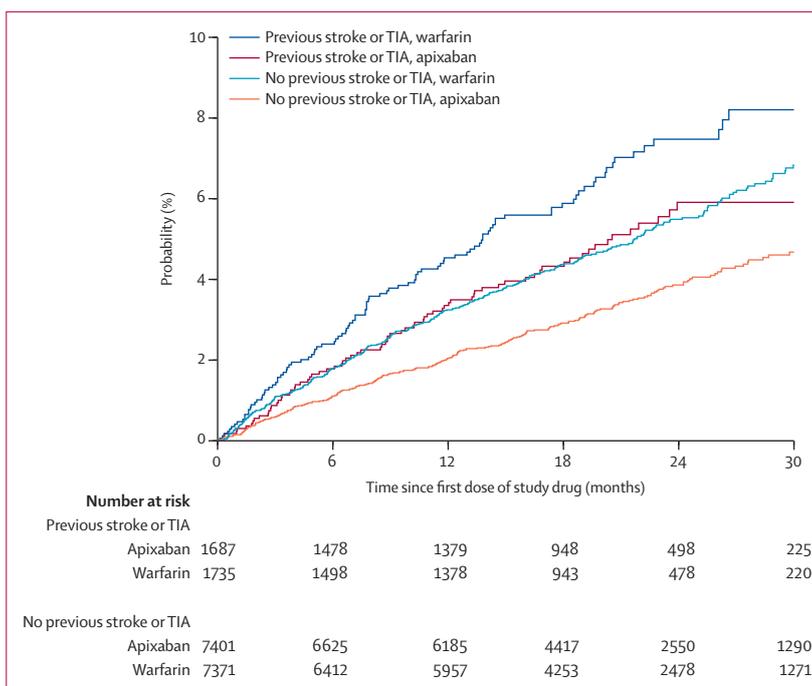
Compared with patients without previous stroke or TIA, patients with previous stroke or TIA were more likely to have a stroke or systemic embolism (HR 2.52, 95% CI 2.09–3.04) or die from any cause (1.27, 1.11–1.45). In the previous stroke or TIA subgroup, the rate of stroke or systemic embolism (2.85 events per 100 patient-years of follow-up) was higher than that in patients without previous stroke or TIA (1.12 per 100 patient-years of follow-up). Figures 1 and 2 show the treatment effect of apixaban compared with warfarin on major study outcomes in patients with and without

previous stroke or TIA. The absolute reductions in stroke or systemic embolism with apixaban were 0.77 events per 100 patient-years of follow-up (95% CI -0.08 to 1.63) in patients with and 0.22 per 100 patient-years (-0.03 to 0.47) in patients without previous stroke or TIA. The relative risk reduction of stroke or systemic embolism with apixaban versus warfarin was similar among patients with and those without previous stroke or TIA (p for interaction=0.71). The reduction in rates of cardiovascular death, disabling or fatal stroke, and all-cause mortality with apixaban versus warfarin was similar in patients with and without previous stroke or TIA (p for interaction=0.53, 0.18, and 0.89, respectively). Similar patterns were noted when only the subgroup of patients who received the reduced dose of apixaban was analysed (data not shown).

Patients who had previous stroke or TIA within 30 days of random allocation (n=234) had higher rates of stroke or systemic embolism (3.71 events per 100 patient-years of follow-up) than those randomly assigned more than 30 days (n=3202) after previous stroke or TIA (2.80 per 100 patient-years of follow-up; HR 1.31, 95% CI 0.76–2.26; appendix). In patients who had previous stroke or TIA within 30 days of random assignment, the rate of stroke or systemic embolism was 2.78 events per 100 patient-years of follow-up in the apixaban group (n=109 patients) compared with 4.55 per 100 patient-years of follow-up in the warfarin group (n=125 patients; HR 0.59, 95% CI 0.20–1.76; appendix). The rate of stroke or systemic embolism in patients randomly assigned to apixaban more than 30 days after their stroke or TIA was 2.44 per 100 patient-years of follow-up compared with 3.14 per 100 patient-years of follow-up in patients treated with warfarin (HR 0.78, 95% CI 0.57–1.07). The treatment effect of apixaban, when compared with warfarin, was similar in patients with a previous stroke or TIA within 30 days and more than 30 days before random allocation (p for interaction=0.69).

Of the 234 patients with previous stroke or TIA within 30 days, 47 had a previous event within 14 days before random allocation, all of which were strokes. Of these, 44 had a stroke between 7 and 14 days, 21 of whom were randomly assigned to apixaban and 23 to warfarin. There were no events (stroke or systemic embolism) among these 44 patients. The remaining three patients had a stroke within 7 days before random allocation.

Compared with patients without previous stroke or TIA, patients with previous stroke or TIA were more likely to have major bleeding (HR 1.37, 95% CI 1.17–1.62) and intracranial bleeding (2.15, 1.57–2.96). The absolute reduction in major bleeding with apixaban compared with warfarin was 1.07 per 100 patient-years (95% CI 0.09–2.04) in patients with and 0.93 per 100 patient-years (0.54–1.32) in those without previous stroke or TIA.



**Figure 3: Time to major bleeding in patients with and without previous stroke or TIA**  
TIA=transient ischaemic attack. Plot shows the Kaplan-Meier estimated probability of an event.

The relative risk reductions in major bleeding (figure 3) and total bleeding with apixaban versus warfarin were similar in both groups (p for interaction=0.69 and 0.70, respectively). Intracranial bleeding was reduced in the apixaban groups from 1.49 per 100 patient-years of follow-up on warfarin to 0.55 per 100 patient-years on apixaban in those with previous stroke or TIA (HR 0.37, 95% CI 0.21–0.67) and from 0.65 per 100 patient-years of follow-up on warfarin to 0.29 per 100 patient-years on apixaban in those without previous stroke or TIA (0.44, 0.30–0.66). Similar patterns were noted when only the subgroup of patients who received reduced-dose apixaban was analysed (data not shown).

118 patients had haemorrhagic strokes. Of the 11 (9%) patients with subdural haematomas, five received apixaban and six received warfarin (seven without and four with previous stroke or TIA). Of the six (5%) patients with subarachnoid haemorrhages, two received apixaban and four received warfarin (five without and one with previous stroke or TIA). Of the 97 (82%) patients with intraparenchymal haemorrhages, 31 received apixaban and 66 received warfarin (59 without and 38 with previous stroke or TIA). Four (3%) patients had haemorrhagic strokes that were not classified in any of the previous three categories.

At 1.8 years (the median follow-up reported), the number needed to treat to avoid one major bleed was 65 (95% CI 49–105) in the group with no previous stroke or TIA and 54 (32–777) in the group with previous stroke

or TIA. Major bleeding was more frequent in patients who had previous stroke or TIA within 30 days of random allocation (5·30 events per 100 patient-years of follow-up) than in those randomly assigned more than 30 days after previous stroke or TIA (3·25 per 100 patient-years of follow-up; HR 1·61, 95% CI 0·99–2·61). Patients with previous stroke or TIA within 30 days of random assignment to apixaban had numerically lower rates of major bleeding (4·88 per 100 patient-years of follow-up) than patients treated with warfarin (5·69 per 100 patient-years of follow-up), but the difference was not significant (HR 0·89, 95% CI 0·35–2·25). Patients randomly assigned to apixaban more than 30 days after stroke or TIA had lower rates of major bleeding (2·71 per 100 patient-years of follow-up) than patients assigned to warfarin (3·79 per 100 patient-years of follow-up; HR 0·72, 95% CI 0·53–0·98). The treatment effect of apixaban compared with warfarin on major bleeding was similar in patients with previous stroke or TIA within 30 days and after 30 days from random allocation (*p* for interaction=0·70).

Among the 44 patients who were randomly assigned between 7 and 14 days after a stroke or TIA, 42 received study drug and therefore were included in the safety analysis. Of these 42 patients, only one had a major bleed (in the warfarin group).

## Discussion

In this subgroup analysis of the ARISTOTLE study, patients with previous stroke or TIA had a two to three times higher risk of stroke or systemic embolism, major bleeding, ICH, and mortality than those without previous stroke or TIA (appendix). Risk of major bleeding was about one-third higher in patients with previous stroke than in those without, whereas rates of gastrointestinal bleeding were similar between groups. Consistent with the main trial results, patients with and without previous stroke or TIA treated with apixaban seemed to have fewer strokes, major bleeds (including ICH), and lower mortality than patients treated with warfarin, although these benefits were not all statistically significant. Because of the higher risk of stroke in patients with previous stroke, the absolute benefits in all outcome events might be larger in this high-risk population (panel).

The stroke rate in the warfarin group in the main ARISTOTLE trial (1·51% per year)<sup>9</sup> was similar to that in the Randomised Evaluation of Long-term Anti-coagulation Therapy (RE-LY) trial (1·71% per year in the warfarin group)<sup>5,18</sup> but lower than that in 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) trial (2·2% per year in the warfarin group),<sup>6</sup> which had a higher risk population, including 52% of patients with previous stroke or TIA. In the about 20% of patients with previous stroke in the

RE-LY trial, findings similar to those in this subgroup analysis were reported, with higher rates for thrombotic and haemorrhagic events in patients with previous stroke than those without and consistent effects of dabigatran, which led to larger absolute reductions of all events in this subpopulation.<sup>19</sup> In ROCKET AF, the previous stroke or TIA subgroup of patients had higher rates of thrombotic events but lower rates of bleeding events than the subgroup of patients without previous stroke or TIA.<sup>20</sup> Patients with a previous stroke or TIA were slightly older than patients without history of stroke or TIA in ARISTOTLE, whereas they were younger in RE-LY and ROCKET AF.

In the ARISTOTLE trial,<sup>9</sup> the reduction in the primary outcome of stroke or systemic embolism was mainly driven by a reduction in haemorrhagic stroke. The absolute reduction in haemorrhagic stroke with apixaban compared with warfarin was 0·60% per year in patients with previous stroke. This finding is reassuring when considering the safety of starting a new treatment for secondary stroke prevention in a high-risk post-stroke population.

Patients with AF and previous stroke or TIA are common in clinical practice, comprising between 15% and 25% of the population in stroke registries.<sup>21,22</sup> Although the fact that these patients are at high risk for recurrent cerebrovascular events and thus warrant anticoagulation is well known, the simultaneous increased risk of bleeding, and particularly ICH, is less well appreciated. Also, previous stroke was associated with higher risk of death, both in ARISTOTLE<sup>9</sup> and in other studies. Therefore, the finding that survival benefits with apixaban in patients with previous stroke are consistent with those in patients without previous stroke is an important result.

The mechanism for the lower rate of intracranial bleeding with apixaban than with warfarin, beyond a more stable anticoagulation, is unknown. This benefit was also noted with dabigatran and rivaroxaban in the RE-LY<sup>5,18</sup> and ROCKET AF<sup>6</sup> trials, suggesting that a high ICH rate might be a problem with warfarin. The ICH rate in the warfarin-treated group in ROCKET AF was lower than that in the comparable group in ARISTOTLE (0·8 vs 1·49 per 100 patient-years). When a patient receiving warfarin is out of therapeutic range, the international normalised ratio is below 2·0 for most of the time, so the lower rates of intracranial bleeding reported in ROCKET AF could be related, in part, to the lower time in therapeutic range in ROCKET AF than in ARISTOTLE. The lower ICH rate on apixaban and dabigatran compared with warfarin might relate to the targeting of a single rather than multiple sites in the coagulation cascade. Another factor might be that the new anticoagulants, by contrast with warfarin, have no direct effect on factor VIIa. The lower bleeding risk associated with apixaban might also contribute to a higher degree of compliance, especially when compared

with that of warfarin, which is now given to only about half of the patients who would benefit from oral anticoagulation.<sup>23</sup>

The possible occurrence of cerebral bleeding and its treatment is a common concern for physicians caring for patients with acute stroke. If life-threatening bleeding cannot be controlled, administration of recombinant factor VIIa or prothrombin complex concentrate can be considered.<sup>24</sup> The absence of antidotes to the new anticoagulants is a clear shortcoming. However, the best way to deal with intracranial bleeding is to prevent it from occurring, something that is more likely to be achieved by the aforementioned oral anticoagulants than by warfarin.

A controversial issue in patients with ischaemic stroke is identifying when anticoagulants can be started safely. Patients with a stroke or TIA within the previous 7 days were excluded from this trial, and 234 patients were enrolled between 8 and 30 days after stroke. This enrolment pattern is similar to those in the previous trials: RE-LY<sup>5,18</sup> excluded patients with a stroke within 14 days or severe stroke within 6 months before screening, and ROCKET AF<sup>6</sup> excluded patients with a severe, disabling stroke within 3 months or any stroke within 14 days before randomisation. The reported risk of ischaemic stroke in patients with AF in the first 2 weeks after ischaemic stroke varies between 0·3% and 1·1% per day.<sup>13,25–30</sup> Serious haemorrhagic transformation typically occurs between 12 h and 4 days after stroke onset in about 1% of strokes in non-anticoagulated patients with AF.<sup>31</sup> In the Heparin in Acute Embolic Stroke Trial (HAEST),<sup>13</sup> low-molecular-weight heparin was compared with aspirin for 14 days in patients with AF with acute ischaemic stroke, and no evidence that low-molecular-weight heparin is superior to aspirin was found. An American Heart Association/American Stroke Association guideline concluded that heparins are not recommended for patients with AF immediately after acute stroke.<sup>32</sup> Aspirin followed by initiation of warfarin for long-term secondary stroke prevention is usual care.<sup>14,33</sup> In the ARISTOTLE trial, 44 patients were randomly assigned to receive apixaban or warfarin within 7–14 days of previous stroke, and there was no stroke or systemic embolism in these patients and only one major bleed in the warfarin-treated group. However, the ARISTOTLE trial excluded patients with stroke within 7 days before enrolment. Therefore, we cannot provide information on the relative risk and benefit of apixaban in the first week after stroke or TIA. Because anticoagulation with apixaban occurs within a few hours after dosing, to begin apixaban treatment about 7 days after stroke onset might be reasonable.

This subgroup analysis has some limitations. Our study included a selected population of patients because this was a clinical trial with need for written consent, such that patients with more severe residual stroke

### Panel: Research in context

#### Systematic review

We searched PubMed with the terms “apixaban”, “warfarin”, “atrial fibrillation”, “stroke”, and “clinical trial” for reports published before March 2012. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial<sup>9</sup> was the only published report of the final results of a clinical trial that compared apixaban with warfarin in patients with atrial fibrillation (AF).

#### Interpretation

The findings from the ARISTOTLE trial showed that, in patients with AF and at least one additional risk factor for stroke, apixaban was superior to warfarin for the prevention of stroke or systemic embolism, and there was significantly less major bleeding and significantly fewer deaths in the apixaban-treated group. In the subgroup results reported here, there was no evidence that the efficacy or safety of apixaban compared with warfarin was different between patients with and without a history of stroke or transient ischaemic attack (TIA). Consequently, the results of the ARISTOTLE overall trial population can be applied to patients with AF and previous stroke or TIA. This analysis also showed that patients with AF who had previous stroke or TIA have higher absolute rates of stroke, ischaemic and haemorrhagic, or systemic embolism than those without, so the absolute benefits of apixaban when compared with warfarin among individuals with AF might be greater for secondary stroke prevention than for primary stroke prevention.

sequelae were likely to be under-represented (only 1·5% of our overall previous stroke population). We also have limited details about the previous strokes. Finally, our trial did not include patients with very recent (within 7 days) previous stroke.

In summary, the relative effects in stroke, bleeding, and mortality with apixaban versus warfarin were similar in patients with AF with and without previous stroke or TIA. Given the higher risk of these outcomes in patients with previous stroke, the absolute benefits with apixaban might be greater in this population. Thus, apixaban seems to be a more effective and safer treatment than warfarin for patients with AF and previous stroke or TIA who are at higher risk of stroke, bleeding, and death.

#### Contributors

JDE, RDL, MCB, CBG, LW, MA, SG, BSL, MR, MH, PM, and JHA were members of the executive or steering committees, or both, and were responsible for the trial protocol and conduct. DMW did the statistical analyses. H-CD was a member of the data and safety monitoring board. JDE wrote the first version of the manuscript, and all authors contributed to all revisions and the final version.

#### Conflicts of interest

JDE has received consulting or advisory board fees from AstraZeneca, Bristol-Myers Squibb; data safety monitoring board fees from Novartis,

Johnson and Johnson, Brigham and Women's Hospital-Boston/Schering-Plough Research Institute; and served on the adjudication committee for the Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial (National Institutes of Health). CBG has received grants from Bristol-Myers Squibb, AstraZeneca, Pfizer, Boehringer Ingelheim, GlaxoSmithKline, the Medtronic Foundation, Merck, Sanofi-Aventis, Astellas, and The Medicines Company; consulting fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Hoffmann-LaRoche, Novartis, Otsuka Pharmaceutical, Sanofi-Aventis, Lilly, Pfizer, and The Medicines Company; and support for travel from Hoffmann-LaRoche, Novartis, and Pfizer. LW has received grants from Bristol-Myers Squibb, Pfizer, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Merck/Schering-Plough; consulting fees from Regado Biotechnologies, Portola, CSL Behring, Athera Biotechnologies, Merck/Schering-Plough, Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb, Pfizer, and GlaxoSmithKline; lecture fees from Bristol-Myers Squibb, Pfizer, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Schering-Plough; and honoraria from Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb, Pfizer, GlaxoSmithKline, and Merck/Schering-Plough. MA has received travel support from Bristol-Myers Squibb and Boston Scientific; advisory board fees from Bayer, Boehringer Ingelheim, Merck Sharp and Dohme, and Sanofi-Aventis; lecture fees from Bayer, Boehringer Ingelheim, Merck Sharp and Dohme, and AstraZeneca; and fees for development of educational presentations from Boehringer Ingelheim. SG has received consulting fees and honoraria from Eisai, Sanofi-Aventis, and Otsuka; and grants from Sanofi-Aventis, Eisai, Boehringer Ingelheim, and Otsuka. BSL has received consulting fees, honoraria, and research support from Bristol-Myers Squibb; and advisory board fees from Merck Sharp and Dohme and Bayer HealthCare. MR has received honoraria from Bristol-Myers Squibb. MH is an employee of Bristol-Myers Squibb. PM is an employee of Bristol-Myers Squibb and has received annual performance-based stock or stock options. JHA has received grants from Merck/Schering-Plough and Regado Biosciences; and consulting fees from Merck/Schering-Plough, AstraZeneca, Boehringer Ingelheim, Ortho-McNeil-Janssen, PolyMedix, Regado Biosciences, and Bayer. H-CD has received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from Abbott, Allergan, AstraZeneca, Bayer Vital, Bristol-Myers Squibb, Boehringer Ingelheim, CoAxia, Covidien, Daiichi-Sankyo, D-Pharm, EV3, Fresenius, GlaxoSmithKline, Janssen Cilag, Knoll, Merck Sharp and Dohme, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, Thrombogenics, Wyeth, and Yamanouchi; and financial support for research projects from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis, and Talecris. The Department of Neurology at the University Duisburg-Essen has received research grants from the German Research Council (DFG), German Ministry of Education and Research (BMBF), European Union, NIH, Bertelsmann Foundation, and Heinz-Nixdorf Foundation. RDL, MCB, and DMW declare that they have no conflicts of interest.

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#### References

- Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; **154**: 1449–57.
- Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; **22**: 983–88.
- Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999; **131**: 492–501.
- Lopes RD, Alexander JH, Al-Khatib SM, et al. Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. *Am Heart J* 2010; **159**: 331–39.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139–51.
- Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**: 883–91.
- Raghavan N, Frost CE, Yu Z, et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. *Drug Metab Dispos* 2009; **37**: 74–81.
- Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011; **364**: 806–17.
- Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365**: 981–92.
- EAFIT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993; **342**: 1255–62.
- Gorter JW. Major bleeding during anticoagulation after cerebral ischemia: patterns and risk factors. Stroke Prevention In Reversible Ischemia Trial (SPIRIT). European Atrial Fibrillation Trial (EAFIT) study groups. *Neurology* 1999; **53**: 1319–27.
- Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; **3**: 692–94.
- Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. *Lancet* 2000; **355**: 1205–10.
- Hart RG, Putnam C. Hemorrhagic transformation of cardioembolic stroke. *Stroke* 1989; **20**: 1117.
- Sacco RL, Foulkes MA, Mohr JP, Wolf PA, Hier DB, Price TR. Determinants of early recurrence of cerebral infarction. The Stroke Data Bank. *Stroke* 1989; **20**: 983–89.
- Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika* 1993; **80**: 557–72.
- Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999; **319**: 1492–95.
- Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L. Newly identified events in the RE-LY trial. *N Engl J Med* 2010; **363**: 1875–76.
- Diener HC, Connolly SJ, Ezekowitz MD, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurol* 2010; **9**: 1157–63.
- Hankey GJ, Patel MR, Stevens SR, et al. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol* 2012; **11**: 315–22.
- Bejot Y, Ben Salem D, Osseby GV, et al. Epidemiology of ischemic stroke from atrial fibrillation in Dijon, France, from 1985 to 2006. *Neurology* 2009; **72**: 346–53.
- Lopes RD, Shah BR, Olson DM, et al. Antithrombotic therapy use at discharge and 1 year in patients with atrial fibrillation and acute stroke: results from the AVAIL Registry. *Stroke* 2011; **42**: 3477–83.
- Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Ann Intern Med* 1999; **131**: 927–34.
- Gill R, Herbertson M, Vuylsteke A, et al. Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. *Circulation* 2009; **120**: 21–27.
- Cerebral Embolism Study Group. Immediate anticoagulation of embolic stroke: brain hemorrhage and management options. *Stroke* 1984; **15**: 779–89.
- Kelley RE, Berger JR, Alter M, Kovacs AG. Cerebral ischemia and atrial fibrillation: prospective study. *Neurology* 1984; **34**: 1285–91.
- Sage JI, van Uitert RL. Risk of recurrent stroke in patients with atrial fibrillation and non-valvular heart disease. *Stroke* 1983; **14**: 537–40.

- 28 Sherman DG, Goldman L, Whiting RB, Jurgensen K, Kaste M, Easton JD. Thromboembolism in patients with atrial fibrillation. *Arch Neurol* 1984; **41**: 708–10.
- 29 Hart RG, Coull BM, Hart D. Early recurrent embolism associated with nonvalvular atrial fibrillation: a retrospective study. *Stroke* 1983; **14**: 688–93.
- 30 Hornig CR, Dorndorf W. Early outcome and recurrences after cardiogenic brain embolism. *Acta Neurol Scand* 1993; **88**: 26–31.
- 31 International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet* 1997; **349**: 1569–81.
- 32 Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation* 2007; **115**: e478–534.
- 33 Hart RG, Palacio S, Pearce LA. Atrial fibrillation, stroke, and acute antithrombotic therapy: analysis of randomized clinical trials. *Stroke* 2002; **33**: 2722–27.