Bleeding During Treatment With Aspirin Versus Apixaban in Patients With Atrial Fibrillation Unsuitable for Warfarin

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

Greg C. Flaker, MD; John W. Eikelboom, MBBS; Olga Shestakovska, MSc; Stuart J. Connolly, MD; Scott Kaatz, DO, MSc; Andrzej Budaj, MD, PhD; Steen Husted, MD, DSc; Salim Yusuf, MBBS, DPhil; Gregory Y. H. Lip, MD; Robert G. Hart, MD

Background and Purpose—Apixaban reduces stroke with comparable bleeding risks when compared with aspirin in patients with atrial fibrillation who are unsuitable for vitamin K antagonist therapy. This analysis explores patterns of bleeding and defines bleeding risks based on stroke risk with apixaban and aspirin.

Methods—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 randomized 5599 patients with atrial fibrillation and risk factors to receive either apixaban or aspirin. Bleeding events were defined as the first occurrence of either major bleeding or clinically relevant nonmajor bleeding.

Results—The rate of a bleeding event was 3.8%/year with aspirin and 4.5%/year with apixaban (hazard ratio with apixaban, 1.18; 95% CI, 0.92–1.51; P=0.19). The anatomic site of bleeding did not differ between therapies. Risk factors for bleeding common to apixaban and aspirin were use of nonstudy aspirin >50% of the time and a history of daily/occasional nosebleeds. The rates of both stroke and bleeding increased with higher CHADS₂ scores but apixaban compared with aspirin was associated with a similar relative risk of bleeding (P interaction 0.21) and a reduced relative risk of stroke (P interaction 0.37) irrespective of CHADS₂ category.

Conclusions—Anatomic sites and predictors of bleeding are similar for apixaban and aspirin in these patients. Higher CHADS₂ scores are associated with increasing rates of bleeding and stroke, but the balance between risks and benefits of apixaban compared with aspirin is favorable irrespective of baseline stroke risk.

Clinical Trial Registration Information—www.clinicaltrials.gov. Unique identifier: NCT 00496769.

(Stroke. 2012;43:3291-3297.)

Key Words: apixaban ◼ atrial fibrillation ◼ clinical trial ◼ factor Xa inhibitor ◼ hemorrhage ◼ risk prediction
sites of bleeding and the clinical and laboratory predictors of major and clinically relevant nonmajor bleeding during apixaban and aspirin therapy in the AVERROES trial. We also assess the risk of bleeding with apixaban versus aspirin in patients determined to be at low, moderate, and high risk of ischemic stroke.

Methods

The design, inclusion criteria, study execution, and main results of the AVERROES trial have been published.7,8 The AVERROES trial-included patients were not candidates for oral anticoagulation with a VKA (eg, warfarin). Reasons for unsuitability for VKA are listed in the main article.8 Investigators were asked to indicate the reason for unsuitability for warfarin, which included an inability to maintain an international normalized ratio within the therapeutic range, international normalized ratio could not be assessed at requested intervals, uncertainty about the patient’s ability to comply with instructions, anticipated difficulty in contacting the patient about urgent dosing changes, uncertainty regarding a favorable balance between the benefits and the risk of therapy for patients with CHADS2=1, or patient refusal. In most patients, multiple reasons for unsuitability for VKA therapy were provided. Salient exclusion criteria relevant to bleeding were recent serious bleeding and active peptic ulcer disease. Patients were randomized to receive apixaban (5 mg twice daily) or aspirin (81–324 mg daily) administered double-blind. A reduced dose of apixaban (2.5 mg twice a day) was assigned to participants who met at least 2 of the following criteria: (1) age ≥80 years; (2) body weight ≤60 kg; or (3) serum creatinine ≥1.5 mg/dL or 133 μmol/L. For this analysis, the estimated glomerular filtration rate was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula, considered to be more accurate than other equations and appropriate for population studies.9 Patients were strongly encouraged to stop open-label aspirin if they were taking aspirin at baseline. Patients who developed a clear indication for antiplatelet therapy during the study were advised to not exceed 100 mg daily of aspirin.

The bleeding outcome of interest for these analyses was the first occurrence of either major bleeding or clinically relevant nonmajor bleeding, both defined in the online-only Data Supplement.

All analyses were based on the intention-to-treat principle. The rates of major and clinically relevant nonmajor bleeding were compared between treatment groups. Aspirin and apixaban were compared with the likelihood ratio test, Cox proportional hazards regression model.

Table 1. Site of Bleeding

<table>
<thead>
<tr>
<th>Site of Bleeding</th>
<th>Major Bleeding</th>
<th></th>
<th></th>
<th>Major or Clinically Relevant Non-Major Bleeding</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin (N=2791)</td>
<td>Apixaban (N=2808)</td>
<td>P Value†</td>
<td>Aspirin (N=2791)</td>
<td>Apixaban* (N=2808)</td>
<td>P Value†</td>
</tr>
<tr>
<td>Intracranial</td>
<td>13 (0.41)</td>
<td>11 (0.35)</td>
<td>0.69</td>
<td>13 (0.41)</td>
<td>11 (0.35)</td>
<td>0.69</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>14 (0.45)</td>
<td>11 (0.35)</td>
<td>0.56</td>
<td>39 (1.25)</td>
<td>42 (1.35)</td>
<td>0.73</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>0</td>
<td>1 (0.03)</td>
<td>...</td>
<td>8 (0.25)</td>
<td>6 (0.19)</td>
<td>0.59</td>
</tr>
<tr>
<td>Superficial/hematoma/puncture site</td>
<td>3 (0.10)</td>
<td>3 (0.10)</td>
<td>...</td>
<td>22 (0.70)</td>
<td>13 (0.41)</td>
<td>0.13</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1 (0.03)</td>
<td>0</td>
<td>...</td>
<td>17 (0.54)</td>
<td>23 (0.74)</td>
<td>0.34</td>
</tr>
<tr>
<td>Ear, nose, and throat**</td>
<td>2 (0.06)</td>
<td>0</td>
<td>...</td>
<td>15 (0.48)</td>
<td>25 (0.80)</td>
<td>0.11</td>
</tr>
<tr>
<td>Surgical bleeding/trauma††</td>
<td>5 (0.16)</td>
<td>6 (0.19)</td>
<td>0.75</td>
<td>8 (0.25)</td>
<td>9 (0.29)</td>
<td>0.80</td>
</tr>
<tr>
<td>Other‡‡</td>
<td>3 (0.10)</td>
<td>13 (0.41)</td>
<td>...</td>
<td>6 (0.19)</td>
<td>14 (0.45)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*One patient in the apixaban group with intracranial site of bleeding was excluded from the analysis of the composite of major and clinically relevant nonmajor bleeding.
†P value is from the likelihood ratio test (Cox proportional hazards regression model). The rates were not compared if no. of events was <5 in either of the treatment groups.
‡An event is the first occurrence of major bleeding (left) and either major or clinically relevant nonmajor bleeding (right) at the specific site. The time to event is the time between the randomization date and the event first occurrence.
§Percent per year is the rate per 100 patient-years of follow-up.
‖Superficial/hematoma/puncture site includes bruising/ecchymosis, conjunctival, and subcutaneous.
¶Genitourinary includes hematuria, urinary tract, and vaginal.
**Ear, nose, and throat includes epistaxis and gingival.
††Surgical bleeding/trauma includes trauma/laceration.
‡‡Other includes intraocular, intra-articular, intramuscular, pericardial, retroperitoneal, and no source identified.
Table 2. Multivariable Analysis of Predictors of the Composite of Major and Clinically Relevant Nonmajor Bleeding in 2 Treatment Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspirin (N=2791)</th>
<th>Apixaban* (N=2808)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI†)</td>
<td>P Value†</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>1.32 (0.88–1.98)</td>
<td>0.18</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.82 (0.54–1.23)</td>
<td>0.33</td>
</tr>
<tr>
<td>Regular alcohol consumption (at least once/wk)</td>
<td>1.08 (0.68–1.66)</td>
<td>0.74</td>
</tr>
<tr>
<td>Prior stroke or transient ischemic attack</td>
<td>1.07 (0.61–1.75)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hypertension, receiving treatment</td>
<td>0.78 (0.48–1.33)</td>
<td>0.35</td>
</tr>
<tr>
<td>Heart failure or LVEF &lt;35%</td>
<td>0.90 (0.61–1.32)</td>
<td>0.59</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>2.30 (1.11–4.27)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes, receiving treatment</td>
<td>0.96 (0.59–1.49)</td>
<td>0.85</td>
</tr>
<tr>
<td>Classification of AF</td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>Persistent versus paroxysmal</td>
<td>0.85 (0.47–1.50)</td>
<td>0.43</td>
</tr>
<tr>
<td>Permanent versus paroxysmal</td>
<td>1.18 (0.76–1.65)</td>
<td>0.72 (0.48–1.08)</td>
</tr>
<tr>
<td>History of cancer</td>
<td>0.96 (0.46–1.79)</td>
<td>0.91</td>
</tr>
<tr>
<td>Ever fainted</td>
<td>0.62 (0.32–1.09)</td>
<td>0.10</td>
</tr>
<tr>
<td>Daily/occasional nosebleeds</td>
<td>2.47 (1.26–4.42)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>1.38 (0.75–2.38)</td>
<td>0.29</td>
</tr>
<tr>
<td>Non-study aspirin &gt;50% of the time</td>
<td>1.89 (1.13–3.02)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hemoglobin† g/L</td>
<td>0.621 (0.419–0.922)</td>
<td>0.02</td>
</tr>
<tr>
<td>Estimated GFR§ ≥60 mL/min versus &lt;60 mL/min</td>
<td>0.66 (0.44–0.98)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; AF, atrial fibrillation; GFR, glomerular filtration rate.

*One patient in the apixaban group with clinically relevant nonmajor bleeding and intracranial site of bleeding was excluded. Furthermore, due to missing values in some of the predictor variables, the total no. of patients used in the multivariable analysis was 5566 (2776 in the aspirin group and 2790 in the apixaban group), and the no. of events was 250 (115 in the aspirin group and 135 in the apixaban group).

†P value is from the likelihood ratio test of the overall significance of a variable in the multivariable Cox proportional hazards regression model. Hazard ratio 95% CI limits are profile likelihood limits.

‡Treated as a continuous variable. Hazard ratio and 95% CI limits are shown for the increase of 2 SDs. For hemoglobin, SD=15.4 g/L.

§Calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.8

The analyses were performed using SAS software, Version 9.2 of the SAS System for SunOS (SAS Institute Inc, Cary, NC).

Results

Clinical characteristics of study participants have been reported in detail7 and are briefly summarized here. Among the 5599 participants, the mean participant age was 70 years, 59% were men, and 14% had a prior stroke or transient ischemic attack. A total of 264 of the 2808 patients in the apixaban group (9%) and 246 of the 2791 in the aspirin group (9%) took additional nonstudy aspirin >50% of the time during follow-up.

After a mean follow-up of 1.1 years, there were 83 major hemorrhages (44 on apixaban, 39 on aspirin, first events) and 180 clinically relevant nonmajor hemorrhages (96 on apixaban, 84 on aspirin, first events). Ten patients (3 on apixaban and 7 on aspirin) had both severities of bleeding. The annual rate of major bleeding was 1.2% with aspirin and 1.4% with apixaban (hazard ratio with apixaban, 1.13; 95% CI, 0.74–1.75; P=0.57), and the annualized rate of clinically relevant nonmajor bleeding was 2.7% with aspirin and 3.1% with apixaban (hazard ratio with apixaban, 1.15; 95% CI, 0.86–1.54; P=0.35). One patient in the apixaban group had an asymptomatic cerebral microbleed.
detected by MRI as part of a prospective substudy. This patient was reported as having a nonmajor intracranial hemorrhage and was excluded from this analysis. The rate of major or clinically relevant nonmajor bleeding was 3.8%/year with aspirin and 4.5%/year with apixaban (hazard ratio with apixaban, 1.18; 95% CI, 0.92–1.51; \( P = 0.19 \)).

Kaplan-Meier cumulative hazard rates show a steady accumulation of hemorrhages during follow-up with no evidence of higher early rates of bleeding (Figure 1A–B).

### Sites of Bleeding

The most frequent site of bleeding with both treatments was gastrointestinal (1.35%/year with apixaban and 1.25%/year with aspirin). The rates of site-specific major or clinically relevant nonmajor bleeding were similar with the 2 antithrombotic treatments (Table 1). Of note the rates of intracranial hemorrhage were 0.41%/year with aspirin and 0.35%/year with apixaban (\( P = 0.96 \)). Of all fatal intracranial hemorrhages, 3 (0.1%/year) occurred in patients assigned to apixaban and 4 (0.13%/year) occurred in those assigned to aspirin.

### Predictors of Bleeding

In multivariable analysis, the only statistically significant independent predictors of major and clinically relevant nonmajor bleeding shared between those assigned to aspirin and apixaban were the use of nonstudy aspirin >50% of the time (\( P = 0.02 \) for both treatments) and a history of daily/occasional nosebleeds (\( P = 0.01 \) and \( P = 0.02 \), respectively). Additionally, there were 4 independent predictors associated with the outcome for one treatment but with a similar hazard ratio for the other treatment, albeit not reaching statistical significance: age (≥75 years versus <75 years), estimated glomerular filtration rate (≥60 mL/min versus <60 mL/min), hemoglobin, and peripheral artery disease (Table 2).

### Bleeding Risk in Selected Subgroups

The relative risks of major or clinically relevant nonmajor bleeding were similar in patients assigned to apixaban compared with aspirin in key subgroups based on baseline characteristics (Figure 2). There were no significant interactions among age, sex, body mass index, study dose of aspirin or aspirin-placebo, or estimated glomerular filtration rate and randomized treatment for the outcome of major and clinically relevant nonmajor bleeding. Using established models to predict bleeding, the relative risks of major or clinically relevant nonmajor bleeding were similar in patients assigned to apixaban compared with aspirin (Figure 3) with no significant interactions between high- and low-risk categories.

### Balance Between Strokes Prevented and Bleeding According to Ischemic Stroke Risk

Compared with aspirin, apixaban consistently reduced the rate of ischemic stroke and systemic embolism irrespective of CHADS\(_2\) score (Table 3). The absolute risk of bleeding with apixaban increased with increasing stroke risk. For low-risk CHADS\(_2\) (score 0–1), the stroke rates were only 0.7%/year, whereas the bleeding event rate was 2.9%/year. For high-risk CHADS\(_2\) (score 3–6), the stroke rate was 1.8%/year, whereas the bleeding rate was 6.1%/year. There was no heterogeneity of treatment effect of apixaban compared with aspirin for bleeding according to CHADS\(_2\) score risk categories. For patients at higher risk for stroke (CHADS\(_2\) 3–6), the difference between ischemic strokes prevented and bleeding was 2.1%/year.
Discussion

The main results of this study are (1) the site-specific bleeding rates for patients with AF judged unsuitable for VKA treatment are not substantially different between apixaban and aspirin; (2) independent predictors of bleeding are similar with aspirin and apixaban; and (3) the balance between strokes prevented and bleeding risk for apixaban compared with aspirin is favorable at all levels of stroke risk. Thus, apixaban is an attractive choice for antithrombotic prophylaxis across the spectrum of ischemic stroke risk in patients with AF unsuitable for warfarin therapy.

A major reason for not using anticoagulants for stroke prevention in AF is fear of bleeding. The rate of major bleeding with warfarin in recently completed clinical trials varied between 1.4% and 3.57%/year.14–18 The rate of major bleeding with dabigatran, a direct thrombin inhibitor, has been reported to be between 2.71% and 3.11%/year depending on the dose.18 Data from anticoagulation clinics have reported the rate of major bleeding to be extremely variable in elderly patients, ranging from 1.87%/year to 7.2%/year.19,20 Although differences in patient populations and bleeding definitions limit cross trial comparisons, the types of patients (age, CHADS2 score) included in AVERROES are similar to those included in other contemporary antithrombotic trials in AF. The low rate of major bleeding in this study with apixaban should help allay fear about bleeding. The risk of major bleeding with apixaban in patients eligible for warfarin is the ARISTOTLE trial was also low, ranging from 0.52% to 2.13%/year depending on the criteria used for major bleeding.21 Another Factor Xa inhibitor, rivaroxaban, has a rate of major and clinically relevant nonmajor bleeding comparable with warfarin.22

The site of major and clinically relevant nonmajor bleeding during treatment with highly efficacious dosages of apixaban in elderly patients with AF were all similar to that seen with aspirin. By contrast, warfarin compared with aspirin16 or dabigatran18 causes more central nervous system bleeding, possibly explained by inhibition of the tissue Factor VIIa complex that is present in high concentration in the brain and critically important in normal hemostasis.23,24 On the other hand, dabigatran etexilate, a drug with low bioavailability, causes more gastrointestinal bleeding than warfarin, possibly due to elevated concentrations

Table 3. Rates of Ischemic Stroke and Bleeding Events According to Risk Categories of CHADS2 Score in 2 Treatment Groups

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>No. Events/ Patient, %/y§</th>
<th>Rate Difference, %/y</th>
<th>P Value†</th>
<th>Rate Difference, %/y</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>106/2788 (3.4)</td>
<td>45/2806 (1.6)</td>
<td>−2.0</td>
<td>0.001</td>
<td>116/2788 (3.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>136/2806 (4.5)</td>
</tr>
<tr>
<td>0–1 (low risk)</td>
<td>18/1022 (1.6)</td>
<td>8/1004 (0.7)</td>
<td>−0.9</td>
<td>0.05</td>
<td>39/1022 (3.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32/1004 (2.9)</td>
</tr>
<tr>
<td>2 (intermediate risk)</td>
<td>37/954 (3.4)</td>
<td>22/1044 (1.9)</td>
<td>−1.6</td>
<td>0.02</td>
<td>40/954 (3.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55/1044 (4.8)</td>
</tr>
<tr>
<td>3–6 (high risk)</td>
<td>51/812 (5.8)</td>
<td>15/758 (1.8)</td>
<td>−4.0</td>
<td>&lt;0.001</td>
<td>37/812 (4.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>49/758 (6.1)</td>
</tr>
</tbody>
</table>

*One patient in the apixaban group with clinically relevant nonmajor bleeding and intracranial site of bleeding was excluded. Only patients who had CHADS2 scores nonmissing were included in the analysis shown. Four patients had CHADS2 score missing (3 in the aspirin group and one in the apixaban group). The total no. of patients used in the analysis of CHADS2 score was 5594 (2788 in the aspirin group and 2806 in the apixaban group).
†P value is from the likelihood ratio test of significance of the effect of apixaban versus aspirin in patients within a risk category (Cox proportional hazards regression model fit separately in each subgroup). P value for interaction is from the Cox model fit to all patients and is 0.37 for ischemic stroke and 0.21 for bleeding events.
‡An event is the first occurrence of ischemic stroke, stroke of uncertain classification or systemic embolism (left), and major or clinically relevant nonmajor bleeding (right). The time to event is the time between the randomization date and the event first occurrence.
§Percent per year is the rate per 100 patient-years of follow-up.
of the drug in the gut as a result of low bioavailability and conversion of the prodrug to dabigatran by gut esterases. Potent inducers of the p-glycoprotein system (like rifampin) may result in increased local levels of dabigatran in the gut because dabigatran exetilate is a substrate for p-glycoprotein. The bleeding profile of apixaban suggests that it is suitable across the spectrum of patients with AF who are at risk for stroke.

Limitations
Clinically relevant nonmajor bleeding was not adjudicated by an independent, blinded events committee although mitigated by blinding of investigators to treatment assignment. Like with all randomized trials, patients enrolled in this study may differ from patients in clinical practice who are thought to be unsuitable for warfarin.

Conclusions
Patients who have bleeding and who are judged unsuitable for warfarin have a relatively low risk of major bleeding or clinically relevant nonmajor bleeding when treated with aspirin or apixaban. The anatomic sites of bleeding and independent predictors of bleeding are similar for apixaban and aspirin and the favorable balance between benefits and risks of treatment are evident at all levels of ischemic stroke risk. The initial step in the decision to prescribe an anticoagulant for stroke prevention in patients with AF involves weighing the benefit of stroke prevention against the risk of bleeding. These data reassure that apixaban is an attractive option for stroke prevention for patients with AF deemed unsuitable for warfarin at all levels of stroke risk.

Sources of Funding
The AVERROES study (NCT 00496769) was funded by Bristol-Myers Squibb and Pfizer.

Disclosures
Dr Flaker serves as a consultant for Bristol-Myers Squibb and Pfizer, Sanofi-Aventis, and Boehringer-Ingelheim. Dr Eikelboom receives consulting fees from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Astra Zeneca, and Novartis and lecture fees from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, and Astra Zeneca. Dr Connolly received payment for serving on the boards of Boehringer-Ingelheim, Sanofi-Aventis, Portola and Merck; consulting fees from Boehringer-Ingelheim, Sanofi-Aventis, Portola, and Merck; and grant support on behalf of his institution, McMaster University, from Boehringer-Ingelheim, Sanofi-Aventis, Portola, and Bristol-Myers Squibb and lecture fees from Boehringer-Ingelheim, Sanofi-Aventis, and Portola. Dr Kaatz received grant support from Boehringer-Ingelheim, Bristol-Myers Squibb, Bayer, Jansen, Johnson and Johnson, Eisai, the National Institutes of Health, Canadian Institute of Health Research, Blue Cross/Blue Shield of Michigan; speaker honorarium from Jansen, Johnson and Johnson, Glaxo Smith Kline, and Eisai; is a consultant for Boehringer-Ingelheim, Bristol-Myers Squibb, Pfizer, Jansen, Johnson and Johnson, Daiichi Sankyo; and is on the membership board for nonprofit organizations AC Forum, National Certification Board of Anticoagulation Providers and National Blood Clot Alliance Medical, and Scientific Advisory Board. Dr Budaj received consulting fees from Sanofi-Aventis, Eli Lilly, Novartis, and Astra Zeneca and grant support both for himself and on behalf of his institution, Grochowski Hospital, Sanofi-Aventis, Boehringer-Ingelheim, Glaxo Smith Kline, Bristol-Myers Squibb, and Astra Zeneca and lecture fees from Sanofi-Aventis, Boehringer-Ingelheim, Glaxo Smith Kline, and Astra Zeneca and reimbursement for travel, accommodations, or meeting expenses from Sanofi-Aventis, Boehringer-Ingelheim, Glaxo Smith Kline, and Astra Zeneca. Dr Yusuf received consulting fees from Boehringer-Ingelheim, Sanofi-Aventis, Novartis, Astra Zeneca, Bristol-Myers Squibb, and Glaxo Smith Kline and grant support from Boehringer-Ingelheim, Sanofi-Aventis, Novartis, Astra Zeneca, Glaxo Smith Kline, and Bristol Myers Squibb. Dr Lip received consulting fees from Astellas, Boehringer-Ingelheim, Bayer, Daiichi, Merck, Portola, Biotronic, Sanofi-Aventis, and Astra Zeneca and grant support on behalf of his institution, City Hospital, from Bayer; lecture fees from Boehringer-Ingelheim, Bayer, Merck, and Sanofi-Aventis; and payment from Boehringer-Ingelheim for developing educational presentations. Dr Hart was paid for services rendered as a member of the Operations and Publications Committee of AVERROES.

References
16. The ACTIVE Writing Group on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Ibresatran for prevention


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*Stroke*. 2012;43:3291-3297; originally published online October 2, 2012;
doi: 10.1161/STROKEAHA.112.664144

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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SUPPLEMENTAL MATERIAL
Appendix

Major bleeding, the primary safety outcome of AVERROES, was defined as clinically overt bleeding accompanied by 1 or more of the following: decrease in hemoglobin of $\geq 2$ g/dl over a 24-hour period, transfusion of $\geq 2$ units of packed red blood cells, bleeding that occurs in a critical site (intracranial, intra-spinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal), or bleeding that was fatal. Clinically relevant non-major bleeding was defined as acute clinically overt bleeding that does not satisfy additional criteria required for the bleeding event to be defined as a major bleeding event but results in hospital admission, physician-guided medical or surgical treatment, or prompting a change in antithrombotic therapy. Examples of clinically relevant non-major bleeding events include 1) epistaxis (nose bleed) during which the subject seeks medical attention from a physician in an emergency room, or requires an intervention, e.g., nasal pack, or experiences a single bleeding episode persists for five minutes or more. 2) gastrointestinal bleeding, defined as vomitus containing frank blood or coffee ground material which tests positive for blood, or endoscopically confirmed bleeding, or frank blood per rectum or melena stools. 3) hematuria which persists for 24 hours or more after instrumentation. 4) bruising/ecchymosis defined as any bruise which is assessed as “unusual” (e.g., greater than expected following surgery). 5) hematoma which is demonstrated radiographically, e.g. by ultrasound, CT, MRI, associated with a drop in hemoglobin with no external evidence of bleeding. 6) hemoptysis, defined as the expectoration of blood or blood-stained sputum. Major bleeding was centrally adjudicated by those unaware of treatment assignment in order to apply uniformly these criteria.