Newer Anticoagulants for Atrial Fibrillation: the Role of Dabigatran, Rivaroxaban, Apixaban and Edoxaban / RELY, ROCKET-AF, ARISTOTLE, & ENGAGE AF TIMI 48 Studies / Safety Issues

Sokratis Pastromas, MD

ABSTRACT
Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and one of the major risk factors for ischemic stroke and thromboembolic events. Vitamin K antagonists (VKA) are considered to be the cornerstone in antithrombotic therapy for many years. Alternatively, antithrombotic drugs such as aspirin or the combination of aspirin and clopidogrel are also used, but without having proved similar or superior in efficacy compared to VKA. Moreover, therapy with VKA has complications and it is also quite demanding, as it often requires close monitoring of anticoagulation therapy. Recently, newer anticoagulants have been developed, which include direct thrombin antagonists, such as dabigatran or factor Xa inhibitors, such as rivaroxaban, apixaban and edoxaban. For each of these novel drugs large phase III clinical trials have been completed and their results have already been published, with the exception of edoxaban. These drugs are more effective compared to conventional therapies and, furthermore, they lack the need for anticoagulation monitoring. With regards to their safety profile, it has been shown to be similar to VKA. Nevertheless, some reports have recently emerged about fatal bleeding episodes after the use of dabigatran, which highlights the need for evidence based prescription of these novel drugs after thorough patient evaluation.

INTRODUCTION
Atrial fibrillation (AF) is the most commonly sustained tachyarrhythmia in the general population affecting about 1-2% of the general population. Its prevalence increases with the age from <0.5% at 40 – 50 years old, to 5-15% at 80 years old and it is estimated to be doubled in the next 50 years. Atrial fibrillation is associated with more hospitalizations, mainly due to ischemic strokes or chronic heart failure decompensation. Ischemic strokes in association with AF are more severe and often fatal. In many cases, patients who survive are disabled and have a high probability for recurrent
episodes. Oral anticoagulant therapy (OAC) with vitamin K antagonists (VKAs) is considered to be the cornerstone for stroke prevention, in patients with AF and major risk factors. Vitamin K antagonists, have proved their efficacy compared to placebo or no treatment, reducing the risk of stroke by 64% in patients with AF. Aspirin and clopidogrel, can be given to patients with minor risk factors, although their efficacy is significantly inferior compared to that of VKAs, according to the results of ACTIVE W study.

However, daily clinical experience shows that the percentage of patients with AF, who need OAC but do not receive any medication, seems to be significant. Data from the BAFTA study showed that only 52% in the whole cohort were aware of the reasons for commencing their warfarin. Based on achieving a balance between stroke risk with low INR levels and an increasing bleeding risk with high INR levels, an INR of 2.0–3.0 is the likely optimal range for the prevention of a stroke and systemic embolism in patients with AF. Over the recent years, new drugs for the prevention of thromboembolism in AF (dabigatran etexilate, apixaban, rivaroxaban, edoxaban etc.) have been evaluated in large clinical trials, regarding their efficacy and safety. The potential benefit of those drugs is mainly the lack of need for INR monitoring.

NEW ANTICOAGULANTS

Because of the difficulties of warfarin therapy and the continuous and increasing number of patients, who need anticoagulation therapy, the introduction of new drugs in the daily clinical practice was imperative. The aim was to produce medications, which fulfill the conditions for the ideal anticoagulant, as it has been established by clinical practice (Table 1). Two main classes of novel anticoagulants have been introduced in the clinical field targeting either the blockade of thrombin (IIa) or factor Xa in the coagulation cascade. Dabigatran etexilate is the main representative of the first class, while rivaroxaban, apixaban and edoxaban belong in the second class. All these novel drugs have reached phase III large multicenter prospective clinical trials for use in AF. The efficacy and the main side effects of these new compounds have been tested in clinical trials for venous thromboembolism, including patients undergoing orthopedic surgery.

DABIGATRAN ETEXILATE

Dabigatran is a new oral pro-drug, which inhibits thrombin directly and reversibly. Its bioavailability is about 6.5% and the half time 12 to 17 hours, with mainly renal excretion. The clinical evaluation of the drug started firstly with large clinical trials (RE-NOVATE, RE-MODEL, RE-MOBILIZE trials) in orthopedic patients, investigating its potential thromboembolism prevention effect, compared to enoxaparin. Noninferiority and similar bleeding rates, compared to enoxaparin, were found in a pooled analysis of the results of these three trials. Subsequently, stroke prevention compared to warfarin in patients with AF was tested in the large phase III trial RE-LY (Randomized Evaluation of Long-term anticoagulation therapy). Patients in this trial were randomized to receive, either a fixed dose of dabigatran (110 or 150 mg bid), or warfarin with a target INR between 2.0 and 3.0 (Table 2). The primary endpoint was stroke or embolism and it occurred as often in patients receiving 110 mg dabigatran, as in patients receiving warfarin (1.5% vs. 1.7%, 95% confidence intervals CI: 0.74 to 1.11, RR:0.91, P=0.34) and less often in patients receiving 150 mg dabigatran (1.1%, relative risk or risk ratio RR: 0.66, 95% CI: 0.53 to 0.82, P<0.01). Analyzing this primary end point, compared to the time in therapeutic range (TTR) of patients, who are receiving warfarin, showed that the beneficial effects of dabigatran, were consistent regardless of INR control. Moreover, dabigatran was superior to warfarin regarding total mortality and cardiovascular events in patients with low TTR.

The major bleeding risk was comparable in patients receiving dabigatran 150 mg bid and in patients receiving warfarin (RR: 0.93, 95% CI: 0.81 to 1.07, P=0.31), but lower in patients who were taking dabigatran 110 mg bid (RR: 0.80, 95% CI: 0.69 to 0.93, P=0.003). Most importantly, the intracranial bleeding was reduced in both doses of dabigatran (0.3% and 0.2% for 150 mg and 110 mg dosing, respectively) compared to warfarin (0.7%). However, dabigatran was associated, in a non-dose-dependent manner, with a small but significant increase in dyspepsia and a non significant increased rate of myocardial infarction compared to warfarin (0.7% vs. 0.5%, P=0.048 for 150 mg and P=0.07 for 110 mg).

On the basis of the results of the RE-LY study in the recent guidelines issued by the European Society of Cardiology (ESC) for AF management, dabigatran is proposed as an alternative to warfarin therapy. In these guidelines, the HAS-BLED score has been introduced for the assessment of the patients’ bleeding risk. Thus, in patients with low bleeding score (0-2) the 150 mg bid dose is proposed, while the 110 mg dose is considered suitable in patients with higher score (≥3). The Food and Drug Administration (FDA) in the USA has approved the 150 mg bid dose in high risk patients with AF and a reduced
**TABLE 2. Phase III Clinical Trials of Dabigatran, Rivaroxaban, Apixaban and Edoxaban**

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Patients’ characteristics</th>
<th>Primary endpoint</th>
<th>Major Bleeding rates</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>Dabigatran 110 mg</td>
<td>- Mean age 71.5 yrs, 63.6% males</td>
<td>Stroke or embolism</td>
<td>[Hgb $\geq$20g/L, transfused $\geq$2 units, or symptomatic bleeding in critical area or organ]</td>
<td>Dabigatran 110 mg non-inferior to Warfarin, 20% less major bleeding events and significantly less intracranial hemorrhage.</td>
</tr>
<tr>
<td></td>
<td>(n=6,015)/150 mg bid</td>
<td>- AF + 1 risk factor, $\sim$33% persistent, 33% paroxysmal, 33% permanent,</td>
<td>- 1.71%/yr Warfarin group</td>
<td>Dabigatran 110 mg vs. Warfarin, $P=0.003$</td>
<td>Dabigatran 150 mg superior to Warfarin with similar rate of major bleeding and significantly less intracranial hemorrhage.</td>
</tr>
<tr>
<td></td>
<td>(n=6,022)</td>
<td>- mean CHADS$_2$: 2.1 CHADS$_0$-1: $\sim$32%, 2: $\sim$35%, $\geq$: $\sim$32%</td>
<td>- 1.54%/yr Dabigatran 110 mg group</td>
<td>Dabigatran 150 mg vs. Warfarin, $P=0.31$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Median follow up: 2 yrs</td>
<td>- 1.11%/yr Dabigatran 150 mg group</td>
<td>Dabigatran 150 mg vs. Dabigatran 110 mg, $P=0.052$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban 20 mg</td>
<td>- Mean age 73 yrs, 60.3% males</td>
<td>Stroke or embolism</td>
<td>[Hgb $\geq$20g/L, transfused $\geq$2 units, or symptomatic bleeding or resulting in death]</td>
<td>Rivaroxaban non-inferior to Warfarin, with non-significant superiority on intention to treat analysis ($P=0.117$), but significant superiority with on-treatment analysis ($P=0.02$)</td>
</tr>
<tr>
<td></td>
<td>od (n=7,131) vs.</td>
<td>- AF+2 risk factors, 81.1% permanent, 17.5% paroxysmal, 1.4% newly diagnosed</td>
<td>- 2.42%/yr Warfarin</td>
<td>Dabigatran ($P=0.58$)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warfarin (7,133)</td>
<td>- mean CHADS$_2$: 3.5, CHADS$_2$: 1: 13%, $\geq$: 87%</td>
<td>- 2.12%/yr Rivaroxaban ($P=0.117$)</td>
<td>3.45% Warfarin vs. 3.6% Rivaroxaban ($P=0.08$)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(target INR 2-3)</td>
<td>- Median follow up: 19 yrs</td>
<td></td>
<td>0.7% Warfarin vs. 0.5% Rivaroxaban ($P=0.02$)</td>
<td></td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>Apixaban 5 mg bid</td>
<td>- Mean age 70 yrs, 59% males</td>
<td>Stroke or embolism</td>
<td>[Hgb $\geq$20g/L, transfused $\geq$2 units, or symptomatic bleeding in critical area or resulting in death]</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>(n=9,120) vs.</td>
<td>- AF+1 risk factor, 84.9% permanent, 15.1% paroxysmal</td>
<td>- 1.60%/yr % Warfarin</td>
<td>3.09%/yr Warfarin vs. 2.13%/yr Apixaban ($P&lt;0.001$)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warfarin (n=9,081)</td>
<td>- mean CHADS$_2$: 2.1, CHADS$_1$: 1, 34%, CHADS$_1$: 2: 35.8%, $\geq$: 30.2%</td>
<td>- 1.27%/yr Apixaban ($P=0.01$)</td>
<td>intracranial hemorrhage: 0.8%/yr Warfarin vs. 0.3%/yr Apixaban ($P&lt;0.001$)</td>
<td>Apixaban is superior to Warfarin in preventing stroke or systemic embolism, caused less bleeding and results in lower mortality</td>
</tr>
<tr>
<td></td>
<td>(target INR 2-3)</td>
<td>- Median follow up: 18 yrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVERROES</td>
<td>Apixaban 5 mg</td>
<td>Mean age 70 yrs, 65% males</td>
<td>Stroke or embolism</td>
<td>[Hgb $\geq$20g/L, transfused $\geq$2 units, or symptomatic bleeding in critical area or resulting in death]</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>bid (n=2,808) vs. Aspirin</td>
<td>- AF+1 risk factor, 84.9% permanent, 15.1% paroxysmal</td>
<td>- 1.2%/yr Apixaban</td>
<td>3.7%/yr Aspirin vs. 1.6%/yr Apixaban ($P&lt;0.001$)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>81-324 mg (n=2,791)</td>
<td>- mean CHADS$_2$: 2.1, CHADS$_0$-1: 37%, 2: 36%, $\geq$: 27%</td>
<td>- 1.6%/yr Apixaban ($P=0.01$)</td>
<td>intracranial hemorrhage: 0.3%/yr Aspirin vs. 0.4%/yr Apixaban ($P=0.83$)</td>
<td>Apixaban superior to aspirin, with similar rate of major bleeding and intracranial hemorrhages and with less discontinuations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Mean follow up: 1.8 yrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENGAGE-AF-TIMI 48</td>
<td>Edoxaban 30 mg/60 mg o.d. vs. Warfarin</td>
<td>21,107 patients with AF (all types), CHADS$_2$: $\geq$2 follow up 24 months</td>
<td>Stroke/systemic embolism</td>
<td>1.2%/yr Apixaban vs. 1.4%/yr Apixaban ($P=0.33$)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>intracranial hemorrhage: 0.5%/yr Apixaban ($P=0.83$)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; bid = twice daily; CHADS2 (score) = Congestive heart failure, Hypertension, Age ($\geq$75 years), Diabetes mellitus, prior Stroke or transient ischemic attack; Hgb = hemoglobin; INR = international normalized ratio; od = once daily; yr(s) = year(s)
SAFETY OF NEWER ANTICOAGULANTS

dosage of 75 mg bid in patients with severe renal insufficiency (creatinine clearance 15-30 ml/min). The Canadian Health Authority has also approved the 110 mg dose, which is recommended for patients with AF older than 80 years old and when the bleeding risk is high. In Europe, dabigatran (150 mg in low risk bleeding patients and 110 mg in high risk bleeding patients) has also gained approval for stroke prevention in patients with nonvalvular AF from the European Medicines Agency (EMA) on April 2011.

RIVAROXaban

Rivaroxaban is an anticoagulant agent, which inhibits directly the activated Xa factor, which is a key factor in the conversion of prothrombin to thrombin. It has a bioavailability of 80% and is excreted mainly, approximately by 66%, by the liver without needing plasma coagulation monitoring. Its plasma half life is 7 to 11 hours but, due to its flat dose response and to the prolonged inhibition of Xa factor, it is administrated once daily. At first, rivaroxaban was approved for the prevention of venous thromboembolism in patients after knee or hip replacement after an extensive clinical trial program, called RECORD, in which it was found to be non-inferior or even superior compared to enoxaparin.

The effect of rivaroxaban in stroke prevention in AF was investigated in the ROCKET AF study (Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation). In this phase III double blind study, 14264, patients were randomized to receive either 20 mg rivaroxaban once a day (qd) or a dose-adjusted warfarin (INR target 2.0-3.0) and they were followed for a period of 24 months (Table 2). Rivaroxaban patients with renal insufficiency (creatinine clearance between 30 and 49 mL/min) received a reduced dose of 15 mg qd. Rivaroxaban was noninferior to warfarin for stroke or embolism in the primary analysis (1.7% per year) compared to the warfarin group (2.2% per year, **P<0.001**). However, conducting an intention-to-treat analysis, superiority was not established, although there was a trend but without statistical significance (2.12% per year for rivaroxaban vs. 2.42% per year for warfarin, **P=0.01** for noninferiority; **P=0.12** for superiority). In general, the bleeding rates were similar to warfarin but intracranial hemorrhage was lower in the rivaroxaban group (**P=0.02**).

Based on the similar efficacy and safety profile to warfarin, rivaroxaban was approved by the FDA on November 2011 and by the EMA for stroke prevention in patients suffering from nonvalvular AF. The once-daily dosing regimen of rivaroxaban is perhaps an important advantage compared to dabigatran, although the results are tempered as the intensity of anticoagulation in ROCKET AF patients receiving warfarin was poorest (TTR range 55%) compared to other trials (the mean TTR in the RE-LY trial was 64%).

APIXABAN

Another factor Xa inhibitor is apixaban, which has been evaluated by two large clinical trials, the ARISTOTLE and AVERROES for stroke prevention in patients with AF. The drug has a bioavailability of 50%, its plasma half life is about 12 hours and it has multiple excretion pathways with renal clearance accounted for ~27% of total clearance. After the positive results of the clinical program ADVANCE 1 & 2 (Apixaban Dosed orally Versus Anticoagulation with Injectable Enoxaparin to Prevent Thromboembolism), apixaban gained approval by the EMA for prevention of thromboembolism, after knee or hip surgery in a dosage of 2.5 mg bid.

In the AVERROES trial, apixaban 5 mg was considered to aspirin 81-325 mg daily in patients with AF unsuitable for therapy with vitamin K antagonists. This trial was terminated early because apixaban displayed efficacy superior to aspirin regarding stroke or embolism (3.7%/year for aspirin vs. 1.6%/year for apixaban, **P<0.001**), while no significant differences in major bleeding were evident (1.2%/year for aspirin vs. 1.4%/year for apixaban, **P=0.33**). Apixaban efficacy in stroke prevention was also compared to warfarin in the ARISTOTLE study, which enrolled patients with AF receiving either 5 mg of apixaban bid or warfarin (INR 2.0-3.0, mean TTR 62.2%). After a mean follow up of 1.1 years, apixaban was found to be noninferior and superior to warfarin for the primary outcome, reducing the risk of stroke or embolic events by 21% (**P<0.01** for noninferiority, **P=0.01** for superiority). Apixaban showed significant better safety profile, compared to warfarin, for both major bleeding episodes and intracranial hemorrhage (**P<0.001**). Substudy data from the ARISTOTLE trial in patients with prior stroke or transient ischemic attack (TIA), showed a constant benefit of apixaban, compared to the general study population (**P=0.71**). Likewise, apixaban seems to be similarly effective in patients with prior stroke or TIA in the AVERROES trial compared to the whole group of the study (**P=0.17**). Apixaban is under review by FDA for getting approval in the field of stroke prevention in patients with AF and the final decision is expected around March 2012.

EDOXABAN

Edoxaban is a reversible direct inhibitor of factor Xa with good bioavailability and a plasma half life of 8-10 hours. It is mainly excreted by the renal system. It is one of the newest compounds in this category and a phase III trial (ENGAGE AF TIMI 48) is being conducted comparing edoxaban at two dosages, 30 and 60 mg qd, with INR adjusted warfarin dosage in patients with a minimum of 2 stroke risk factors other than AF. In this study, it is possible to reduce by the edoxaban dosage by 50% in patients with increased risk of bleeding, so it is the first study in this category of new anticoagulants, which is going to compare more than two dosages of the new drug with warfarin. The enrollment has been completed with 21,107
patients and the final completion of the trial is estimated in March 2012.30

ARE THERE ANY DIFFERENCES BETWEEN THE NOVEL ANTICOAGULANTS IN SAFETY AND EFFICACY?

It is a fact that, when drugs belonging to a new category are introduced in the clinical field, the question always arises, which of them is the safest and the most effective, compared to conventional therapies. Vitamin K antagonists have proved, for many years, their efficacy in the prevention of embolic events in patients with AF in clinical practice as well as through many clinical trials. The new thrombin and factor Xa inhibitors have advantages, as they can be prescribed in patients who are considered to be unsuitable for VKA therapy, and most importantly there is no need for a cumbersome INR monitoring. As noted, in the RE-LY study dabigatran 150 mg bid was superior to warfarin; while apixaban was superior to warfarin and to aspirin in the ARISTOTLE and AVERROES studies, respectively. On one hand, rivaroxaban in the ROCKET AF study had superior efficacy compared to warfarin in the on-treatment analysis, but on the other hand, this was not confirmed in the intention-to-treat analysis. At this point it should be emphasized that the patient populations had differences in these trials (Table 2). Thus, the ROCKET AF study enrolled older patients (mean age 73 years), with at least two risk factors (congestive heart failure, hypertension, stroke or TIA), higher mean values of CHADS2 score (~3.5) and lower median TTR values for warfarin (58%) compared to other trials. Of course, it should also be emphasized that ROCKET AF patients’ characteristics, are more compatible with real life conditions, since the general population with AF is aged with comorbidities and always suboptimal INR values. Apixaban is the only novel anticoagulant, which in AVERROES trial was compared with aspirin in patients with mean CHADS2 score of 2.1 unwilling or considered medically unsuitable for therapy with a VKA and showed superiority in the prevention of stroke or embolism without significant difference in bleeding events. According to the investigators of the study, apixaban is superior to the combination of clopidogrel plus aspirin (study ACTIVE A) and non inferior to warfarin, which was proved with the results of the ARISTOTLE study.30

With regards to the adverse effects of these drugs, the main problem that remains is the bleeding episodes, which in the case of intracranial hemorrhage for example would be fatal. Dabigatran 110 mg bid in the RE-LY trial caused significant fewer bleedings, compared to warfarin, while rivaroxaban in the ROCKET AF study had similar bleeding rates to warfarin with significant fewer intracranial hemorrhages. Apixaban seemed to be safer compared to warfarin in this field in the ARISTOTLE study and similar to aspirin in the AVERROES study. The clinical practice of course is many times different than clinical trial conditions, especially when a new drug is introduced in the market. Thus, although the latest guidelines from the American College of Cardiology have proposed dabigatran 150 mg as a class I anticoagulant drug for patients with nonvalvular AF with same safety profile to warfarin, during the last several months several cases of serious bleedings have been described. Thus, the EMA issued in November 2011 an update reporting 256 fatal bleeding cases worldwide (21 of them in Europe) and focusing in the assessment of renal function before starting treatment with dabigatran.31 Likewise, a few days later the FDA issued a similar warning concerning the safety of dabigatran.32 Concerns about bleeding have continued and the Institute of Safe Medication Practices in USA announced that dabigatran adverse reactions involving bleeding were higher compared to warfarin in the first quarter of 2011, with a considerable percentage of intracranial hemorrhage in the elderly patients.33 One other issue that is unclear is the periprocedural efficacy and adverse effects of the new OACs. The results of a recently published small prospective trial, showed that in patients undergoing AF ablation, continuation of dabigatran during the periprocedural period is associated with an increased risk of bleeding (14% vs. 6%, P=0.031) and composite of bleeding or embolic complications (16% vs. 6%; P=0.009) compared with uninterrupted warfarin therapy.34 Obviously, a serious disadvantage of these compounds, mainly for patients with comorbidities, is that in case of serious bleeding, there is no effective antidote like vitamin K for VKA. Dabigatran can be eliminated either by dialysis, or after administering charcoal within 2 hours after the last dose.35 In contrast, rivaroxaban and apixaban cannot be eliminated by dialysis due to their binding to proteins. A small study showed that prothrombin complex concentrate (PCC) could to be an effective antidote for rivaroxaban, but not for dabigatran. Similarly, recently published data from an in vitro study indicate that PCC and recombinant factor VIIa significantly reversed the anticoagulant effect of edoxaban.37

CONCLUSION

It is clear that the need of new oral anticoagulants for the prevention of stroke in AF is undeniable as the population of patients is growing and there is a tendency to adopt more convenient therapies. Recently, data from a meta-analysis showed that self-monitoring of oral anticoagulation was not significantly superior to usual care in reducing thromboembolic events in patients with AF, when the difference was superior in young people with prosthetic valves.38 According to investigators, patients with AF were mostly older and not aware for the thromboembolic risk of AF, compared to patients with prosthetic valves. Prescription for the new OACs must be car-
ried out after first assessing the profile of each patient and the potential hazard of stroke and bleeding using CHADS2/VASC and HAS-BLED scores. However, patients with labile INRs are not necessarily the best candidates for the new OACs either, especially if the underlying reason is poor compliance, particularly, as the new OACs have relatively short half-lives and omission of doses can be catastrophic. Finally, financial issues are very important, and the cost-effectiveness analyses for the new OACs have to include not only the price of the drug, but also the costs of the whole spectrum of anticoagulation monitoring which is necessary for VKA.9,10

REFERENCES

24. Connolly SJ, Eikelboom J, Connolly SJ, et al; for the AVERROES steering committee and investigators. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from
AVERROES, a randomised trial. *Lancet Neurol* 2012 Feb 1. [Epub ahead of print]


