

# Old and new oral anticoagulants for secondary stroke prevention in atrial fibrillation

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## ABSTRACT

Vitamin K antagonists, such as warfarin, used in oral anticoagulation therapy currently represent the standard drugs for the primary and secondary prevention of stroke in non-valvular atrial fibrillation (AF), with a relative risk reduction close to 70%. Newer oral anticoagulants, such as direct thrombin inhibitors (*i.e.*, dabigatran) and direct factor Xa inhibitors (*i.e.*, apixaban and rivaroxaban) have been recently compared with warfarin in large randomized trials for stroke prevention in AF. The new oral anticoagulants showed, compared with warfarin, no statistically significant difference in the rate of stroke or systemic embolism in secondary prevention (patients with previous transient ischemic attack or stroke) subgroups. With regard to safety, the risk of intracranial bleeding was reduced with new anticoagulants compared with warfarin. Indirect treatment comparisons of clinical trials on secondary prevention cohorts showed no significant difference in efficacy among apixaban, rivaroxaban, and dabigatran; but dabigatran 110 mg was associated with less intracranial bleedings than rivaroxaban.

## Introduction

About 20% of ischemic strokes are cardioembolic and, among the cardioembolic sources, non-valvular atrial fibrillation (NVAF) represents the most frequent abnormality. Moreover, in patients with cryptogenic stroke, NVAF, more often in the paroxysmal form, may be detected in a significant number of cases by means of prolonged electrocardiogram (ECG) monitoring or implanted loop recorder.

The mean stroke rate in NVAF is 4.5% per year, as reported in the placebo-treated groups of primary prevention studies,<sup>1</sup> but this risk varies 20-fold depending on patient's age and other clinical features.<sup>2</sup>

Prior stroke or transient ischemic attack (TIA) is one of the most important risk factors<sup>3</sup> and the annual stroke recurrence rate after stroke/TIA is 12% in NVFA patients without antithrombotic treatment.<sup>4</sup>

Although stroke guidelines<sup>5</sup> recommend oral anticoagulation (OAC) with vitamin K antagonists (VKAs) in the secondary stroke prevention of NVAF patients, this therapy is still underused because of concerns about the increased risk of extra- or intracranial hemorrhages and the need for careful monitoring of the treatment.

Therefore the new non-VKA oral anticoagulants (*i.e.*, factor Xa-inhibitors and direct thrombin inhibitors), which seem to overcome the drawbacks of VKAs and to improve patient management, represent a great opportunity.

The objective of the present narrative review is to analyze the efficacy and safety of old and new OAC in the secondary prevention of stroke related to NVAF.

We performed a literature search of published studies from the Cochrane library, Medline and from reference lists of relevant articles on anticoagulant therapy in AF.

## Warfarin for secondary stroke prevention related to non-valvular atrial fibrillation

### *Adjusted-dose warfarin compared with placebo*

The Cochrane review (2004)<sup>6</sup> reports two trials of secondary stroke prevention. The combination of their results shows that warfarin reduces the risk of recurrent stroke by 64% and increases the risk of major extracranial hemorrhages by 4-fold, but not the risk of intracranial bleeds.

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In the meta-analysis by Hart *et al.* of 6 randomized trials (2007),<sup>7</sup> 20% of patients had had previous stroke or TIA. Warfarin reduces the risk of recurrent stroke by about two thirds compared with placebo. With warfarin there is a non-significant increase in major bleeds (2.8% on warfarin vs 0.7% on placebo).

The main study is the *European atrial fibrillation trial* (EAFT, 1993)<sup>5</sup> which shows that warfarin [target international normalized ratio (INR 2.5-4.0)] reduces the absolute risk (AR) of recurrent stroke by 8% per year (stroke rate on warfarin 4% vs 12% on placebo), therefore 80 strokes are prevented per 1000 patients treated.

#### *Adjusted-dose warfarin compared with antiplatelet agents*

The Cochrane review (2004)<sup>8</sup> reports two trials of secondary stroke prevention in which warfarin was compared with antiplatelet drugs.

In the first (EAFT, 1993),<sup>4</sup> warfarin (target INR 2.5-4) has been compared with aspirin (300 mg/day) with a follow-up of 2.3 years. In this study the AR for all recurrent strokes was reduced by 6% with warfarin (stroke rate on warfarin 4% vs 10% on aspirin), therefore resulting in 60 fewer recurrent strokes per year per 1000 patients treated.

Major extracranial bleedings were more frequent with warfarin (2.8% per year) than with aspirin (0.9% per year).

The second study is the *Studio italiano fibrillazione atriale* (SIFA, 1997)<sup>9</sup> in which warfarin (target INR 2.0-3.5) has been compared with indobufene (100-200 mg/day) with a follow-up of 1 year. With warfarin there was a not statistically significant AR reduction of 1%.

In the meta-analysis by Hart *et al.* (2007)<sup>7</sup> of 12 trials, which compared warfarin with antiplatelet therapy, 24% of patients had had previous stroke or TIA. Warfarin reduces the risk of recurrent stroke by about 40% compared with antiplatelet agents.

Among the 12 trials, the *ACTIVE-W (atrial fibrillation clopidogrel trial with irbersartan for prevention of vascular events)* (2006)<sup>10</sup> has shown that warfarin (target INR 2.0-3.0) is approximately 40% more efficacious than the combination of aspirin (75-100 mg/day) with clopidogrel (75 mg per day) (C+A).

Among patients with prior stroke or TIA (15% secondary prevention cohort of 6706 patients), the AR reduction of stroke with warfarin was 3.23% (stroke rate on warfarin 2.99% vs 6.22% on C+A).

Major bleedings occurred with a similar annual rate (2.75% on warfarin versus 2.63% on C+A).

The more recent *Birmingham atrial fibrillation treatment of the aged study* (BAFTA, 2007)<sup>11</sup> compared warfarin (target INR 2-3) with aspirin (75 mg/day). 13% of 973 patients had a history of stroke or TIA (secondary stroke prevention cohort). The in-

cidence of recurrent stroke was 3.1% on warfarin and 8.0% on aspirin, that is an AR reduction of 5%, which represents 50 fewer recurrent strokes per year per 1000 patients treated.

#### *Comments on vitamin K antagonists therapy*

OAC therapy with VKAs is the mainstay treatment for secondary stroke prevention in NVAF patients with an AR reduction of 8% vs placebo, of 5-6% vs aspirin, and of 3% vs dual antiplatelet therapy.

A decrease in the stroke rate over the years has been observed in patients treated with warfarin. This might be due to improved identification and treatment of vascular risk factors, differences in INR control, or differences in the populations of patients.

The disadvantages of VKAs are well known: narrow therapeutic window (INR 2-3), variability in dose-response, slow onset and offset of action, interactions with many drugs and foods rich in vitamin K. The low therapeutic index needs careful monitoring because an INR of 1.7 doubles the risk of ischemic stroke and the increase in bleeding becomes exponential for INR values >4.5.<sup>12</sup>

The fear of an intracranial hemorrhage or major bleeds, above all in elderly patients, and the concerns about poor patient compliance restricts more widespread use of warfarin therapy in clinical practice despite its recognized efficacy in stroke prevention.

It is estimated that approximately 50% of appropriate AF patients do not receive warfarin, and that 25% of patients who begin taking warfarin quit during the first year.<sup>13</sup>

In a recent Italian study of 7148 patients with AF admitted in cardiology and internal medicine hospital centers, OAC was prescribed in 55% of patients with NVAF (64% of cardiology patients and 46% of internal medicine patients).<sup>14</sup>

Furthermore, in real practice patients spend 30% to 50% of the treatment time outside the therapeutic range.<sup>15</sup>

The annual incidence, during VKA therapy, is 2-5% for major bleeding, 0.5-1% for fatal bleeding, and 0.2-0.4% for intracranial hemorrhages (ICH), varying with intensity of anticoagulation and age.<sup>16</sup>

In the BAFTA trial<sup>11</sup> (patients aged  $\geq 75$  years), the incidence of major extracranial hemorrhages was lower and no more hazardous than with aspirin (1.9% vs 2.0% per year). In this study, the annual risk of major hemorrhages rose with age both with warfarin and aspirin with an incidence of 3% in people aged  $\geq 85$  years.

A meta-analysis of patients aged  $\geq 75$  years showed that OAC therapy was more effective than aspirin for secondary stroke prevention (the annual rate of ischemic stroke was 4% for OAC and 10% for aspirin), but at the cost of higher risk of major bleedings (9

more major bleeds per 1000 patients treated per year).<sup>17</sup>

In a prospective study on very old patients ( $\geq 80$  years of age) on VKA treatment for AF treated in experienced centers, Poli *et al.*<sup>18</sup> found a low rate of bleedings (1.73 per 100 patients/year), explained at least in part by the good quality of the INR control.

Agarwal *et al.*,<sup>19</sup> analyzing randomized controlled trials (RCTs) of the last ten years, found that the incidence of stroke in patients with NVAF taking warfarin was 1.66% per year and the risk increased with progressively increasing CHADS<sub>2</sub> score in patients aged  $\geq 75$  years, in female patients and in patients with previous stroke or TIA. The risk of major bleeding varied from 1.40% to 3.4% per year and the risk of intracranial hemorrhage from 0.33% to 0.80% per year.

The risk of intracranial bleeding in real practice may be higher as in the RCT there is an underrepresentation of older patients who have the highest frequency of leukoaraiosis and amyloid angiopathy increasing the risk of ICH.<sup>20</sup>

### New oral anticoagulants

The new oral anticoagulants (NOAC) include direct thrombin inhibitors (dabigatran) and factor Xa antagonists (rivaroxaban, apixaban).

These agents can be given in fixed doses, do not require regular coagulation monitoring, have more rapid onset and offset and have few clinically relevant drug-drug interactions.

### Dabigatran for secondary stroke prevention related to non-valvular atrial fibrillation

*Dabigatranetexilate*, a prodrug of active dabigatran, is rapidly absorbed, achieving peak plasma concentration 1.5 h after oral ingestion with an elimination half-life of 12 to 17 h. After oral administration, it is rapidly hydrolyzed by esterases in plasma and liver to activate dabigatran through a mechanism that is independent from the cytochrome p450 pathway. Dabigatran elimination occurs up to 80% by

renal excretion and blood levels of the drug are influenced by renal function. Therefore patients with impaired renal function and low body weight may have a higher risk of bleeding. The risk of hemorrhage is increased also by dabigatran's interaction with p-glycoprotein inhibitors including verapamil, amiodarone, dronedarone and quinidine, which raise dabigatran serum concentration considerably. Plasma dabigatran levels fall below the therapeutic threshold 15 h after the administration of the final dose in patients without significant renal impairment.<sup>21</sup>

The *Randomized evaluation of long-term anticoagulant therapy (RE-LY)* trial (2009)<sup>22</sup> randomized 18,113 patients with non-NVAF and at least 1 risk factor for stroke to dabigatran 110 mg or 150 mg twice a day or warfarin (INR, 2 to 3), for approximately 2 years. Patients who had a creatinine clearance of less than 30 mL/min or liver disease were excluded from RE-LY.

Diener *et al.*<sup>23</sup> investigated the efficacy and safety of dabigatran (110 mg and 150 mg twice a day vs warfarin) on secondary stroke prevention in a *predefined subgroup analysis of RE-LY study* (20% of patients in the RE-LY study had had TIA or stroke at least 2 weeks before the randomization).

The study showed that (Table 1): i) the incidence of stroke or systemic embolism was not significantly reduced with 110 mg and 150 mg of dabigatran compared with warfarin; ii) there was a significant reduction in hemorrhagic stroke with 110 mg and 150 mg of dabigatran compared with warfarin; iii) there was a significant reduction in the rates of vascular death and all-cause mortality with dabigatran 110 mg, but not with dabigatran 150 mg, compared with warfarin; iv) dabigatran 110 mg, but not 150 mg, significantly reduced the risk of major bleeding compared with warfarin; v) the rate of intracranial hemorrhage was reduced significantly with 110 mg and 150 mg of dabigatran compared with warfarin; vi) gastrointestinal bleeding was significantly increased with 150 mg of dabigatran compared with warfarin; while the risk was similar between 110 mg of dabigatran and warfarin.<sup>23</sup>

**Table 1. Effects of dabigatran and warfarin on the incidence of stroke or systemic embolism and major bleeding (expressed as percent per year) in RE-LY patients with previous stroke or transient ischemic attack.**

$\beta$	Dabigatran 110 mg		Warfarin % per year	Dabigatran 150 mg	
	% per year	ARR		% per year	ARR
All cases of stroke or systemic embolism	2.32	0.46	2.78	2.07	0.71
Hemorrhagic stroke	0.08	0.69	0.77	0.20	0.57
Vascular death	1.90	1.10	3.00	2.97	0.03
Major bleeding	2.74	1.41	4.15	4.15	0
Intracranial bleeding	0.25	1.03	1.28	0.53	0.75
Gastrointestinal bleeding	1.39	0.02	1.41	2.32	0.91*

ARR, absolute risk reduction. \*Absolute risk increase. Data from Diener *et al.*, 2010.<sup>23</sup>

### Comments on dabigatran therapy

Overall, in patients with previous stroke or TIA, both 110 mg and 150 mg twice daily of dabigatran are similar to or more efficacious than warfarin, even though the difference is not statistically significant, with regard to the prevention of stroke and systemic embolism (approximately 5-7 fewer events/1000 patients/year), with a greater decrease in hemorrhagic stroke than in ischemic or unknown stroke. The dose of 110 mg reduces the risk of intracranial bleeding (approximately 10 fewer events/1000 patients/year) and of major bleeding, with a net clinical benefit when all vascular and bleeding events are combined. The dose of 150 mg also reduces the rate of intracranial bleeding (approximately 8 fewer events/1000 patients/year), but increases significantly gastrointestinal bleedings (excess of 9 events/1000 patients/year).

Wallentin *et al.*<sup>24</sup> analyzed the outcomes of the RE-LY Study in relation to the time in therapeutic range (TTR) of the warfarin population. Overall, patients on warfarin spent 64% of the time in the therapeutic range. They found that the rate of intracranial bleeding is lower with both doses of dabigatran compared to warfarin across all INR control ranges.

Eikelboom *et al.*<sup>25</sup> analyzed, in the RE-LY Study, the risks and benefits of dabigatran versus warfarin in older patients. The risk of bleeding increased with increasing age and with decreasing creatinine clearance. In patients aged >75 the risk of major bleeding with both doses of dabigatran was similar or higher compared with warfarin, whereas the risk of intracranial bleeding was lower, irrespective of age, with both doses of dabigatran compared with warfarin.

A recent reanalysis of intracranial bleeding in the RE-LY study confirmed lower rates of intracerebral hemorrhage in patients assigned to both doses of dabigatran than in warfarin patients.<sup>26</sup>

In the event of bleeding or other situations, the increase in activated partial thromboplastin time, prothrombin time and thrombin time (TT) can provide an approximation of excessive anticoagulant activity, while the INR test is insensitive to dabigatran. For a quantitative measurement of dabigatran plasma concentrations, only the dabigatran calibrated Hemoclot thrombin inhibitor assay (a diluted TT) is available.<sup>27</sup>

As there is no specific antidote, the event of major hemorrhage should be treated by discontinuation of the drug, induction of diuresis and, as in VKA-associated bleeding, the administration of prothrombin complex concentrate. In the murine model of dabigatran-associated intracerebral hemorrhage, prothrombin complex concentrate reduced hematoma size.<sup>28</sup>

The low plasma protein binding of dabigatran (<35%) suggests that dialysis may be useful although there is only limited experience with this approach.<sup>29</sup>

There is ongoing controversy as to whether throm-

bin inhibitors raise the risk of myocardial infarction. The main RE-LY study<sup>22</sup> showed a small increase in the rate of myocardial infarction with dabigatran (approximately an excess of 2 events/1000 patients/year). A recent reanalysis of patients' ECGs, however, identified 28 silent myocardial infarctions (distributed over the three groups), which were not included in the original analysis. When included in the data set, the numerical increase in myocardial infarction was no longer significant.<sup>30</sup>

Also Hohnloser *et al.*<sup>31</sup> described, in a sub-group analysis of the RE-LY trial, a non-significant increase in myocardial infarction with dabigatran compared to warfarin, but other myocardial ischemic events, including unstable angina, need for coronary revascularization, cardiac arrest, or cardiac death, were not increased.

The meta-analysis by Uchino and Hernandez of 7 randomized trials<sup>32</sup> confirmed a 33% higher relative risk of myocardial infarction in patients taking dabigatran (but with a very small absolute risk increase, *i.e.*, 0.27% per year).

Long-term data, after 2.3 years of additional treatment after the RE-LY trial, showed low and unchanged rates of stroke or systemic embolism on dabigatran 110 mg and 150 mg, including a low rate of hemorrhagic stroke. A higher rate of major bleeding was observed with dabigatran 150 mg compared with dabigatran 110 mg (RELY-ABLE, 2013).<sup>33</sup>

The Danish cohort study,<sup>34</sup> after dabigatran post-approval availability, confirmed in an *everyday clinical practice* population markedly lower intracranial bleeding rate with both doses of 110 mg and 150 mg of dabigatran compared with warfarin, and lower gastrointestinal bleeding only with dabigatran 110 mg.

### Apixaban for secondary stroke prevention related to non-valvular atrial fibrillation

*Apixaban*, a direct factor Xa inhibitor, is rapidly absorbed with a peak plasma concentration of 3 h and a half-life of 8 to 15 h. 25% of elimination is *via* renal excretion. Apixaban interacts only with drugs that are potent cytochrome CYP3A4 inducers (phenytoin or carbamazepine) or inhibitors (ketokonazole).<sup>35</sup>

The *Apixaban versus acetylsalicylic acid [ASA] to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES) trial* (2011)<sup>36</sup> was designed to determine the efficacy and safety of apixaban versus aspirin. Apixaban, at a fixed dose of 5 mg twice a day (or reduced dose of 2.5 mg twice a day in patients with a predefined risk profile), was compared with aspirin at a dose of 81 to 324 mg/day. Diener *et al.*<sup>37</sup> investigated the efficacy and the safety of apixaban, compared with aspirin, on secondary stroke prevention in 764 patients with AF and previous stroke or TIA (*pre-*

*specified subgroup analysis of the AVERROES trial).*

The main results were the following (Table 2): i) the incidence of all cases of stroke or systemic embolism was significantly reduced in the apixaban group compared with the aspirin group; ii) there was a non-significant reduction in the rate of vascular death and all-cause mortality with apixaban compared with aspirin; iii) the rate of all major bleedings was not significantly increased with apixaban; iv) the risk of gastrointestinal bleeding and intracranial hemorrhage was not statistically different between apixaban and aspirin.

In the *Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial* (2011),<sup>38</sup> apixaban at a dose of 5 mg twice daily (or a predefined reduced dose), was compared with warfarin (INR 2.0 to 3.0).

Easton *et al.*<sup>39</sup> investigated the efficacy and the safety of apixaban, compared with warfarin, in secondary stroke prevention, in 3436 patients with atrial fibrillation and previous stroke or TIA more than 30 days before random allocation (only 234 patients were included between 8 and 30 days after stroke) (*pre-specified subgroup analysis of the ARISTOTLE trial*).

The main results were the following (Table 3): i)

the incidence of all cases of stroke or systemic embolism was not significantly reduced in the apixaban group compared with warfarin group; ii) there was a significant reduction in hemorrhagic stroke in the apixaban group compared with warfarin; iii) the vascular death from any cause was similar in both groups; iv) the rate of intracranial bleeding was reduced significantly with apixaban compared with warfarin; v) the rate of gastrointestinal bleeding was not significantly different between apixaban and warfarin.<sup>39</sup>

#### *Comments on apixaban therapy*

In secondary stroke prevention in AF patients, apixaban 5 mg twice a day demonstrated superior efficacy over aspirin (approximately 65 fewer events/1000 patients/year) with a greater risk of major bleeding (excess of 10 events/1000 patients/year).<sup>37</sup>

Compared with warfarin, apixaban reduced the risk of stroke or systemic embolism (8 fewer events/1000 patients/year, mainly less hemorrhagic stroke) and caused less bleeding (approximately 10 fewer major bleedings/1000 patients/year) with a more substantial reduction in intracranial bleeding and a trend toward lower risk for gastrointestinal bleeding.<sup>38</sup>

**Table 2. Effects of apixaban and aspirin on the incidence of stroke or systemic embolism and major bleeding (expressed as percent per year) in AVERROES patients with previous stroke or transient ischemic attack.**

	Apixaban % per year	Aspirin % per year	ARR
All cases of stroke or systemic embolism	2.39	9.16	6.77
Hemorrhagic stroke	0.27	1.07	0.80
All-cause death	5.78	7.92	1.14
Major bleeding	4.10	2.89	1.21*
Intracranial bleeding	1.17	1.56	0.39
Gastrointestinal bleeding	0.84	1.31	0.47

ARR, absolute risk reduction. \*Absolute risk increase. Data from Diener *et al.*, 2012.<sup>37</sup>

**Table 3. Effects of apixaban and warfarin on the incidence of stroke or systemic embolism and major bleeding (expressed as percent per year) in ARISTOTLE patients with previous stroke or transient ischemic attack.**

	Apixaban % per year	Warfarin % per year	ARR
All cases of stroke or systemic embolism	2.46	3.24	0.78
Hemorrhagic stroke	0.40	1.00	0.60
Vascular death	2.35	2.41	0.06
Major bleeding	2.84	3.91	1.07
Intracranial bleeding	0.55	1.49	0.94
Gastrointestinal bleeding	0.66	0.80	0.14

ARR, absolute risk reduction. Data from Easton *et al.*, 2012.<sup>39</sup>

### Rivaroxaban for secondary stroke prevention related to non-valvular atrial fibrillation

*Rivaroxaban*, a direct factor Xa inhibitor, has a rapid onset of action with a time to peak of 3 hours and a half-life of 6 to 10 h. The drug is eliminated up to two thirds by the kidneys. Rivaroxaban has few interactions with other drugs with the exception of drugs that are potent cytochrome CYP3A4 inducers (phenytoin or carbamazepine) or inhibitors (ketokonazole).<sup>40</sup>

The *Rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonist for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF) trial*<sup>41</sup> compared rivaroxaban 20 mg once daily (or a reduced dose of 15 mg in patients with a creatinine clearance of 30-49 mL/min) with adjusted-dose warfarin (INR 2.0-3.0) in more than 14,000 high risk patients with NVAf (with a CHADS<sub>2</sub> score  $\geq 2$  and half with prior stroke). Hankey *et al.*<sup>42</sup> investigated the efficacy and safety of rivaroxaban compared with warfarin on secondary stroke prevention in 7468 patients with AF and previous stroke or TIA (*pre-specified subgroup analysis of the ROCKET AF trial*). The study included patients 14 days after acute stroke and 3 months after severe disabling stroke.

The main results were the following (Table 4): i) the incidence of all cases of stroke or systemic embolism was not significantly different between the rivaroxaban and warfarin group; ii) the rate of hemorrhagic stroke and vascular death was not different between the two groups; iii) the incidence of major bleeding was not different, but less fatal bleeding occurred with rivaroxaban; iv) the rate of intracranial hemorrhage was not significantly reduced with rivaroxaban compared with warfarin.<sup>42</sup>

#### Comments on rivaroxaban therapy

Rivaroxaban in secondary stroke prevention related to AF was not inferior to warfarin for the prevention of stroke and systemic embolism, with a trend toward less hemorrhagic stroke (warfarin patients

were in therapeutic range of INR only 58% of the time, less than in other trials).

With regard to safety, rivaroxaban has a comparable risk for major bleeding and a non-significant reduction of intracranial hemorrhage.<sup>42</sup>

#### Comments on the safety profile of new oral anticoagulation

All three new non-VKA anticoagulants are equivalent or even superior to warfarin for secondary stroke prevention related to AF, but the mean time in therapeutic range for warfarin treatment was 64%, 62% and 55% respectively in the three main trials of new anticoagulants, and the difference in relative efficacy versus warfarin, at least for dabigatran 110 mg and for rivaroxaban, was not significant when the time in therapeutic INR range increased over 65%.

With regard to safety, the new anticoagulants are associated with a decreased risk for intracranial bleeding (7-10 fewer hemorrhagic events/1000 patients/year for dabigatran and apixaban, and non-significant difference for rivaroxaban), whereas the risk of intracranial bleeding related to warfarin therapy is high even with excellent INR control.<sup>24</sup>

The risk of major bleeding is significantly reduced by dabigatran 110 mg (but not by the 150 mg dose) compared to warfarin. Apixaban shows a trend toward lower risk for gastrointestinal bleeding.

Banerjee *et al.*<sup>43</sup> showed that all three new anticoagulants appear superior to warfarin for the net clinical benefit (balancing ischemic stroke against intracranial hemorrhage) when risk of stroke and bleeding are both high as in secondary stroke prevention.

The meta-analysis of Ntaios *et al.*<sup>44</sup> of all three studies on new non-VKA anticoagulants in patients with AF and previous stroke or TIA showed a 50% significant reduction of hemorrhagic stroke with NOAC when compared with warfarin. With regard to safety, the non-VKAs were also associated with a significant reduction in intracranial bleedings compared with warfarin, and a trend of more gastrointestinal bleedings mainly due to high-dose dabigatran.

Schneeweiss *et al.*<sup>45</sup> by means of an adjusted indi-

**Table 4. Effects of rivaroxaban and warfarin on the incidence of stroke or systemic embolism and major bleeding (expressed as percent per year) in ROCKET AF patients with previous stroke or transient ischemic attack.**

	Rivaroxaban % per year	Warfarin % per year	ARR
All cases of stroke or systemic embolism	2.79	2.96	0.17
Hemorrhagic stroke	0.34	0.46	0.12
Vascular death	2.93	3.00	0.07
Major bleeding	3.13	3.22	0.09
Intracranial bleeding	0.59	0.80	0.21

ARR, absolute risk reduction. Data from Hankey *et al.*, 2012.<sup>42</sup>

rect comparison, found that apixaban had a significantly lower risk of major bleeding compared with dabigatran 150 mg or rivaroxaban among patients with CHADS<sub>2</sub> ≥ 3.

An indirect comparison analysis published by Rasmussen *et al.*<sup>46</sup> showed that, for secondary prevention, apixaban, rivaroxaban, and dabigatran had broadly similar efficacy for the main endpoints. Less hemorrhagic stroke, vascular death, major bleeding, and intracranial bleeding occurred with dabigatran 110 mg twice a day than with rivaroxaban.

However, indirect comparison can be exposed to potential flaws and only a direct head-to-head comparison trial would allow drawing valid conclusions.

Overall, the three new anticoagulants have good efficacy and safety profiles without the need for anticoagulation monitoring; therefore they offer a good therapeutic option especially for patients with NVAf and previous stroke or TIA. In fact, we know that previous stroke/TIA is one of the most important risk factors for anticoagulation-associated intracranial bleeding,<sup>3,4</sup> therefore this favorable safety profile of the new anticoagulants can have a major impact on clinical treatment of patients with previous stroke/TIA and AF. In these patients the net clinical benefit of NOAC is likely to be greater because of less intracranial bleeding.

Also the NOAC edoxaban (a direct acting oral factor Xa inhibition) showed a significant reduction in hemorrhagic stroke and other subtypes of intracranial bleeding compared with warfarin.<sup>47</sup>

The last comprehensive meta-analysis of all four NOAC recently published by Ruff *et al.*<sup>48</sup> confirmed that overall intracranial bleeding was reduced by half with NOAC compared with warfarin.

The lower risk of intracranial bleeding with NOAC compared with warfarin might be related to the different effect on blood coagulation. The new NOAC inhibit only one coagulation factor whereas warfarin affects the activity of factor II, VII, IX, and X in plasma and interferes with the formation of tissue factor-VII<sub>a</sub> complex particularly abundant in the brain.<sup>25</sup>

Even if NOAC do not have specific reversal agents, there is no evidence that major bleeding associated with NOAC has more serious clinical consequences than warfarin-associated bleeding.<sup>26,34,48</sup>

The management of patients on NOAC suffering from major bleeding should include the same interventions used with patients on warfarin.

The development of specific antidotes capable of neutralizing NOAC (*i.e.*, the recent monoclonal antibody idarucizumab for dabigatran) will offer an important treatment option.

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