For over half a century oral anticoagulation in atrial fibrillation (AF) was limited to the use of vitamin K antagonists (VKA). Although millions of patients have benefited from drugs like warfarin and phenprocoumon, they come with a large list of disadvantages/problems that result in substantial mortality/morbidity as well as underutilisation of anticoagulation (1). With the aim to avoid these problems the pharmaceutical industry has recently succeeded to develop oral anticoagulants that are prone to change the scope of anticoagulation dramatically, which is particularly important for the millions of patients with AF.

The new oral anticoagulants fall into two broad categories, the oral direct thrombin inhibitors (e.g. dabigatran) and the oral factor Xa inhibitors (e.g. rivaroxaban, apixaban) (1). Dabigatran was the first of the novel oral anticoagulants just recently approved by the FDA for stroke prevention in AF. The landmark phase 3 clinical trials for these substances, the RE-LY (dabigatran), AVERROES (apixaban) and ROCKET-AF (rivaroxaban) trials, are the focus of this article, given the extensive debates and discussions over comparing their trial designs, study populations and their results.

### RE-LY

RE-LY (Randomised Evaluation of Long term anticoagulant therapy) was a randomised open-label clinical phase III trial comparing fixed blinded doses of dabigatran (110 mg or 150 mg twice daily) with adjusted dose warfarin (international normalised ratio [INR] 2.0–3.0) (2). A total of 18,113 patients with non-valvular AF within the last six months prior to randomisation and at least one additional risk factor were randomised. A total of 31.9% of the patients had a CHADS2 score of 0 or 1, 35.6% had a score of 2, and 32.5% had a score of 3–6, respectively (2). Patients with a stroke within 14 days of randomisation and patients with a creatinine clearance of <30 ml/minute were excluded. By trial design, half the patients were warfarin naïve, and the efficacy and safety results in warfarin naïve patients were similar to that seen in warfarin experienced patients (3).

The 150 mg BID dabigatran treatment was superior to warfarin treatment. The primary outcome of stroke or systemic embolism occurred in 1.71% of patients per year in the warfarin group, in 1.54% of patients per year in the 110 mg BID dabigatran group (p=0.34), and in 1.11% of patients per year in the 150 mg BID dabigatran group (p<0.001), respectively. The rate of major bleeding was 3.57% per year in patients treated with warfarin, 2.87% per year in patients treated with 110 mg BID dabigatran (p=0.003) and 3.32% in patients treated with 150 mg BID dabigatran (p=0.31) (4). The rate of haemorrhagic stroke was reduced with both doses of dabigatran compared to warfarin treatment (0.12% per year with 110 mg and 0.10% per year with 150 mg vs. 0.38% with warfarin, p<0.001).

Warfarin needs to be monitored by determining the INR, but dabigatran does not require monitoring. A recently published subgroup analysis of the RE-LY trial found no significant interactions between the time within the therapeutic range with warfarin treatment and both doses of dabigatran, thereby confirming the benefit of the 150 mg BID dose of dabigatran at reducing stroke independent of the quality of warfarin treatment (5). Another subgroup analysis of patients with prior stroke or transient ischaemic attack (TIA) showed non-inferiority of both doses of dabigatran compared with warfarin in preventing stroke, but did not show superiority of dabigatran in this subgroup of patients with a CHADS2 score of ≥2 (6).

### AVERROES

The AVERROES (Apixaban versus ASA to reduce the risk of stroke) trial was a double-blind, randomised comparison of the oral factor Xa inhibitor apixaban versus aspirin for stroke prevention in patients with atrial fibrillation who were not suitable for oral anticoagulation with a VKA. Patients were randomised to receive either apixaban 5 mg BID or aspirin (81–324 mg QD). 5600 Patients were enrolled in AVERROES, the study was terminated early after an interim analysis revealed an over 50% reduction in the primary endpoint of stroke or systemic embolism in patients treated with apixaban compared to patients receiving aspirin (7, 8).

Inclusion criteria were age >50 years, documented AF within six months prior enrolment and at least on risk factor for stroke. Furthermore patients had to be judged unsuitable for oral anticoagulation with a VKA either by demonstrating that previous therapy was unsuitable or by the expectation that initiation of therapy would be unsuitable (7). The AVERROES data demonstrated that 39.5% of randomised patients had received prior oral VKA...
and 60.5% had not. A total of 72% of all randomised patients had a CHADS\textsubscript{2} score of ≤2 and 28% had a score of ≥3 (8).

The primary endpoint of stroke and systemic embolism occurred in 3.9% per year of aspirin-treated patients versus 1.7% per year with apixaban treatment (p<0.001). The rate of major bleeding was 1.2% for aspirin and 1.4% for apixaban (p=0.33). There was no significant difference in haemorrhagic stroke with a rate of 0.2% per year in both treatment groups. Also, aspirin was significantly less well tolerated compared to apixaban. Thus, in patients who fail VKA or refuse VKA, aspirin is clearly an inferior drug for stroke prevention, and is not safer in terms of major haemorrhage or intracranial bleeding – and is less well tolerated than the oral anticoagulant, apixaban.

ROCKET-AF

In ROCKET-AF (Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) a total of 14,264 patients with AF were randomised in a double-blind, double dummy manner to receive either the factor Xa inhibitor rivaroxaban 20 mg QD (15 mg QD if creatinine clearance 30–49 ml/min) and 60.5% had not. A total of 72% of all randomised patients had a CHADS\textsubscript{2} score of ≤2 and 28% had a score of ≥3 (8).

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The primary endpoint of stroke and non-CNS embolism occurred in 2.12% per year in patients treated with rivaroxaban and in 2.42% of patients treated with war-
farin (p=0.117). Non-inferiority was established with an on-treatment analysis, and rivaroxaban was clearly non-inferior to warfarin; however, when assessed with an intention to treat analysis for superiority, rivaroxaban did not reach non-inferiority criteria compared to warfarin (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.74–1.03) although superiority was achieved with the less conservative superiority on-treatment analysis (HR 0.79, 95%CI 0.65–0.95) (9). Major bleeding occurred in 3.6% of patients in the rivaroxaban group versus 3.45% in the warfarin-treated group (p=0.576). The rate of intracranial haemorrhage was significantly lower with rivaroxaban treatment compared to warfarin treatment (0.49% vs. 0.74%, p=0.019).

Commentary

The RE-LY trial demonstrated that dabigatran 150 mg BID is a real alternative to warfarin in AF patients with superior efficacy for the prevention of stroke or systemic embolism. Furthermore, a recent network meta-analysis and indirect comparison of dabigatran with aspirin or the combination of aspirin and clopidogrel suggests that dabigatran is also very effective in comparison to antiplatelet therapy, without a significant increase in intra- or extracranial haemorrhage (10).

The majority of patients enrolled in RE-LY had a CHADS2 score of ≤2 (2). A subgroup analysis in patients with prior stroke who predominately had a CHADS2 score of ≥3 did not demonstrate superiority of 150 mg BID dabigatran although still showing non-inferiority compared to warfarin (6). Furthermore in this subgroup, the 110 mg BID dose was similar to the 150 mg BID dose for any of the endpoints except for a reduction in vascular death (p=0.038) in patients with previous stroke or TIA (6). Patients with established atherothrombosis often (11.7%) present with AF (11), thereby representing a group that is at high risk for bleeding events while simultaneously also being at a high risk for stroke or systemic embolism. This patient group traditionally experiences under-utilisation of oral anticoagulation as clinicians are in fear of bleeding events under triple therapy (dual antiplatelet therapy and oral anticoagulation) (11, 12). Thus, the available novel oral anticoagulant dabigatran may represent a viable alternative to warfarin in this setting. However, it is still not clear whether the increased rate of myocardial infarction in patients that were treated with dabigatran in the RE-LY trial are a statistical aberrance (4) or due to a protective effect of warfarin against myocardial infarction (13). In the original report of the RE-LY data (2) the rate of myocardial infarction was significantly increased in the patients treated with 150 mg BID dabigatran compared to the warfarin group; however, a more detailed analysis including silent myocardial infarctions based on the new appearance of pathological electrocardiographic Q-waves did not reveal significant differences between dabigatran and warfarin (4).

The results of the AVERROES trial strongly suggest that the factor Xa inhibitor apixaban could replace aspirin in patients which are judged to be not suitable for oral anticoagulation with warfarin. Apixaban has a half-life comparable to dabigatran and is cleared via multiple elimination pathways suggesting minor predisposition for drug interactions (14). Similar to dabigatran in the RE-LY trial, apixaban was administered BID in AVERROES. However, apixaban is not yet approved and as suggested by a meta-analysis (10) it remains to be determined whether patients unsuitable for warfarin treatment would be suitable for dabigatan, the only currently Food and Drug Administration (FDA) approved alternative to warfarin in patients with AF.

Rivaroxaban is currently the first novel oral anticoagulant from the group of direct factor Xa inhibitors that has been shown to be at least non-inferior to warfarin for the prevention of stroke in moderate to high risk patients with AF (9). Interestingly, although the half-life is substantially lower compared to dabigatran, in ROCKET-AF rivaroxaban was administered as a dose of 20 mg QD (15). However, despite the potential variance of the level of factor Xa inhibition during the 24-hour (h) period following oral intake, rivaroxaban provided a protection against stroke and non-central nervous system (CNS) embolism equally (if not better) to warfarin in moderate to high-risk patients. The control group of patients in ROCKET-AF had a median time within the INR range of 2.0–3.0 of 57.8%. In contrast to this, the control group in RE-LY was slightly better controlled in their warfarin therapy with a median time within the therapeutic range of 67%.

The RE-LY trial was conducted as a prospective randomised open trial with blinded endpoint evaluation (PROBE) design, whilst the ROCKET-AF and AVERROES trials were conducted in a double blind design, with (in the case of ROCKET-AF) sham INRs (7, 16). Arguments for and against a PROBE design (vs. double blind) have been made (17). Of note, four of the early placebo-controlled trials against warfarin were open-label trials, and the drug effects in the open-label trials were comparable with the SPINAF trial, the only completed double-blind AF stroke trial and the double-blind Canadian study, which was prematurely terminated. An open design would allow management of inter-current events based on the characteristics of the anticoagulant agent rather than manage all patients as if they were on warfarin, and is also more likely to be representative of true differences in the management of warfarin and dabigatran in daily practice, and this is clearly evident by the availability of cardioversion data whilst taking dabigatran, as a post-hoc subgroup observational study (18).

In contrast, a double-blind methodology is considered to be complex (and expensive), requiring dummy/sham INRs and management assuming that patients are assigned to warfarin. However, this design is still regarded by the purists as the best way of conducting a trial to ensure lack of bias. An often-quoted example is the SPORTIF programme with the oral direct thrombin inhibitor, ximelagatan, where the SPORTIF V trial was a double blind trial conducted in North America, whilst the SPORTIF III trial was a PROBE design trial conducted in the rest of the world, excluding North America (19). Whilst the primary endpoint rate for ximelagatan was similar in both trials, event rates on warfarin were different, with a trend towards being higher than ximelagatan in
SPORTIF III and lower In SPORTIF V. Nonetheless, a pre-planned pooled analysis showed non-inferiority of ximelagatran to warfarin, the differences in event rates on warfarin may reflect differences in blood pressure control and other cardiovascular prevention strategies, and only the double blind SPORTIF V trial was considered by the FDA approval process.

Ultimately, the ‘real’ test of a PROBE versus double-blind design would come with regulatory approval (or not) and the FDA did approve dabigatran 150 mg BID for stroke prevention in AF, although superior efficacy was not allowed in the approval label. Of interest, the FDA also approved 75 mg BID for patients with a creatinine clearance of 15–30 ml/min, even though this dose has not been tested in a trial setting or in this specific patient population (20).

One of the most challenging questions for the new oral anticoagulant reagents is the question of once or twice a day dosing. Dabigatran with a terminal half-life between 8.8 to 13 h and BID application reveals a drop of only around 50% between peak and trough plasma concentration (1, 21). Rivaroxaban with a half-life of 3.2–9.1 h and a once daily application clearly has a higher difference between peak and trough concentration (14). Of note, apixaban was given twice a day and does have a half-life of 8–15 h (1, 14). Whether these striking differences in the 24-h coverage of anticoagulant effects are relevant in a prophylactic setting such as the prevention of thrombus development in the left atrium during AF, where clinical practice assumes that several hours (hence the 48-h guideline) are needed to build a thrombus, is currently unclear. Overall, only a head-to-head comparison of rivaroxaban and dabigatran in patients with AF would allow drawing scientifically valid conclusions about which drug we should use in which setting and population of patients. Nonetheless in the light of a recently published subgroup analysis of the RE-LY trial in patients with prior stroke or TIA (6), rivaroxaban appears to be similarly effective as the 150 mg BID dose of dabigatran in high-risk patients.

What do current guidelines say?

Both the Canadian Cardiovascular Society and the European Society of Cardiology recently updated their guidelines for the treatment of patients with AF. The Canadian Cardiovascular Society gives a conditional recommendation of high quality of evidence that when oral anticoagulation is indicated, most patients should receive dabigatran in preference to warfarin. Furthermore it is recommended that the 150 mg BID dose of dabigatran should be preferred to the 110 mg BID dose (see www.cccsguidelineprograms.ca).

The European Society of Cardiology includes the use of dabigatran in their updated guidelines as an alternative to oral anticoagulation with VKA in patients in whom oral anticoagulation is recommended. Also the European guidelines contain a more detailed advice on the use of the two different studied doses of dabigatran: Patients judged to be at a low risk of bleeding, which could be assessed with the HAS-BLED score (22), should receive 150 mg BID dabigatran. Patients with an elevated risk of bleeding (HAS BLED score ≥3) are recommended to receive the 110 mg BID dabigatran dose (23).

The new American Heart Association guidelines on stroke, which were published online two days after the FDA approval for dabigatran for stroke prevention in patients with AF, do not yet contain a specific recommendation for the use of dabigatran in patients with AF. However, they note that an alternative to warfarin without significant drug and food interactions, which does not require coagulation monitoring, would represent a major advance for patients with AF who are at risk for stroke (24).

Conclusion

With the recent FDA, Canadian and European approvals of dabigatran etexilate for the prevention of stroke in patients with AF, a new era in oral anticoagulation has begun. Dabigatran is a real alternative to warfarin and has been shown to be superior to warfarin at a dose of 150 mg BID in patients with low to moderate risk. Furthermore, there is no need to monitor anticoagulant activity in patients treated with dabigatran, which itself is a major advance and could have potential implications for patients that were judged unsuitable for oral anticoagulation with warfarin.

Alternatively, this patient population (that is, those who ‘fail’ or refuse warfarin) could substantially benefit in the near future from treatment with apixaban as the AVERROES trial demonstrated a dramatic reduction in stroke or systemic embolism in comparison to aspirin. Rivaroxaban inhibits the coagulation cascade upstream of dabigatran and has been shown to be non-inferior to warfarin with a single oral dose per day in patients with AF and at moderate to high risk for stroke. Once we see the approval of oral factor Xa inhibitors for the prevention of stroke in AF, differences in pharmacokinetic and potential side effects are likely to influence the decision about the most suited oral anticoagulant drug for the individual patient. Of note, both dabigatran and rivaroxaban are associated with less intracranial bleeding, compared to warfarin. Overall, the new oral anticoagulants represent a long sought-after advance in medical therapy and are predicted to safe lives and prevent disabilities in thousands of patients with AF.

References


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