Summary

Atrial fibrillation is the most common sustained cardiac arrhythmia. Thromboembolic events related to atrial fibrillation result in significant morbidity, mortality and increases in the cost of healthcare. For decades, vitamin K antagonists have been the mainstay of long-term oral thromboprophylactic anticoagulant therapy. Although these drugs are effective, the narrow therapeutic range, the numerous drug-drug and drug-food interactions constitute limitations, which have driven the development of new anticoagulant agents. The emerging oral anticoagulant agents are target selective, have more predictable pharmacokinetic and pharmacodynamic parameters and do not require routine monitoring. Recent trials have demonstrated the safety and efficacy of the new direct thrombin inhibitor dabigatran as well as for the selective factor Xa inhibitors rivaroxaban and apixaban. This article reviews the current literature and highlights the challenges associated with the use of new oral anticoagulants for atrial fibrillation in daily practice.

Key words: atrial fibrillation; stroke; oral anticoagulation

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with increasing prevalence and incidence with age and a considerable impact on morbidity and mortality [1, 2]. The major complication of AF is the occurrence of stroke. AF is associated with a 5-fold increased stroke risk overall and a 2-fold higher risk of stroke after adjustment for other risk factors [3]. The average annual rate of stroke among patients with AF without implementation of any type of preventive treatment is 5% [4]. AF-related strokes are more severe and associated with increased morbidity and mortality in comparison with non-AF-related strokes [5, 6]. It is also worth noting that based on the results of the on-treatment analysis of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study, the occurrence of stroke or transient ischae mic attack (TIA) is an independent predictor of mortality among patients with AF and the use of anticoagulants markedly reduces the risk of death [7]. Therefore, antithrombotic management is a mainstay in the treatment of patients with AF.

For decades, vitamin K antagonists (VKAs) have been the main treatment option for the prevention of thromboembolic events among patients with AF. Warfarin has been shown to reduce the risk of stroke by 64% in comparison with placebo or no treatment in patients with AF [8]. Despite the fact that the use of warfarin is independently associated with improved survival among patients with AF, the actual prescription rate of VKA is limited from 48 to 65% of suitable anticoagulation candidates [9–11]. The considerable under-utilisation of VKA is due to the limitations of VKA treatment, such as narrow therapeutic range, drug and food interactions, slow onset of action, and requirement of coagulation monitoring [12]. Thus, use of VKA represents a therapeutic challenge for both patients and physicians, due to the concerns about suboptimal treatment monitoring and increased risk of haemorrhagic complications. Efficacy and safety of anticoagulation vary in relation to the quality of control of the international normalised ratio (INR). Prolonged time in the target INR range of 2.0 to 3.0 (time in therapeutic range [TTR]) is associated with reduced risk of ischaemic stroke, major haemorrhage, and reduced mortality rates [13, 14]. However, in a recent meta-analysis, TTR reached only 55% in patients with AF, with even poorer control among those treated in a community care setting [11]. Some limitations are certainly defined by the treating physician or the medical infrastructure. For instance, achievable TTR values of 70 to 90% have been demonstrated in Scandinavian cohort studies. The abovementioned limitations encountered with the use of VKA in patients with AF have prompted inten-
sive research for novel anticoagulants. Two main classes of anticoagulant agents have emerged, targeting key factors for the coagulation cascade: thrombin (FIIa) and the activated factor Xa. The oral direct thrombin inhibitor, dabigatran etexilate, is a representative of the first class. The second group of Xa inhibitors includes several agents at different stages of clinical development, with rivaroxaban and apixaban having already completed phase III trials with results that hold promise for use in everyday clinical practice and edoxaban in a runner-up position. This review focuses on recent trials investigating these substances for stroke prevention in AF.

**Oral thrombin inhibition: dabigatran etexilate**

Dabigatran etexilate is an oral direct thrombin inhibitor, with a predictable anticoagulant effect that obviates the need for regular coagulation monitoring and lack of clinically meaningful drug and food interactions. The drug has a half-life of up to 17 hours with a twice-daily dosing regimen. After an extensive clinical programme for prevention of thromboembolism in orthopaedic patients, the Randomized Evaluation of Long-term anticoagulation therapy (RELY) trial, a large, open-label, phase III trial, compared 2 different doses of dabigatran given twice daily (110 and 150 mg) versus warfarin (target INR 2.0–3.0) in patients with AF with a primary efficacy endpoint of stroke or systemic embolism and a primary safety endpoint of major bleeding [15]. Event rates were 1.69% per year under treatment with warfarin, compared to 1.53% per year for dabigatran 110 mg (relative risk (RR), 0.91; 95% confidence intervals (CI), 0.74–1.11; p <0.001 for non-inferiority) and 1.11% per year in the group that received dabigatran 150 mg (RR 0.66; 95% CI 0.53–0.82; p <0.001 for superiority). The rate of major bleeding was 3.36% per year in the warfarin group, compared with 2.71% per year in the group receiving 110 mg of dabigatran (RR 0.80; 95% CI 0.69–0.93; p = 0.003) and 3.11% per year in the group receiving 150 mg of dabigatran (RR 0.93; 95% CI 0.81–1.07; p = 0.31). The rates of intracranial haemorrhages were 0.7% per year in the warfarin group, compared to 0.2% per year with dabigatran 110 mg (RR 0.31; 95% CI 0.20–0.47; p <0.001) and 0.3% per year with 150 mg of dabigatran (RR 0.40; 95% CI 0.27–0.60; p <0.001). The significantly lower rate of intracranial bleeding was consistent in both doses of dabigatran irrespective of the level of TTR achieved. The mortality rate was 4.13% per year in the warfarin group, compared with 3.75% per year with 110 mg of dabigatran and 3.64% per year with 150 mg of dabigatran. Whether the slightly increased myocardial infarction signal is relevant (0.82% vs 0.64% p = 0.09) is subject of discussion. In recent guidelines issued by the European Society of Cardiology (ESC), dabigatran was proposed as an alternative to adjusted-dose VKA therapy in patients with AF in need of thromboprophylaxis. Recommendations on dose selection have been introduced on the basis of individual bleeding risk as assessed by HASBLED score. The 150 mg dose is indicated for patients with low bleeding risk (score 0–2), while the 110 mg dose is reserved for high-risk patients (score >3). In Canada, dabigatran gained approval for prevention of stroke and systemic embolism in patients with AF with the 110 mg bid dose recommended for elderly patients >80 years and patients at high risk of bleeding. On the other hand, the Food and Drug Administration (FDA) approved only the 150 mg bid dabigatran dose, with a dosing recommendation of 75 mg bid in patients with severe renal insufficiency (creatinine clearance 15–30 ml/min), triggering controversy regarding the decision to reject the lower dabigatran dose. The FDA reported that the single approval for the 150 mg dose was justified by the trade-off between prevention of stroke and risk of haemorrhage. Concerns were raised that the fear of bleeding would lead to an inappropriately high prescription rate of the lower dose resulting in inferior efficacy.

**Oral factor Xa inhibitors**

**Rivaroxaban**

Rivaroxaban is an oral FXa inhibitor that inhibits FXa in its free and prothrombin-bound states. In the double blinded “Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation” (ROCKET AF) study, rivaroxaban 20 mg once daily (or 15 mg daily for patients with creatinine clearance 30–45 ml/min) was compared with INR-adjusted warfarin for stroke prevention in AF [16]. Concerning the primary endpoint, stroke or systemic embolism, rivaroxaban proved non-inferior when compared with warfarin (HR 0.79; 95% CI 0.66–0.96; p <0.001) with event rates of 1.71 and 2.16% per year, respectively. In the on-treatment analysis rivaroxaban demonstrated superiority even to warfarin (HR 0.79; 95% CI 0.66–0.96; p = 0.001) with event rates of 1.7% and 2.15%, respectively. However, in the intention-to-treat analysis, statistical superiority was not observed with yearly event rates of 2.12% with rivaroxaban and 2.42% with warfarin (HR 0.88; 95% CI 0.74–1.03; p = 0.117). This difference between the intention-to-treat and the on-treatment analyses with regard to the superiority of rivaroxaban is likely due to several factors. Probably in the intention-to-treat analysis, the long period during which events were recorded following discontinuation of rivaroxaban might have introduced events in both groups leading to loss of significance in this analysis. On the other hand the poor adherence to rivaroxaban raised concerns about the relevance of the on-treatment analysis in the real-world clinical prac-
than one third of patients were considered unsuitable due to their own refusal to take VKA. The conclusion of AVERROES is that whenever aspirin is the only option for stroke prevention in patients with AF, apixaban should be preferred. The large phase III trial Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) was designed to compare apixaban 5 mg twice a day versus warfarin (INR 2.0–3.0) for stroke prevention in patients with AF [19]. All enrolled patients had at least one other risk factor for stroke, such as age ≥75 years, hypertension, symptomatic heart failure within the previous 3 months, or previous stroke or systemic embolism. Apixaban was administered at 5 mg or 2.5 mg in patients older than 80 years, with a body weight less than 60 kg or a serum creatinine level above 133 μmol/l. The primary efficacy outcome of the trial – stroke or systemic embolism – occurred in fewer patients assigned to apixaban as opposed to warfarin (HR 0.79; 95% CI 0.66–0.95; p <0.001 for non-inferiority and p = 0.01 for superiority of apixaban). This apixaban-associated reduction in the primary efficacy outcome was consistent across all major subgroups. The apparent better efficacy of apixaban over warfarin resulted from a lower rate of haemorrhagic stroke with the oral factor Xa inhibitor (HR 0.51; 95% CI 0.35–0.75; p <0.001); neither rates of ischaemic or uncertain type of stroke (HR 0.92; 95% CI 0.74–1.13; p = 0.42) nor rates of systemic embolism (HR 0.87; 95% CI 0.44–1.75; p = 0.70) were significantly different between the two treatment arms. The key secondary efficacy outcome, all-cause mortality, was also reduced in the apixaban group (HR 0.89; 95% CI 0.80–0.998; p = 0.047). Major bleeding, the primary safety outcome of the trial, was significantly lower in the apixaban group than in the warfarin group (HR 0.69; 95% CI 0.60–0.80; p <0.001). This finding was consistent across all major subgroups except when presence of diabetes mellitus was considered. Greater reductions were found in individuals who did not have diabetes compared with patients with the disease. All other assessed classifications of bleeding, including GUSTO severe bleeding, GUSTO moderate or severe bleeding, TIMI major bleeding, TIMI major or minor bleeding, and any bleeding, were also substantially lower in the apixaban group.

Edoxaban, betrixaban

Edoxaban is another promising factor direct Xa inhibitor with a half-life of 8 to 10 hours that is mainly eliminated via the renal route. A large phase III trial (Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation, ENGAGE AF TIMI 48) comparing 2 different doses of edoxaban versus warfarin for prevention of stroke and systemic embolism in patients with AF has completed recruitment and study completion is estimated in March 2012. Patients were randomised to edoxaban 60 mg (CHADS2 risk score
Based on these findings, phase-III clinical trials are currently planned by the distributing pharmaceutical company.

A challenge to face: which anticoagulant to choose?

As the list of novel anticoagulants is increasing, physicians will face the challenge of which agent to prescribe. While only head-to-head comparisons can provide evidence-based decisions, indirect comparison of treatment efficacy and safety of novel anticoagulants based on the existing trials is prone to bias and misleading.

Study designs

Differences in study design remain a matter of debate. The RELY trial was a prospective randomised open trial with blinded end point evaluation (PROBE) design with blinded patient randomisation to different dabigatran doses, while AVERROES, ARISTOTLE, and the ROCKET-AF trial were double-blinded. Although the double-blind design is a priori, considered ideal due to elimination of bias, the PROBE trial in patients with AF. Based on these findings, phase-III clinical trials are currently planned by the distributing pharmaceutical company.

### Table 1

Characteristics of current oral anticoagulants.

<table>
<thead>
<tr>
<th></th>
<th>Warfarin/phenprocoumon</th>
<th>Rivaroxaban</th>
<th>Dabigatran etexilate</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Impaired synthesis of vitamin K-dependent coagulation factors</td>
<td>Direct factor Xa inhibition</td>
<td>Direct thrombin inhibition</td>
<td>Direct factor Xa inhibition</td>
<td>Direct factor Xa inhibition</td>
</tr>
<tr>
<td>Formulation</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Dose adjustment</td>
<td>Dependent on individual INR values</td>
<td>Dose adjustment for CrCl</td>
<td>Dose adjustment for age and CrCl</td>
<td>Dose adjustment for age, CrCl and body weight</td>
<td>Dose adjustment CrCl and body weight</td>
</tr>
<tr>
<td>Onset of action</td>
<td>36–72 h</td>
<td>2–4 h</td>
<td>0.5–2 h</td>
<td>1–3 h</td>
<td>1–3 h</td>
</tr>
<tr>
<td>Half-life</td>
<td>20–60 h</td>
<td>9–13 h</td>
<td>12–14 h</td>
<td>8–15 h</td>
<td>9–11 h</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Unpredictable and individual</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>Potential drug interactions</td>
<td>CYP 3A4 inhibitors</td>
<td>CYP 3A4 and p-gp inhibitors</td>
<td>p-gp inhibitors</td>
<td>CYP 3A4 inhibitors</td>
<td>CYP 3A4 and p-gp inhibitors</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Routine monitoring required</td>
<td>No routine monitoring required</td>
<td>No routine monitoring required</td>
<td>No routine monitoring required</td>
<td>No routine monitoring required</td>
</tr>
<tr>
<td>Renal elimination</td>
<td>92% (inactive metabolites)</td>
<td>33%</td>
<td>80%</td>
<td>40%</td>
<td>35%</td>
</tr>
<tr>
<td>Antagonists</td>
<td>Vitamine K, FFP, PCC</td>
<td>PCC, FFP, rFVIIa</td>
<td>Experimental antibody, FFP, PCC?</td>
<td>PCC and FFP, specific antidote in development</td>
<td>PCC and FFP, specific antidote in development</td>
</tr>
<tr>
<td>Approval for non-valvular AF</td>
<td>Marketed</td>
<td>Marketed (USA)</td>
<td>Marketed (Japan, USA, EU)</td>
<td>Expected</td>
<td>On-going phase III trial</td>
</tr>
</tbody>
</table>

INR = international normalised ratio; CrCl = creatinine clearance; CYP 3A4 = Cytochrome P450 3A4; p-gp = p-glycoprotein; FFP = fresh frozen plasma; PCC = prothrombin complex concentrates.

Examples of corresponding drug classes:
- CYP 3A4 inhibitors: ritonavir, indinavir, clarithromycin, ketoconazole, verapamil, diltiazem.
- p-gp inhibitors: verapamil, cyclosporine, amiodarone.
Patients, none of these patients were included in ROCKET-AF. Whereas 87% of the patients included in ROCKET-AF had a CHADS2 score of 3 or more, their proportion within the study population was 32% in RELY and 30% in ARISTOTLE. Prior stroke, TIA, or systemic embolism occurred in 55% of the patients in ROCKET-AF and was about 19–20% in RELY and ARISTOTLE. These differences in baseline characteristics may explain the lower mean TTR achieved in the ROCKET-AF control group (55%) compared with the RELY (64%) and ARISTOTLE (62%) trials. Therefore, cross trial comparisons of TTR are hampered by the differences between the study populations.

Dosing regimen and drug compliance

Differences in dosing regimen may considerably affect drug compliance. In this regard, the once-daily dosing regimen of rivaroxaban and edoxaban offers a practical advantage in terms of convenience and patient compliance over the twice daily regimen of dabigatran and apixaban. This argument is further strengthened by the fact that treatment with anticoagulants is lifelong, in patients who usually feel well and therefore carry a high risk of missing doses and exposing themselves to the risk of breakthrough thrombosis.

Managing bleeding complications

Due to their predictable pharmacodynamics, this new generation of anticoagulants does not require regular monitoring. However, despite the clinical benefits of these drugs, bleeding remains a feared complication because there are limited strategies for reversal of the anticoagulant effects of these agents, especially in emergent cases when immediate reversal is necessary. Laboratory assessments of anticoagulant effect can be monitored by the activated prothrombin time and thrombin time, ecarin clotting time, chromogenic FX assays, or anti-FXa assay, although none of these

<table>
<thead>
<tr>
<th>Drug</th>
<th>RELY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE AF-TIMI 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td>Dose</td>
<td>150 mg / 110 mg</td>
<td>20 mg /15 mg</td>
<td>5 mg</td>
<td>60 mg / 30 mg</td>
</tr>
<tr>
<td>Frequency</td>
<td>Twice daily</td>
<td>Once a day</td>
<td>Twice daily</td>
<td>Once a day</td>
</tr>
<tr>
<td>Study design</td>
<td>PROBE</td>
<td>Double blinded</td>
<td>Double blinded</td>
<td>Double blinded</td>
</tr>
<tr>
<td>Enrolled patients</td>
<td>18 113</td>
<td>14 266</td>
<td>18 206</td>
<td>&gt;21 000</td>
</tr>
<tr>
<td>AF criteria</td>
<td>One episode within 6 months</td>
<td>At least two episodes within 6 months</td>
<td>At least two episodes within 12 months</td>
<td>One episode within last 12 months</td>
</tr>
<tr>
<td>VKA naive %</td>
<td>50%</td>
<td>38%</td>
<td>40%</td>
<td>40% (goal)</td>
</tr>
<tr>
<td>Mean CHADS2 Score</td>
<td>2.1 / 2.2</td>
<td>3.5</td>
<td>2.1</td>
<td>Not available</td>
</tr>
<tr>
<td>Follow up duration (median)</td>
<td>2 years</td>
<td>1.94 years</td>
<td>1.8 years</td>
<td>Not available</td>
</tr>
</tbody>
</table>

**Table 2**

Characteristics of phase III trials.

- **AF** = atrial fibrillation; **VKA** = vitamin K antagonists.
methods have been standardised and approved by authorities for evaluation of the anticoagulant level of this new class of drugs.

In the case of bleeding complications, because of the lack of available antidote, discontinuation of the drug, mechanical compression, and administration of transfusional represent the mainstay of treatment. Activated charcoal may also constitute an option in the case of a recent overdose. In an open-label study, dabigatran was given to six patients with end-stage renal failure on haemodialysis, and it was estimated that two-thirds of the drug could be removed by dialysis within two hours of administration [22]. However, because rivaroxaban and apixaban are bound to plasma proteins (95% and 86% respectively), dialysis is not an option for elimination of these agents. In animal models, recombinant FVIIa, activated prothrombin complex concentrates (APCC), and PCC have been shown to reverse the anticoagulant effects of factor Xa inhibitors [23–25]. The use of recombinant activated factor VII, provided inconsistent results in clinical trials, suggesting that its use in the emergent setting is currently not well established. Recombinant FXa concentrate is another potential antidote; however, no interventions have been shown to reverse clinical bleeding with these agents so far [26].

In a more recent clinical study, the use of prothrombin complex concentrates was shown to effectively reverse the anticoagulant effects of rivaroxaban but not dabigatran [27]. Rivaroxaban prolonged the activated prothrombin time and PCCs were able to immediately reverse this prolongation in healthy volunteers. Similar results were seen when the endogenous thrombin potential was used as a measure of anticoagulant effect. In the case of dabigatran, however, similar rates of reversal were not seen, implying that PCCs are not effective at reversing its anticoagulant effects. Although this trial may have important clinical implications, the effect of PCC has yet to be confirmed in patients with bleeding events who are treated with these anticoagulants.

Cost-effectiveness

Cost-effectiveness will have a major impact on selection of new agents in daily practice. Dabigatran etexilate was introduced to market in the United States at a price of $6.75 per day for the AF indication, lower than its current price in most European countries where it has been approved in a different dose for short-term prevention of venous thrombo-embolism in patients undergoing orthopaedic surgery of the hip or knee. In the meantime (April 2012) a price of USD 3–4 is observed. Recently, economical evaluations of dabigatran in non-valvular atrial fibrillation have been conducted in the US, Canada, and Great Britain [28–30]. Overall, the studies found that the use of dabigatran, in particular at a regimen of 150 mg twice daily, was associated with positive net health benefits when compared with warfarin. In quantitative benefit-harm analysis, the benefits of reduced bleeding rates with the lower dose were offset by reduced efficacy in stroke prevention. Another important finding was that the cost-effectiveness of dabigatran was markedly reduced in centres that achieve good TTR or in patients with well-adjusted INR.

The price of rivaroxaban and apixaban for stroke prevention in AF has not yet been set and quantitative benefit-harm analyses with those agents are still lacking. The use of all these agents will be influenced by reimbursement policies for medication, INR checks, hospitalisation, rehabilitation stays, and other direct costs associated with management of patients with AF at risk of stroke.

VKA: are they here to stay?

While VKA have limitations, they remain cheaper and very well established. So, the question that will come up as new agents hit the market is: when should a clinician switch a patient over to the new agents?

Currently physicians suffer from the lack of corresponding guidelines, which will be established as more

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Table 3

<table>
<thead>
<tr>
<th></th>
<th>Primary endpoint of stroke or systemic embolism</th>
<th>Haemorrhagic stroke</th>
<th>Ischaemic stroke</th>
<th>Major bleeding</th>
<th>All cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event rate</td>
<td>HR</td>
<td>p ARR</td>
<td>Event rate</td>
<td>HR</td>
</tr>
<tr>
<td>RELY</td>
<td>Dabigatran</td>
<td>150 mg</td>
<td>1.11%</td>
<td>p.y.</td>
<td>0.66 &lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>1.69%</td>
<td>p.y.</td>
<td>0.38%</td>
<td>p.y.</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Apixaban</td>
<td>5 mg</td>
<td>1.27%</td>
<td>p.y.</td>
<td>0.79 &lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>1.60%</td>
<td>p.y.</td>
<td>0.47%</td>
<td>p.y.</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>Rivaroxaban</td>
<td>20 mg</td>
<td>1.53%</td>
<td>p.y.</td>
<td>0.91 &lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>2.2%</td>
<td>p.y.</td>
<td>0.44%</td>
<td>p.y.</td>
</tr>
</tbody>
</table>

p.y. = per year; HR = hazard ratio; p = p-value; ARR = absolute risk reduction.
and more new drugs gain approval and first head to head comparisons arise. Recent studies however found that superior efficacy of the new drugs are offset when compared to warfarin in patients with well-adjusted INR. Therefore, VKA may remain the mainstay in patients already on VKA with excellent INR control and in those in which the use of novel agents is contraindicated. Dabigatran, for instance, is contraindicated in patients with renal insufficiency below CCr 30 ml/min because it is mainly renally excreted. Also, in contrast to VKA, the safety of this new drug class in valvular AF patients, those with mechanical heart valves, those with rhythm control interventions, and those in particular on anti-platelet drugs has not yet been established.

**Anticoagulation in elderly patients: new anticoagulants, new opportunities?**

The prevalence of AF increases with advancing age, ranging from only 0.1% in subjects under 55 year to >10% in subjects above 80 years of age [31]. Consequently, with a rapidly aging population, it is clear that AF and AF-related stroke are an expanding healthcare concern. Despite strong reasons to believe that VKA reduce stroke and improve net clinical benefit in elderly patients, they are used in only one third of eligible patients over the age of 85 years [32]. The decision to withhold anticoagulation in the elderly with AF in the absence of formal contraindications is multi-factorial, often the result of a combination of underestimating of thrombo-embolic risk, overestimation of bleeding risk in particular intracranial haemorrhage and the need for monitoring. Fear of interactions with concomitant medication might also play a role. Data from a prospective study of hospitalised AF patients above 65 years, identified older age, cognitive impairment, history of falling, history of haemorrhage, patient preference and terminal illness as independent baseline predictors of not receiving warfarin at discharge [33]. Of particular concern in an aging population are VKA-associated intracranial haemorrhages (ICH). Although the incidence of ICH is low (0.7%, including haemorrhagic stroke, in elderly patients treated with warfarin in the BAFTA study), ICH does account for almost 90% of deaths from VKA-associated bleeding, and the majority of disability in survivors [34, 35]. One strategy to minimise the risk of bleeding complications in daily practice is often to specifically target a low INR in elderly AF patients. Lowering the INR target from 3–4.5 to 2.5–3.5 was shown to decrease the risk of major haemorrhage, mainly because of a reduction in ICH [36]. In any case, there is no consensus on this strategy particularly because low target INR is not consistently associated with a lower rate of ICH but with an increased risk of ischaemic stroke. Hence, European and North-American guidelines do not recommend lower INR levels in the elderly.

A significant interaction between age and treatment assignment was observed in terms of major bleeding complications in the RELY trial. In patients aged <75 years, dabigatran 110 mg was associated with a lower risk of major bleeding (1.89 vs 3.04%, p <0.001), while the risk was similar in patients aged 75 and older (4.43 vs 4.37%, p = 0.89). In contrast, 150 mg dabigatran also was associated with a lower risk of major bleeding in patients younger than 75 (2.12 vs 3.04%, p <0.001), versus a trend towards more major bleeding complications in those above 75 years of age (5.10 vs 4.37%, p = 0.07). Although the interaction was significant for extracranial bleeding, there was no interaction with age for ICH. These analyses imply that all bleeding complications including ICH are consistently lower with both doses of dabigatran compared to VKA in younger patients, while in those aged ≥75 years, ICH risk is lower but extracranial bleeding risk is similar or higher with both doses of dabigatran. Intuitively, these results from RELY trial appear to be especially appealing for stroke prevention in an elderly AF population: the observation that 110 mg dabigatran bid is associated with similar efficacy to warfarin for preventing stroke and systemic emboli and significantly less ICH and haemorrhagic stroke without increasing major bleeding is of particular importance for elderly patients in need of effective anticoagulation. In particular, elderly AF patients now treated with anti-platelet agents or not receiving antithrombotic therapy at all might now be considered for stroke prophylaxis with dabigatran. In Canada and in the EU, regulatory agencies recommend the use of dabigatran 150 mg BID for patients below 80 years of age and the 110 mg BID dose for patients with an age of 80 years and above. The selected age cut-off was based on a favourable benefit/safety profile of the 110 mg bid dose in the 3016 patients above 80 years in RELY: hazard ratio 0.68 (95% CI 0.44–1.05) for stroke and systemic emboli and 1.12 (0.84–1.149) for major bleeding events.

Although more detailed subgroup analysis among elderly patients have not yet been presented, results presented in the ROCKET AF and ARISTOTLE Trial suggest at least that efficacy and safety profile of both drugs are consistent irrespective of age.

**Concluding remarks**

The increased epidemiological burden of AF combined with the broadening of the eligibility criteria for anticoagulation treatment among patients with AF will enhance the impact of under-utilisation of VKAs for thromboprophylaxis of patients with AF. From a pragmatic point of view, major benefit on a population basis will be gained not only by improving treatment efficacy compared with standard therapy among those already on VKAs but primarily by initiating anticoagulants in patients considered unsuitable or unwilling to take...
VKAs. Based on current results and first experiences in outpatient settings, apixaban and rivaroxaban may be favoured in patients with renal failure, while apixa- ban may be preferred to other anticoagulants in pa- tients at higher bleeding risk. Currently dabigatran and apixaban appear as a valuable alternative to VKA in the elderly, and in patients with elevated CHADS Score, rivaroxaban could take a leading position. Over- all, the new oral anticoagulants represent a major ad- vance in medical therapy.

References