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Overview

Stroke and atrial fibrillation

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INTRODUCTION

Atrial fibrillation (AF) and its consequences are one of today's main epidemiologic concerns. 4.5 to 6 million Europeans and 2.3 to 5.1 million Americans are affected by AF which is the most common sustained arrhythmia in the general population (1–5). AF is the strongest risk factor for stroke but also increases the risk of heart failure, dementia and death (2, 5). AF has a strong negative impact on patients' quality of life and causes large socioeconomic costs where more than half are related to complications of AF (6). The prevalence of AF is expected to increase by at least 50% within the next 20 years (7). The relationship between atrial fibrillation and stroke, the prevention of stroke and the acute treatment of stroke due to atrial fibrillation are discussed in this review.

EPIDEMIOLOGY

The life-time risk of developing AF is high. Two population-based studies, the Framingham Study and the Rotterdam Study found that the life-time risk was one in four for both men and women after the age of 40 years, compared to breast cancer which affects one in eight women, or heart failure affecting every fifth individual *(1)*.

With the ageing population, the prevalence and incidence of AF are also increasing. The prevalence of AF ranges from 2.5% in individuals over 40 years of age, 6% in those older than 65, to 12–16% in those over 75 years. AF affects more than 1% of the population, with 70% of patients aged between 65 and 85 years *(8)*. Cardiovascular risk factors such as heart failure, hypertension, valvular heart disease and diabetes are other important predictors for AF. New risk factors such as genetic disposition, obesity, metabolic syndromes, sleep apnea syndrome, endurance sports, increased pulse pressure and subclinical atherosclerosis are also increasingly being recognized *(9)*.

Paroxysmal AF (PAF) which constitutes 1/3 of all AF cases carries the same stroke risk as permanent or persistent AF *(10–12)*. PAF also seems to be more prevalent than persistent AF in acute stroke and TIA patients *(13)*. However, the recognition of PAF remains clinically problematic because most patients with PAF are asymptomatic *(14)*. Continuous ECG monitoring can register up to 40% of cases, whereas pacemaker recordings can reveal as many as 88% *(15, 16)*.

AF represents a great burden for the patient and the society. AF symptoms (palpitations, fatigue, chest pain, dizziness, light headedness, syncope and dyspnoea) have a strong negative impact on patients' quality of life, regardless of their frequency or duration *(17, 18)*. AF represents a great public health issue which is expected to increase over the next decades due to aging population and improved cardiac disease management. It accounts for more hospitalizations than any other

arrhythmia *(19)*. In 1995, there were more than 1.6 million consultations, and more than 59 000 hospitalizations due to AF in the UK (20). In Denmark this number has increased by 60% in the last 20 years *(21)*.

STROKE

Risk

AF is the cause of 15–20% of all ischemic strokes *(22)*. It is also an independent risk factor for stroke severity, recurrence and post-stroke mortality *(23)*. A Scottish population based study showed that both male and female AF patients had a significant increase in all-cause mortality, cardiovascular events, fatal or non-fatal stroke, and heart failure *(2, 24)*. New onset AF is an independent predictor of in-hospital mortality, longer intensive care unit stay, and longer overall hospital stay *(25)*.

AF should be considered when assessing cryptogenic strokes, which account for approximately one third of first ever ischemic strokes. It is possible that 25–50% of cryptogenic strokes may be due to undetected AF *(26)*. Asymptomatic AF can also cause cryptogenic transient ischemic attacks (TIA). Following prolonged monitoring of asymptomatic patients, 85% of AF episodes lasted less than 30 seconds *(27)*. A magnetic resonance (MR) study performed on more than 2000 asymptomatic AF patients found that 10.7% of participants had at least one silent cerebral infarction (SCI). In the Framingham Offspring Study which was the first to demonstrate a significant relationship between AF and SCI, a doubled risk for SCI was found in persons with AF compared to those without AF. Silent or asymptomatic strokes are valuable predictors for clinical strokes and dementia *(28)*. The Rotterdam study showed a 3 fold risk increase for stroke in elderly people with SCI, and 2.3 fold risk increase for dementia with a steeper decline in cognitive function *(29)*. It has, however, to date not been shown that screening for and the appropriate treatment of AF reduce the number of patients in the population with SCI.

Atrial fibrillation and stroke severity:

There is evidence suggesting that patients with AF have more severe strokes than their age-matched counterparts who suffer strokes due to other etiologies *(30–32)*. A sub-group analysis of patients with AF and stroke in the North Dublin Population Stroke Study showed that AF-associated stroke occurred in one third of all patients. This study also showed that AF was associated with recurrent, severe and disabling strokes, a higher frequency of total and partial anterior circulation infarct syndromes and a lower frequency of lacunar infarct syndromes. 79% of strokes were classified as cardio-embolic according to the TOAST system. Functional recovery following stroke was similar in the AF and non-AF group. However, stroke survivors with AF had a greater disability at 7 and 90 days following the event, even though at 90 days there was no difference in mortality rate or stroke recurrence *(33)*. Although previous studies have reported worse disability in AF-associated strokes compared to non-AF strokes, it remains unclear whether this is a consequence of co-morbidities or greater stroke severity in AF stroke sufferers *(3, 34)*. Consistent with previous studies, an Italian population-based study showed that AF was associated with older age, worse post-stroke functional status, and greater acute stroke severity, leading to greater disability within the first three days after stroke onset *(30)*. Their data suggests that AF-associated strokes may be more common than previously considered, occurring in approximately one third of all ischemic strokes, widely described as prior, new and paroxysmal *(30)*. A retrospective study showed AF was present in 20.3% of acute stroke patients, with a higher frequency of a bed-ridden state in AF-associated stroke patients compared to patients without AF (41.2% vs. 23.7%) (31). Ischemic stroke associated with AF was typically more severe, and the severity increased independent of advanced age and other risk factors *(31)*.

A greater stroke severity in association with AF has also been reported by clinical and pathological studies. MRI studies have shown greater volumes of more severe hypoperfusion leading to larger infarctions and greater risk of severe hemorrhagic transformation. AF commonly results in the sudden occlusion of large cerebral arteries by a cardiac embolus. As a result, there may be insufficient time to allow for the development of a collateral blood supply, compared with patients with arterial stenosis *(35, 36)*. This in turn may result in larger areas of infarction, explaining at least in part the poorer outcome of severe hypoperfusion seen in AF patients. Another potential explanation is the increased likelihood of impaired cardiac output with inadequate compensation by cerebral autoregulation *(37)*.

Ethnic differences have been studied in a Mexican American (MA) population-based study of stroke/TIA patients with AF. MA were found to have more than doubled risk of recurrent stroke and more severe recurrent stroke than non-Hispanic whites (NHW) *(38)*. However, there was no ethnic difference in post-stroke mortality. Possible explanations were differences in warfarin use, INR monitoring or a greater frequency of non-cardioembolic recurrent strokes in MA than NHWs. The authors found this surprising, since recurrent strokes themselves are potent predictors of mortality, and that MAs had more recurrent strokes that were more severe. This better than expected mortality rate of Hispanics has been noticed in other diseases, and is termed the »Hispanic paradox« *(40)*.

The National Acute Israeli Stroke Survey (NASIS) examined the potential effect of pre-admission anticoagulation on stroke severity and outcome in patients with AF *(39)*. They found that effective anticoagulation therapy is associated with decreased stroke severity, improved functional outcome, and better survival in patients with AF admitted with acute brain ischemia *(39)*. Two previous retrospective studies also showed decreased disability and 30-day mortality rates after ischemic stroke in patients with pre-stroke anticoagulation *(40, 41)*. Effective anticoagulation was not associated with an increased risk

of symptomatic hemorrhagic transformation during hospitalization *(39)*. It was suggested that this may be explained by potential underlying mechanisms such as reduced stroke severity associated with therapeutic anticoagulation which might reflect a decrease in cardioembolic strokes, which are often more severe and usually include a high proportion of TACI. In this study none of the patients admitted with therapeutic INR levels experienced TACI. Effective anticoagulation probably also results in smaller emboli which cause occlusions in smaller arteries. Patients admitted with sub-therapeutic anticoagulation showed intermediate findings in stroke severity and outcome.

Two studies which assessed outcome following thrombolysis in patients with and without AF found that stroke patients with AF had poorer outcomes *(42, 43)*. It was suggested that this may be due to the physiology of clot lysis, which depends on size, site of occlusion, clot composition, surface area of the clot exposed to the blood flow, and penetration of t-PA into the clot. Old and large thrombi may be more resistant to thrombolytic therapy than fresh and smaller ones. AF stroke patients may therefore experience older and larger thrombi, which are more resistant to thrombolytic therapy. The association between AF and the increased risk of death in the first four weeks following the stroke may be explained by the sudden occlusion of larger vessels, without sufficient collateral flow leading to large infarction. Baseline NIHSS were also found to be significantly higher in patients with AF-related stroke. Both early neurologic deterioration (END) and early recurrent ischemic strokes (ERIS) after thrombolysis is associated with AF *(44)*.

Assessment of stroke risk

Since AF patients have a considerably higher risk of stroke and thromboembolism compared to age-matched controls with sinus rhythm, proper assessment of their stroke risk is essential. Identifying independent risk factors for stroke in patients with atrial fibrillation allows risk stratification in individual patients *(47)*. Patients with non-valvular AF have an average absolute stroke risk of 3–4% per year, but this can vary 20-fold depending on patient age and other clinical features *(48, 49)*.

The assessment of individual stroke risk can be done by stroke risk schemes. The detailed CHA_2DS_2-VASc score includes heart failure, hypertension, age ≥75 years, diabetes mellitus and previous stroke/TIA, vascular disease (previous myocardial infarction, peripheral artery disease, and aortic plaque), age 65–74 years and sex (female) (Figure 1). CHA_2DS_2-VASc is based on a point system in which 2 points are assigned for a history of stroke/TIA and age >75 years and 1 point each for the remaining the risk factors. When CHA_2DS_2-VASc ≥1 anticoagulation is recommended by the American College of Chest Physicians guidelines and is awaited in the new European guidelines *(45)*. CHA_2DS_2-VASc is based on the previous $CHADS_2$ where additional risk factors were incorporated *(46)* in order to identify those patients with a very low stroke risk where anticoagulation is not necessary *(17, 46–50)*. Estimated yearly stroke risk is approximately 2% with CHA_2DS_2-VASc-score of 2, but 4% with $CHADS_2$ of 2. CHA_2DS_2-VASc also seems to be better in identifying patients with a considerably increased risk *(51)*. It has been validated in independent cohorts, among elderly, in pure anticoagulation cohorts and cohorts from general practice *(46, 52–54)*. In addition to the risk factors included in CHA_2DS_2-VASc, smoking seems to be associated with increased stroke risk whereas alcohol seems to have some protective effect *(51)*.

What drives thrombogenesis in AF?

The underlying mechanisms for thrombogenicity in AF are complex and only partly understood. More than 150 years ago Rudolf Virchow purposed the triad of pathological changes in vessel wall, blood flow and constituents of the blood as an explanation for thrombus formation *(55)*. Today, the triad is recognized as endothelial/endocardial dysfunction, hemodynamic disturbances with stasis and turbulence and pathological changes in hemostasis, thrombocytes and fibrinolysis. Abnormal blood flow in AF is manifest as stasis within the left atrium, partly related to the loss of atrial systole. Such abnormal stasis can be visualized using transoesophageal echocardiography as spontaneous echo contrast in the left atrium, which is an independent predictor of thromboembolism in AF patients. Blood constituent factors include haemostatic and platelet activation as well as inflammation and growth factor changes *(55)*. Studies have shown that levels of coagulation markers, such as increased D-dimer levels, remain elevated even during anticoagulation therapy *(56)*. During periods with sinus rhytm elevated coagulation activity has also been demonstrated in the left atria in patients with PAF *(57)*.

Stroke prevention in atrial fibrillation

The role of anticoagulation in stroke prevention has been investigated in several randomized studies where selection of patients for anticoagulation, comparison of antiplatelets versus anticoagulation, and risk stratification for patients with AF with and without other risk factors for stroke have been thoroughly assessed *(45, 58, 59)*. Anticoagulation therapy in AF reduces the stroke risk by 2/3 and all-cause mortality by 1/4 compared to no treatment *(60)*. It is increasingly evident that treatment decisions have to be based on individual risk assessment. When CHA_2DS_2-VASc ≥1 anticoagulation seems to be the most effective treatment to prevent thromboembolic events *(45)*. This implies that all patients with AF should be considered for anticoagulation, except patients <65 years of age with no other risk factors. When CHA_2DS_2-VASc = 0, as in AF patients <65 years and no other risk factors there is not net benefit from anticoagulation compared to no therapy, due to the low underlying risk of stroke *(45, 48)*. Even in the elderly anticoagulation is the most effective antithrombotic treatment *(48)*. The treatment of patients >75 years of age was studied in the BAFTA trial which showed that warfarin was 65% more effective than aspirin in this high risk elderly population.

However, the bleeding risk was equal in the two groups *(61)*. Patients who cannot tolerate anticoagulation therapy may be considered for aspirin but this treatment has a very limited prophylactic effect.

There is also a need for a simple scheme to determine the risk of bleeding in patients considered for anticoagulation. Some previously proposed schemes have been difficult to use in every day practice because they were too complex. They were derived from studying the general population which does not reflect an AF population. A simple bleeding scheme, HAS-BLED was therefore proposed in 2011 (Table 2). HAS-BLED was derived from a »real world« cohort of 3978 European subjects with AF in the EuroHeart Survey (Table 2) *(62)*. It includes the most important risk factors for bleeding complications: Hypertension, Abnormal renal or hepatic function, prior Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65), Drugs (NSAIDs/antiplatelets) or alcohol abuse. Each factor is given one point if present. A HAS-BLED score of =3 indicates a 'high bleeding risk', where regular reviews of the patient should be carried out following the initiation of antithrombotic therapy. HAS-BLED has been validated in several populations *(63)*.

Target level of anticoagulation (INR) have varied from study to study *(59)*. It has been shown that the risk of stroke for patients with AF rises steeply below an INR of 2.0 *(64)* and the risk of hemorrhage increases rapidly at levels of INR >4.0 *(65)*. The recommended therapeutic INR range is 2.0 to 3.0 (target INR of 2.5) *(17, 45)*. Despite guideline recommendations, practice data bases show that 40%–50% of patients with AF are not treated with anticoagulation, even when they have a substantial risk for stroke *(66–69)*. Only 10–20% of patients admitted with stroke who had a previous stroke or TIA received anticoagulation with an INR in therapeutic range *(70, 71)*. A study in AF patients >80 years showed that 26% ceased warfarin within the first year of therapy, mostly due to bleeding concerns *(72)*. The situation was similar in patients with secondary prevention after an AF related stroke where only 45% continued warfarin therapy after 2 years. AF patients who have a stroke on warfarin in therapeutic range have a better outcome than patients with lower INR values *(67, 69, 73)*.

The main limitations with warfarin treatment are the narrow therapeutic window and the need of monitoring with regular INR controls. Good anticoagulation control is defined as an INR in the therapeutic range =70% of the time. Despite frequent controls INR values are outside the therapeutic range almost half of the time *(74)*. This is partly due to interactions with other drugs and foods. Other limitations are a slow onset of effect, metabolic variability and genetic polymorphisms.

Aspirin

Aspirin is often prescribed instead of oral anticoagulant therapy in AF owing to the perception that it is just as effective as warfarin and that the bleeding risk is lowered. However, the evidence of aspirin as stroke preventive treatment in AF is scarce. The most conclusive evidence for antithrombotic therapy in AF comes from a meta-analysis by Hart and co-workers, in which RCTs of antithrombotic therapy for stroke prevention in non-valvular AF were reviewed *(60)*. When the analyses were confined to the aspirin-only trials a non-significant risk reduction of 19% (95% CI – 1% to 35%) was found compared with placebo (3,990 participants in seven trials). The SPAF-1 trial was stopped at an interim stage because of the clear superiority of warfarin treatment over aspirin.

Combined aspirin and clopidogrel therapy

Dual aspirin and clopidogrel therapy was proposed as an alternative to warfarin for stroke prevention in AF, because of its use to reduce of thrombosis in coronary stents and to improve thrombotic outcomes after acute coronary syndromes. The Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE) was, stopped before completion because of the clear superiority of warfarin over a combination of aspirin and clopidogrel *(49)*. A sub-group analysis showed that patients who had previously been treated with warfarin, or had good anticoagulation control derived the most benefit from warfarin treatment. Combined aspirin and clopidogrel therapy was also compared with aspirin monotherapy in the ACTIVE-A trial where patients with AF who were considered unsuitable for warfarin or had refused warfarin therapy were studied. This RCT showed a 28% reduction in the risk of stroke with aspirin and clopidogrel treatment compared with aspirin alone. However, the risk of major bleeding with aspirin and clopidogrel therapy was 2% per year, which was more than 50% higher than with aspirin alone and comparable with major bleeding rates seen in warfarin-treatment trials *(49)*.

New oral anticoagulants

Recently new oral anticoagulants (NOACs) have been introduced for the prevention of stroke in AF. They are direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) and have several benefits compared to warfarin. They have high specificity, fixed oral dosing, no interaction with food, few interactions with other drugs, no need for anticoagulation monitoring, and a rapid onset and offset of action.

Dabigatran

Dabigatran (Pradaxa) is a competitive and reversible direct thrombin inhibitor, administered orally as a pro-drug, dabigatran etexilate *(75, 76)*. Dabigatran has a predictable coagulation-inhibiting effect without interacting with food, although food does delay the time to maximal absorption by approximately 2 hours *(77, 78)*. Around 80% of systemically available dabigatran is eliminated via the kidneys *(79)*. The CYP3A4 isoenzyme is not involved in dabigatran's metabolism, although there is a chance of interaction with drugs that are metabolized by this route (such as atorvastatin) *(80)*. Dabigatran

TABLE 1

Clinical characteristics composing the risk score CHA_2DS_2-VASc for thromboembolic events in atrial fibrillation (based on Lip et al.(46)):

CHA_2DS_2-VASc	Clinical characteristics	Score if present
C	Congestive heart failure (reduced left ventricular function, ejection fraction =40 %)	1
H	Hypertension	1
A2	Age =75 years	2
D	Diabetes	1
S2	History of stroke/TIA	2
V	vascular disease (previous myocardial infarction, peripheral artery disease, and aortic plaque)	1
A	Age 65-74 years	1
Sc	Sex category: female	1
Max score		9

TABLE 2

Clinical characteristics comprising the HAS-BLED bleeding risk score.

HAS-BLED	Clinical characteristics	Score if present
H	Hypertension	1
A	Abnormal renal and Liver function (1 point each)	1 or 2
S	Previous stroke/TIA	1
B	Bleeding	1
E	Elderly =65 years	
L	Labile international normalized ratios	1
D	Drugs or alcohol (1 point each)	1
Max score		9

Hypertension' is defined as systolic blood pressure =160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine =200 mmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin x 2 upper limit of normal, in association with aspartate aminotransferase / alanineaminotransferase / alkalinephosphatase x 3 upper limit normal, etc.). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g., 60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc. INR ¼ international normalized ratio. (based on Pisters *et al.(62)*).

interacts with amiodarone, quinidine, ketoconazole and verapamil. The interaction, however, does not require dose adjustments according to the US Food and Drug Administration (FDA). The European label recommends use of the low dose of 110mg twice daily (bid.) in patients on verapamil (http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf). The use of dabigatran with rifampicin or ketoconazole should be avoided. As dabigatran is primarily eliminated renally, the EU label indicates severe renal impairment [creatinine clearance (CrCl) less than 30ml/min] as a contraindication. However, the FDA has approved a lower 75mg bid. dose for patients with a CrCl of 15–30 ml/min (Pradaxa US prescribing information 2011, (http://bidocs.boehringeringelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf). The assessment and regular control of kidney function is important especially in the elderly. In an initial dose finding study in patients with atrial fibrillation, the so-called PETRO study, 502 patients documented as having atrial fibrillation with coronary artery disease plus at least one additional risk factor was given three different doses of dabigatran etexilate: 50, 150 or 300 mg bid or warfarin at target INR levels between 2.0 and 3.0 *(81)*. Some of the patients were also receiving ASA (81 or 325 mg/day). The primary endpoint was bleeding complications. The study showed that a dose of 50mg of dabigatran etexilate bid was possibly too low and that 300mg of dabigatran etexilate bid (particularly in those also receiving ASA) was associated with a high risk of bleeding complications. Based on these results and pharmacokinetic modeling, doses of 110 and 150mg bid. dabigatran were chosen for the phase III trial.

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial was a large international,

multi center randomized trial that included 18 113 patients with non-valvular atrial fibrillation, and at least one additional risk factor for stroke *(82)*. Patients were randomized to one of two blinded doses of dabigatran, either 110 mg bid. (1195 had prior stroke, and 4820 had no prior stroke), or 150mg bid. (1233 had prior stroke, and 4843 had no prior stroke), or open-label warfarin (INR 2.0–3.0; 1195 had prior stroke, and 4827 had no prior stroke). The median follow-up period was 2 years, and patients with severe renal insufficiency (CrCl less than 30ml/min) were excluded from study participation. Events were blinded and independently adjudicated following a PROBE design (prospective randomized open with blinded endpoint evaluation). The primary outcome was the composite of stroke or systemic embolism. The primary outcome event rates were 1.71% per year in the warfarin group, and 1.54% per year in the dabigatran 110 mg group (RR with dabigatran, 0.90, 95% CI 0.74–1.10; P<0.001 for non-inferiority), and 1.11% per year in the dabigatran 150mg group (RR 0.65, 95% CI 0.52–0.81; P<0.001 for superiority) *(82)*. Major bleeding rates were 3.57% per year in the warfarin group, 2.87% per year in the dabigatran 110mg group (RR 0.80, 95% CI 0.70–0.93; P=0.003), and 3.32% per year in the dabigatran 150mg group (RR 0.93, 95% CI 0.81– 1.07; P=0.31). The hemorrhagic stroke rate was 0.38% per year with warfarin, 0.12% per year with dabigatran at the 110mg dose (RR 0.31, 95% CI 0.17–0.56; P<0.001), and 0.10% per year with dabigatran at the 150mg dose level (RR 0.26, 95% CI 0.14–0.49; P<0.001) *(82)*. Mortality rates were 4.13% per year in the warfarin group, 3.75% per year with dabigatran 110mg (RR 0.91, 95% CI 0.80–1.03; P=0.13), and 3.64% per year with dabigatran 150mg (RR 0.88, 95% CI 0.77–1.00; P 0.051) *(82)*.

A subgroup analysis included the secondary stroke prevention part of the RE-LY study exploring the treatment effects of dabigatran versus warfarin in patients who had a prior stroke or TIA *(83)*. Regarding stroke or systemic embolism, a finding consistent with the results in the main RE-LY study was found in patients with prior stroke or TIA (RR 0.84, 95% CI 0.58–1.20 for dabigatran 110mg versus warfarin and RR 0.75, CI 0.52–1.08 for dabigatran 150mg versus warfarin). The rate of major bleeding was significantly lower in patients with dabigatran 110 mg (RR 0.66, 95% CI 0.48–0.90) and similar in those on 150 mg dabigatran (RR 1.01, 95% CI 0.77–1.34) compared to those on warfarin. With one exception (vascular death) all interaction p values were non-significant, indicating that the results in the subgroup of patients with TIA or stroke were comparable to those in the main study *(83)*. In the RE-LY study, intracranial bleeding rates for all patients were lower in the dabigatran groups than in the warfarin group (110mg b.i.d. dose: RR 0.30, 95%CI 0.19–0.45; 150mg bid. dose: RR 0.41, 95% CI 0.28–0.60; P<0.001 superior to warfarin for both dabigatran doses) *(82, 84)*. Intracranial bleeding rates were also lower in patients with prior stroke or TIA compared with warfarin (P=0.001 for dabigatran 110 mg; P=0.007 for dabigatran 150mg) *(83, 85)*. The bleeding risk was increased by the concomitant use of dabigatran and antiplatelet therapy *(83, 85)*, which also increased bleeding risk in patients on warfarin treatment. Dabigatran had a higher drop-out rate, due to gastrointestinal adverse events (e.g. dyspepsia), and was associated with a small non-significant numerical increase in myocardial infarctions compared with warfarin *(82)*. In conclusion, dabigatran is an important addition to the treatment options for stroke prevention in atrial fibrillation. Dabigatran has been approved for use at the 150mg bid. dose in the USA (35), and for both doses in Europe.

Rivaroxaban

Rivaroxaban is administered in a fixed oral dose and exhibits dose-dependent pharmacokinetics. It has a dual mode of elimination; one-third of the active drug is eliminated unchanged in the urine, and two-thirds is metabolized by the liver (of which half is excreted via the kidneys, and half excreted via the hepato-biliary route) *(86)*.The pharmacokinetics and pharmacodynamics of rivaroxaban are not influenced by sex or weight to the degree that dose adjustments are required *(87)*. There is relevant interaction with strong inhibitors of both CYP3A4 and P-glycoprotein such as azole antimycotics or HIV protease inhibitors *(88, 89)*. Pharmacokinetic and pharmacodynamic analyses have also indicated that although drug clearance is affected by renal function to some degree, rivaroxaban can be used effectively in patients with mild-to-moderate renal impairment (CrCl 30–79 ml/min) *(90)*. The prevention of stroke in patients with atrial fibrillation was investigated in the rivaroxaban (20mg or 15mg once daily in patients with a creatinine clearance 30–49 ml/min) compared to warfarin in a phase III, double-blind, double dummy trial (ROCKET AF) *(91)*. The patients included in ROCKET AF had higher risk of stroke than in the studies on the other new oral anticoagulants (RE-LY and ARISTOTLE) *(82, 92)*. A total of 7131 patients were randomized to rivaroxaban and 7133 to warfarin. The rate of the primary endpoint in the per-protocol analysis was 1.7% per year for rivaroxaban compared with 2.2% per year for warfarin (HR 0.79, 95% CI 0.66–0.96; P<0.001 for non-inferiority) *(91)*. In the intention-to-treat population rivaroxaban was also non-inferior to warfarin (2.1 versus 2.4% per year, HR 0.88, 95% CI 0.75–1.03; P<0.001 for non-inferiority; P=0.12 for superiority). Principal safety endpoint rates (major and non-major clinically relevant bleeding) were similar in both groups (14.9 versus 14.5% per year; HR 1.03, 95% CI 0.96–1.11; P=0.44 for superiority). Intracranial (0.5 versus 0.7% per year, HR 0.67, 95% CI 0.47–0.93; P=0.02) and fatal bleeding (0.2 versus 0.5% per year, HR 0.50, 9% CI 0.31–0.79; P=0.003) rates were lower with rivaroxaban. Adverse events were similar across groups. There was a small but significant increase in the number of epistaxic events in the rivaroxaban group (10.1 versus 8.6% in the warfarin group; P<0.05) *(91)*.

The subgroup analysis of 7468 patients with prior TIA or stroke showed higher stroke rates in patients with prior TIA or stroke compared with 6796 patients without

previous cerebrovascular events (e.g. in the warfarin arm, 2.6% per year in those with prior TIA/stroke versus 1.7% per year in those without). The relative treatment effects of rivaroxaban versus warfarin were not statistically different between patients with and without prior TIA or stroke *(93)*. Another ROCKET-AF subgroup analysis assessed the risks and benefits of the rivaroxaban 15mg o.d. dose in 2950 patients with moderate renal impairment (CrCl 30–49 ml/ min) at enrolment *(94)*. Although patients with moderate renal impairment had higher rates of stroke, and bleeding than those without, regardless of treatment, the lower rivaroxaban dose yielded efficacy and safety results consistent with the overall ROCKET-AF trial *(94)*.

Apixaban

There are two studies investigating the effect of apixaban in prevention of stroke in patients with atrial fibrillation. In the ARISTOTLE study, 18 201 patients with atrial fibrillation were treated with 5 mg oral doses of apixaban bid. or warfarin *(92)*. The rate of primary outcome (stroke and systemic embolism) after a median 1.8 years of follow-up was 1.27% per year in the apixaban group, and 1.60% per year in the warfarin group (HR 0.79, 95% CI 0.66–0.95, P=0.01 for superiority). The rate of major haemorrhage was 2.13% per year in the apixaban group compared with 3.09% per year in the warfarin group (HR 0.69, 95% CI 0.60–0.80, P<0.001). Mortality was reduced by 11% (HR 0.89, 95% CI 0.80–0.99; P=0.047). Apixaban reduced the rate of haemorrhagic stroke (HR 0.51, 95% CI 0.35–0.75; P<0.001), but did not significantly reduce the rate of ischemic, or uncertain type of stroke (HR 0.92, 95% CI 0.74–1.13; P 0.42). The investigators also reported fewer discontinuations in the apixaban arm compared with warfarin (25.3 versus 27.5%, respectively; P=0.001), with similar adverse event profiles observed.

In the AVERROE trial apixaban was compared with acetylsalicylic acid in AF patients who had a contraindication to or were unwilling to take oral anticoagulants *(98)*. The study was terminated prematurely owing to the clear superiority of apixaban over ASA for the primary efficacy outcome (composite of stroke/systemic embolism). There were 51 primary outcome events (1.6% per year) among patients assigned to apixaban, and 113 (3.7% per year) in patients assigned to aspirin (HR 0.45; 95% CI 0.32–0.62, P<0.001). There were 44 cases of major bleeding (1.4% per year) in the apixaban group, and 39 (1.2% per year) in the aspirin group (HR with apixaban, 1.13; 95% CI 0.74–1.75; P=0.57), there were 11 cases of intracranial bleeding with apixaban, and 13 with aspirin (0.4% per year in both arms, HR 0.85, 95% CI 0.38–1.90; P=0.69). In 764 patients with prior TIA or stroke there were 10 primary outcome events in those randomized to apixaban (2.5% per year), and 33 in those randomized to aspirin (8.3% per year), showing that the treatment effects for apixaban compared with aspirin were comparable between patients with atrial fibrillation with and without prior TIA or stroke.

Apixaban is eliminated approximately 25% renally and 75% through hepato-biliary elimination *(95, 96)*. Clinical findings suggest that apixaban interacts with strong CYP3A4 inhibitors such as ketoconazole *(97)*.

Acute treatment in patients with ischemic stroke due to atrial fibrillation

Information is limited regarding the safety of intravenous thrombolysis in patients under anticoagulant treatment, given that this was an exclusion criterion in previous clinical trials. In a Spanish study of 1482 ischemic stroke patients, 4.7% received oral anticoagulation. The mean INR was 1.3 (range 0.9–2.0). Anticoagulation was associated with higher mortality (OR 2.2 95% CI 1.1–4.2 p= 0.03). However, clinical outcomes were independent of INR values. Intravenous thrombolysis was assessed as safe in patients on warfarin with INR <2 as there was no increase in symptomatic intracranial hemorrhage *(99)*. Furthermore, results from SITS-ISTR also showed that atrial fibrillation was associated with higher mortality in young ischemic stroke patients who were given intravenous thrombolysis *(100)*. In patients with the new oral anticoagulants individual assessment for time for last tablet intake, renal function and patient compliance can be of help when making a decision regarding thrombolytic therapy in addition to measuring APTT and INR. When it is longer than 6 hours since last tablet intake or INR and APPT are normal the risk of hemorrhage after thrombolytic therapy is probably low. APPT and the INR may, however, be normal in patients taking Rivaroxaban or Apixaban. Patients who cannot be treated with thrombolysis should be considered for mechanical thrombectomy.

CONCLUSIONS

The new oral anticoagulants have been show to be as good as or better than VKAs for stroke prevention in AF. This is accomplished with a lower risk for bleeding, especially intracranial hemorrhage. The new anticoagulants have also several additional advantages such as fewer interactions with other drugs and food and no need for monitoring. Patients who are regulated well on VKAs should probably continue their medication unless they themselves wish to change their treatment. There is, however, growing evidence that the new anticoagulants are now the treatment of choice for patients with newly diagnosed AF and an increased stroke risk. Compliance and adherence should be stressed due to their quick onset and offset of action. These new treatment possibilities must be accompanied by increased awareness of AF in the general population and increased knowledge regarding the dangers of AF amongst medical personnel who come in contact with potential patients. This will hopefully in the future lead to a decrease in the number of patients who suffer ischemic stroke due to atrial fibrillation.

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