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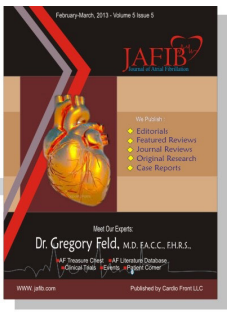

Prevention of Stroke by Antithrombotic Therapy in Patients with Atrial Fibrillation

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Abstract

Atrial Fibrillation (AF) is the most common clinically significant sustained cardiac arrhythmia, a major risk factor for strokes whether it is symptomatic or silent. The older $CHADS_2$ score and the newer CHA_2DS_2-VASc are well validated to determine stroke risk and guide initiation of antithrombotic therapy, but haemorrhagic risk has to be respected as well, and scores such as HAS-BLED should be widely used. Old fashioned warfarin became standard of care outperforming antiplatelets in every trial but novel classes of anticoagulants that overcome many of warfarin drawbacks have been introduced and are already guideline recommended regiments. Nevertheless their use poses new questions that have to been answered in the near future.

Introduction

Epidemiology

The most part of morbidity and mortality associated with atrial fibrillation (AF) is due to thrombo-embolic complications, primarily involving the cerebrovascular system and resulting in ischemic stroke.

Compared to subjects with normal sinus rhythm (SR), those with AF have a 40 to 90% higher risk of overall mortality.[1] AF increases the risk of stroke 4-to-5 fold,[2] is responsible for 15-20% of all ischemic strokes[3] and an independent risk factor for their severity and recurrence.[4]

The systematic review from the Stroke Risk in Atrial Fibrillation Working Group identified the following independent risk factors for stroke: prior stroke or transient ischemic attack, increasing age, history of hypertension, diabetes mellitus, structural heart disease and obesity.[5] Without antithrombotics, the risk of ischemic stroke in patients with AF, is 5% per year.[6]

Pathophysiology

AF is a progressive disease that becomes more difficult to treat with increasing duration and as older cardiologists stated "AF begets AF".This is known to be true and is a result of electrical, contractile, and structural remodelling of the atria, which creates a fertile environment for the propagation of AF.

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Electrical remodelling

At rapid atrial rates, such as those observed during fibrillation paroxysms, intracellular changes in calcium handling shorten action potential duration. Even in the case of prolonged atrial fibrillation, electrical remodeling reverses quickly and completely once sinus rhythm is restored.

Contractile Remodelling

It occurs rapidly. The abnormal calcium handling at the high rates of contraction seen in atrial fibrillation may be responsible for loss of contractility. The contractile remodelling may be responsible for the most destructive consequence of AF, stroke. Impaired atrial contraction leading to stasis of blood, primarily in the left atrial appendage, is thought to be the major contributor to the development of blood clots, thus promoting thromboembolic events.

Structural Tissue Remodelling

Occurs after periods of weeks or months and in this case we have macroscopic and microscopic changes in the myocardium, which contribute to contractile dysfunction and decreased cardiac output. [7]

The remodelling changes may still be reversible during early phases of the arrhythmia, but may provoke relevant and permanent atrial damage during later stages of AF and associated diseases. In the timeline AF becomes from paroxysmal (self-terminating usually within 48h or in fewer than 7 days) persistent (lasts longer than 7 days or required termination by cardioversion) and possibly more resistant to cardioversion and eventually permanent (exists for more than one year). On the other hand major risk factors for AF (such as HTN or HF) if left untreated continue to aggravate the substrate for the genesis and the propagation of the arrhythmia. By preventing AF (and effectively treating its risk factors) the remodeling may become less progressive, reducing fibrosis, inflammation, atrial hypertrophy, and other adaptation processes. This is the rationale of advocates of early and aggressive rhythm control strategies that may also lower the risk of complications associated with AF, like stroke and heart failure, but such an approach remains to be proved.[8]

Antithrombotic Treatment

Anticoagulation treatment should be given not only to eligible patients (according to their risk for stroke) with persistent or permanent AF, but also to those with paroxysmal AF, who should be regarded as having the same risk. Numerous risk factors have been used to formulate various AF stroke risk stratification scores. Due to its simplicity and ease of use, the $CHADS_2$ score has become the most commonly used in clinical practice.[9] A refined version of the well established $CHADS_2$ score (1 point each for a history of HF, HTN, age>75 years, and DM, and 2 points for a history of stroke or transient ischemic attack), $CHA2DS_2$-VASc score [assigns one point each for a history of HF, HTN, age 65–74, DM, vascular disease (prior myocardial infarction, peripheral artery disease, aortic plaque), and female gender, and two points each for age ≥75 years, or a history of stroke/transient ischemic attack], uses what was previously referred to as "less well-validated or weaker stroke risk factors" (female sex, age 65 to 74 years, and vascular disease), emphasizes to better clarify risk in $CHADS_2$ score 1 category.[10] The CHA_2DS_2VASc score outperformed the $CHADS_2$ score in identifying 'truly low risk' individuals who do not need antithrombotic therapy, whilst those with >= 1 stroke risk factors should be considered for oral anticoagulation therapy (either vitamin K antagonists, or newer oral antithrombotics).

The intensity of anticoagulation involves a balance between prevention of thromboembolism and haemorrhage. The use of HAS-BLED (Hypertension, Abnormal kidney and/or liver function, Stroke, Bleeding, Labile INRs, Elderly, Drugs and/or alcohol), score should be used in order to assess the risk of bleeding in AF patients and is a good occasion to consider correctable risk factors for bleeding (eg. uncontrolled BP, concomitant NSAIDs etc).[11] A risk score ≥ 3 deserves caution. In a 5-year retrospective study at Brigham and Women's Hospital to determine aetiology and outcomes of anticoagulant-associated adverse events, 48.8% were medication errors, 30.5% adverse drug reactions, 20.7% both, and 70% of them were preventable.[12]

VKAs and Studies of VKAs vs Antiplatelets

In the SPAF (Stroke Prevention in Atrial Fibrilla-

tion) III study,[13] 1,044 patients with atrial fibrillation were randomized to standard adjusted-dose warfarin or low-intensity, fixed-dose warfarin plus aspirin. After a mean follow-up of 1.1 years the study was prematurely terminated due to an excessive rate of stroke and systemic embolism in the combination group compared to standard warfarin therapy (7.9% versus 1.9% per year; p<0.0001). In the CAFA (Canadian Atrial Fibrillation Anticoagulation) study,[14] 378 patients with atrial fibrillation were randomized to either warfarin or placebo. The annual rate of stroke and systemic embolic events was more than halved in the warfarin group (2.5%) compared to placebo (5.2%). In the Veteran Affairs Stroke Prevention trial,[15] 525 patients with nonrheumatic atrial fibrillation and without history of stroke were randomized to low-intensity warfarin or placebo. Stroke rates were reduced by 21% in the warfarin compared to the placebo group (hazard ratio: 0.79; 95% CI: 0.52-0.90). In the AFASAK-2 (Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation) study,[16] 677 patients with atrial fibrillation were randomized in four groups: fixed minidose warfarin, fixed minidose warfarin plus aspirin, aspirin, and adjusted-dose warfarin. The cumulative stroke and systemic embolic event rates were 5.8%, 7.2%, 3.6%, and 2.8% respectively in the four groups, but statistical significance was not achieved. In a randomized general practice primary prevention study performed in the Netherlands,[17] 729 patients with atrial fibrillation were randomized in three groups: standard anticoagulation, very low intensity coumarin or aspirin. Standard anticoagulation was associated with a 22% reduction of stroke risk compared to aspirin (hazard ratio: 0.78; 95% CI: 0.34-1.81).

In a multicenter, randomized Italian study,[18] fixed minidose of warfarin was compared to adjusted dose warfarin in 303 patients with nonrheumatic atrial fibrillation. Ischaemic stroke was significantly less frequent in patients assigned to standard therapy than in patients assigned to fixed minidose warfarin (3.7% versus 0% per year; p=0.025. In the SPAF-I (Stroke Prevention in Atrial Fibrillation),[19] 1,330 patients with nonrheumatic atrial fibrillation were randomized to warfarin, aspirin or placebo if eligible for anticoagulation, and aspirin or placebo in ineligible for anticoagulation. Warfarin reduced the risk for ischemic stroke and systemic embolism by 67% compared to placebo (95% CI: 27-85%). In the BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) study,[20] 973 old patients with atrial fibrillation were randomized to warfarin or aspirin. Warfarin therapy significantly reduced the risk for stroke and arterial embolism compared to aspirin (1.8% versus 3.8% per year; relative risk:0.48; 95% CI: 0.28-0.80; p=0.003).

The atrial fibrillation Clopidogrel Trial with Irbesartan for the prevention of Vascular Events-Warfarin arm trial (ACTIVE-W), compared clopidogrel plus aspirin with oral anticoagulation therapy with warfarin for prevention of vascular events in atrial fibrillation with an average of two stroke risk factors. Anticoagulation therapy was superior to the combination of clopidogrel plus aspirin (RR reduction for primary outcome 44%) with no differences in bleeding events between treatment arms.[21] The aspirin arm (ACTIVE A) trial assessed whether the addition of clopidogrel to aspirin would reduce the risk of vascular events in atrial fibrillation patients who were considered unsuitable for therapy with oral anticoagulationwith warfarin. Major vascular events were reduced by 11% in patients receiving the combination aspirin–clopidogrel vs. aspirin alone, primarily due to a reduction in the rate of stroke with clopidogrel although at the price of increased risk of major haemorrhages.[22]

Oral anticoagulation with VKA (with target INR 2–3) is the current guideline recommended standard of care for stroke prevention in AF in moderate- and high-risk patients. VKAs are highly effective when INR is maintained at an appropriate therapeutic range (INR 2–3) for the majority of time (60-70%).

Nevertheless, VKAs come with a large list of drawbacks that result in substantial mortality/morbidity and costs as well as underutilisation of anticoagulation (under 60% of eligible patients), particularly in the elderly and in secondary stroke prevention patients.[23] In a recent a time-trend analysis from 1999 to 2008 within the UK General Practice Research Database General Practice Research Database there was a relatively high, and possibly inappropriate, level of anticoagulant prescribing in lower risk patients (those with a $CHADS_2$ score of 0) and no increase in the use of anticoagulants with increasing stroke risk. In contrast, antiplatelet prescribing increased significantly with increas-

ing $CHADS_2$ score, indicating that GPs might be responding to increasing thromboembolic risk by prescribing an antiplatelet agent rather than an anticoagulant.[24]

The aforementioned disadvantages and drawbacks in the use of VKAs have led to the development of novel oral anticoagulants with the potential to change the approach of AF- related thromboembolism/stroke prevention.

New and Investigational Antithrombotic Agents

The new oral anticoagulants (NOACs) are direct thrombin (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and many trials examining their use in AF have published or are in final phase (RE-LY, ROCKET-AF, AVERROES, ARISTOTLE, and ENGAGE-AF).

RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

Dabigatran was evaluated in an open-label, Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) trial in which it was compared with warfarin in 18113 patients with non valvular AF.[25] The mean $CHADS_2$ score was 2.1. Two doses of dabigatran (110mg and 150mg BID) were evaluated. The 150 mg BID dabigatran regimen was superior to warfarin. The primary outcome of stroke or systemic embolism occurred in 1.71, 1.54(p=0.34) and 1.11% (p<0.001) of patients per year in the warfarin group, in the 110 mg dabigatran BID and in the 150 mg BID dabigatran group respectively. The rate of major bleeding was 3.57% per year in warfarin arm, 2.87% in 110mg BID dabigatran arm (p=0.003) and 3.32% 150mg BID dabigatran arm (p=0.31). The rate of haemorrhagic stroke was reduced with both doses of dabigatran compared to warfarin treatment (0.12% and 0.10% per year with 110 mg and 150 mg BID respectively vs. 0.38% with warfarin, p<0.001). Myocardial infarction had a trend to be more frequent with dabigatran 110mg (RR 1.29; 95% CI: 0.96 to 1.75; P=0.09) and 150 mg (RR 1.27; 95% CI: 0.94 to 1.71; P=0.12).

Dabigatran does not require INR monitoring. However, there is no specific antidote for it (t ½ = 12-17 hours), but only supportive therapy for severe haemorrhage. It was approved by the FDA and EMA for the prevention of stroke and systemic embolism in patients with non valvular AF. American College of Cardiology Foundation/ American Heart Association/Heart Rhythm Society focussed update,[26] gave dabigatran a class IB recommendation for AF Thus, it was the first new oral anticoagulant to become available for clinical use in >50 years.

In a Cost-Effectiveness analysis of Dabigatran for Stroke Prophylaxis in Atrial Fibrillation, for patients with the lowest stroke rate ($CHADS_2$ stroke score of 0), only aspirin was cost-effective. For patients with a moderate stroke rate ($CHADS_2$ score of 1 or 2), warfarin was cost-effective unless the risk of hemorrhage was high or quality of international normalized ratio control was poor (time in the therapeutic range <57.1%). For patients with a high stroke risk ($CHADS_2$ stroke score ≥3), dabigatran 150 mg (twice daily) was cost-effective unless international normalized ratio control was excellent (time in the therapeutic range >72.6%). Neither dabigatran 110 mg nor dual therapy (aspirin and clopidogrel) was cost-effective. [27]

In a recent meta-analysis of noninferiority RCTs seven trials were selected (N = 30,514), (2 studies of stroke prophylaxis in AF, 1 in acute venous thromboembolism, 1 in ACS, and 3 of short-term prophylaxis of deep venous thrombosis). Dabigatran was significantly associated with a higher risk of MI or ACS than that seen with agents used in the control group (dabigatran, 237 of 20 000 [1.19%] vs control, 83 of 10 514 [0.79%]; OR, 1.33; 95% CI, 1.03-1.71; P=.03).[28] Nevertheless, in another meta-analysis of the RE-LY trial, events pre-specified as "net clinical benefit" (all strokes, systemic embolism, MI, PE, major bleeding, all-cause death) occurred 7.34%/yr on dabigatran 110 mg, 7.11%/yr on dabigatran 150 mg, and 7.91%/yr on warfarin (HR 0.92 (95% CI 0.81-1.01; p=0.09) for dabigatran 110 mg and 0.90 (95% CI 0.82-0.99; p=0.02 for dabigatran 150 mg).[29]

ROCKET-AF Trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)

In this trial a total of 14264 patients with AF (87% with a $CHADS_2$ score of ≥ 3) were randomised

in a double-blind, double dummy manner to either rivaroxaban 20 mg OD (15 mg if CrCl= 30-49 ml/min) or dose adjusted warfarin (INR 2.0-3.0).[30] The primary endpoint of stroke and non-cerebral embolism occurred in 2.12% per year of patients treated with rivaroxaban and in 2.42% of patients treated with warfarin (p=0.117). Overall, rivaroxaban was non inferior to warfarin. Although major bleeding occurred in comparable rates (3.6% for rivaroxaban, 3.45% for warfarin p=0.576), rates of intracranial haemorrhage were significantly lower with rivaroxaban (0.49% vs 0.74%, p=0.019). On November 2011, the FDA approved Rivaroxaban for stroke prophylaxis in patients with non-valvular AF.

In a double-blind, placebo-controlled trial Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 46 (ATLAS ACS 2–TIMI 51), 15,526 patients with a recent ACS were assigned to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months. The primary efficacy end point was a composite of death from cardiovascular causes,

The Role of Contractile Remodelling

Contractile remodelling usually assessed by echocardiographic parameters plays a role most notably for pharmacological and electrical cardioversion and ablation of early AF types.[52,56,57] It seems to be less important for surgical ablation of longstanding AF, although we could demonstrate a weak trend in univariate analysis toward better atrial contractility in patients who regained sinus rhythm after AF ablation and mitral valve surgery.[28] At least two reports on catheter ablation of paroxysmal and persistent AF suggest that left atrial function assessed by 2D speckle tracking before ablation or by intracardiac Doppler measurement after ablation predicts AF recurrence.[57,58]

Myocardial infarction, or stroke. Rivaroxaban significantly reduced the primary efficacy end point, as compared with placebo, (hazard ratio in the rivaroxaban group, 0.84; 95% confidence interval [CI], 0.74 to 0.96; P=0.008), with significant improvement for both the twice-daily 2.5-mg dose (9.1% vs. 10.7%, P=0.02) and the twice-daily 5-mg dose (8.8% vs. 10.7%, P=0.03). Compared with placebo, rivaroxaban increased the rates of major bleeding (2.1% vs. 0.6%, P<0.001) and intracranial hemorrhage (0.6% vs. 0.2%, P=0.009), without a significant increase in fatal bleeding (0.3% vs. 0.2%, P=0.66) or other adverse events. The twice-daily 2.5-mg dose resulted in fewer fatal bleeding events than the twice-daily 5-mg dose (0.1% vs. 0.4%, P=0.04).[31]

ARISTOTLE Trial(Apixaban for Reduction In Stroke and Other ThromboembolLic Events in Atrial Fibrillation)

Apixaban was studied in a head-to-head comparison 5.0 mg twice daily, versus warfarin (target international normalized ratio, 2.0 to 3.0) in patients with AF. ARISTOTLE trial randomized 18,201 AF patients.[32] After a median follow-up of 1.8 years, the rate of the primary outcome (risk of ischemic or hemorrhagic stroke stroke or systemic embolism) was 1.27% per year in the apixaban group, vs 1.60% per year in the warfarin group (HR with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority; P=0.01 for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (HR, 0.69; 95% CI, 0.60 to 0.80; P<0.001), and the rates of death from any cause were 3.52% and 3.94%, respectively (HR, 0.89; 95% CI, 0.80 to 0.99; P=0.047) being the first study of this new kind of drugs to confer a mortality benefit.

AVERROES Trial (Apixaban versus Acetylsalicylic Acid to Prevent Strokes)

The AVERROES trial was a double-blind, randomised comparison of the oral factor apixaban versus ASA for stroke prevention in patients with AF not suitable for OAC with a VKA. Patients were randomised to either apixaban 5 mg BID or ASA (81-324 mg daily). Patients on apixaban had lower rates of stroke and systemic embolism (HR 0.45; 95% confidence interval [CI], 0.32 to 0.62; P<0.001) and overall mortality (HR, 0.79; 95% CI, 0.62 to 1.02; P = 0.07) compared to ASA. There was no significant difference in the rate of major bleeding (1.2% for ASA and 1.4% for apixaban p=0.33) or haemorrhagic stroke (0.2% per year in both treatment groups).[33]

Unlike ATLAS ACS 2 for Rivaroxaban, Apixaban for Prevention of Acute Ischemic Events (APPRAISE-2) trial was terminated prematurely (N= 7392) because of an increase in major bleeding events with apixaban in the absence of reduction in recurrent ischemic events.[34] Major bleeding occurred in 1.3% of patients who received apixaban vs 0.5% in those who received (hazard ratio with apixaban, 2.59; 95% CI, 1.50 to 4.46; P=0.001). A greater number of intracranial and fatal bleeding events occurred with apixaban than with placebo.

What Do the Guidelines – Recommendations Say about Novel Anticoagulants?

As mentioned before American College of Cardiology Foundation/American Heart Association/ Heart Rhythm Society focussed update, gave dabigatran a class IB recommendation for AF [26] as follows : "Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance < 15 mL/min) or advanced liver disease (impaired baseline clotting function)".

American College of Chest Physicians Antithrombotic Therapy for Atrial Fibrillation Guidelines [35]state that it would be reasonable for VKA-experienced patients who are well controlled (ie, INR within therapeutic range a high proportion of the time) to continue on VKA therapy if they are satisfied with it and are tolerating it well rather than switching to dabigatran. They cite evidence from meta-analyses of RCTs[36] (twenty-two trials, with a total of 8413 patients) that home monitoring of VKA therapy reduces thromboembolic events by 42% compared with usual monitoring with no increased risk for a major bleeding event, which is similar to the 33% relative reduction in stroke achieved with dabigatran 150 mg bid compared with VKA therapy. Therefore they conclude that any advantages of dabigatran with respect to thromboembolism would likely not exist for patients able to home monitor their INRs. Nevertheless the burdens of VKA therapy related to dietary restrictions and drug interactions will still exist, and there will be a cost for the home monitoring device and test strips. Their final recommendation for patients in favor of oral anticoagulation is dabigatran 150 mg twice daily (since current evidence suggests net clinical benefit at the 150-mg dose) rather than adjusted-dose VKA therapy (Grade 2B).

Canadian Cardiovascular Society Atrial Fibrillation Guidelines Focused 2012 Update suggest, that when OAC therapy is indicated, most patients should receive dabigatran, rivaroxaban, or apixaban (once approved by Health Canada), in preference to warfarin (Conditional Recommendation, High-Quality Evidence). Compared with warfarin, both dabigatran and apixaban are more efficacious than warfarin for the prevention of stroke and systemic thromboembolism, while rivaroxaban is noninferior to warfarin. Apixaban causes less major bleeding than warfarin, while in comparison with warfarin there is no more major bleeding with either dabigatran 150 mg or rivaroxaban. [37]

European Society of Cardiology 2012 focused update of the Guidelines for the management of atrial fibrillation [38] foreword is that there is still limited experience with these agents, therefore strict adherence to approved indications and careful post-marketing surveillance are strongly recommended. Using data from Danish nationwide cohort study for dabigatran, rivaroxaban, and apixaban[39] they conclude that at a $CHA2DS_2$-VASc score of 1, apixaban and both doses of dabigatran (110 mg b.i.d. and 150 mg b.i.d.) had a positive net clinical benefit while, in patients with $CHA2DS_2$-VASc score ≥2, all three novel OACs were superior to warfarin, with a positive net clinical benefit, irrespective of bleeding risk. Briefly they recommend that when adjusted-dose VKA cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, dabigatran, rivaroxaban, apixaban is recommended (Class I B). Finally the aforementioned ESC update gives priority to NOAC over VKAs stating that where OAC is recommended, one of the NOACs should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit (Class II A).

Controversies and Points For Further Research

There are many data now with more than 60.000 patients showing that new oral anticoagulants that do not require INR monitoring, seems to be particularly promising according to recent studies. Nevertheless there are some interesting aspects in their use that deserve cautious use and further research.

1. The lack of widely available methods to measure the therapeutic inhibition of factor II or X for a particular patient. This seems to be of minor concern since other well established anticoagulant regiments such as low molecular weight heparins need specialized procedures (ie anti Xa levels) to measure their efficacy. Nevertheless the latter are easily available for the most hospitals.

2. The lack of specific antidotes to reverse their actions will be an emerging problem as their use increases.

3. The economical aspects of their use. Originally approved for DVT prevention after orthopedic operations (i.e. limited numbers of patients and short duration of treatment) their new indication for stroke – STE prevention in atrial fibrillation broadens considerably their target group, and the duration of treatment since they will be used for lifelong prevention. So lower prices have to be expected by the industry, particularly in times of austerity.

4. The lack of data regarding arterial blood pressure control of participants both in older antithrombotic and NOAC trials. Information regarding blood pressure is limited and fragmented, and data for in-study and final blood pressure levels, blood pressure control and concomitant antihypertensive medication are lacking. Nevertheless, atrial fibrillation and arterial hypertension frequently coexist and are both associated with increased stroke rates. A large number of trials has shown that antihypertensive treatment is accompanied by marked reduction in the incidence of stroke[40] and that the degree of protection against stroke is related to the degree of BP reduction .[41]More importantly, it has been estimated that even slightly (2 mmHg) lower systolic blood pressure would result in about 10% lower stroke mortality rates.[41] Based on these findings, it seems rational to assume that even small differences in blood pressure might greatly affect the outcome of a study in which stroke is the primary endpoint, as is the case in atrial fibrillation studies.

5. Almost all guideline updates mentioned above favor a preferential but cautious use of NOACs since their generalized use implicates exposure of populations with characteristics far beyond those studied in their major trials. For example there are no data regarding dosages or efficacy – safety in patients with severe CKD (excluded from trials), low body mass index and in the presence of hepatic dysfunction. On the other hand given their relative short half lives compliance and adherence to treatment is crucial, especially such that patients would be left without any anticoagulation protection if more than one dose were missed.[38] Finally as with all newer drugs their off label use e.g. for anticoagulation in the presence of mechanical prosthetic heart valves,[42] can be catastrophic.

6. Finally, there is an ongoing issue affecting all antithrombotic strategies. There is extensive evidence that the stroke-risk of paroxysmal AF patients is comparable to that among patients with persistent or permanent AF. Is there a threshold AF burden to require antithrombotic therapy? In the TRENDS study [43] patients with cardiac rhythm management devices and ≥1 stroke-risk factor (mean $CHADS_2$ = 2.2) were followed for a mean of 1.4 years. Burden of AF was quantified as the longest total daily duration of atrial tachycardia (probable AF) during a 30-day monitoring period. The risk ratio (RR) for AF-burden ≥ 5.5 hours was 2.20 (stroke/TIA/STE incidence 2.4% per year). In the Asymptomatic AF and stroke evaluation in pacemaker patients and the AF reduction atrial pacing trial (ASSERT) they included hypertensive patients older than 65 years old, under antihypertensive treatment, without receiving anticoagulation therapy. A total of 2580 patients were enrolled and monitored for 3 months to detect subclinical atrial tachyarrhythmias, and they followed them for a mean of 2.5 years for the primary outcome of ischemic stroke or systemic embolism. At three months, subclinical atrial tachyarrhythmias had been detected by the pacemaker in 10% [44] and were associated with increased risk of clinical atrial fibrillation (hazard ratio, 5.56; 95% CI, 3.78 to 8.17; P<0.001) and of ischemic stroke or system-

ic embolism (hazard ratio, 2.49; 95% CI, 1.28 to 4.85; P=0.007), and remained predictive of stroke risk even after adjustment for stroke risk factors. These two studies demonstrate a clear association between device-detected AT and stroke/STE. The ASSERT trial demonstrates that episodes as short as 6 minutes are markers for the development of clinical AF and for stroke/STE risk. However, the absolute stroke risk was lower in ASSERT patients than in clinical AF patients and there was typically a delay of many months between the appearance of device-detected AT and the occurrence of stroke/STE.[37]

Conclusions

The use of antithrombotics for stroke prevention in AF has been historically suboptimal. The introduction and guideline adoption of NOACs is a step forward and should at least theoretically diminish any reluctance to provide such a treatment due to VKAs drawbacks. The use of currently used simplified scores for stroke and hemorrhagic risk assessment can lead to better implementation of guidelines. Nevertheless there are some questions and concerns (as for every recently introduced drug) that have to be addressed and answered in the near future.

Disclosures

No disclosures relevant to this article were made by the authors.

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