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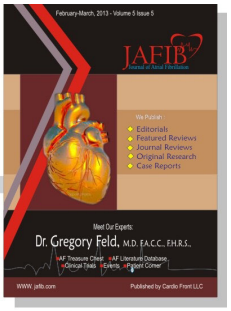

New Stroke Prophylaxis Options in Atrial Fibrillation Patients

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Abstract

Atrial Fibrillation (AF) is an epidemic that is increasing in size and scope. AF can have many symptoms and cause a variety of negative health impacts.The most important health risk of AF is the increased risk of stroke and systemic thromboembolism.Oral anticoagulation with warfarin has been the gold standard for stroke risk reduction in AF, but new drugs and treatment strategies for AF are changing clinical practice. These new advances could offer better tailoring of treatments to patients with high risk of stroke while reducing the potential bleeding complications.

Introduction

Atrial Fibrillation (AF) is a growing public health problem expected to affect up to 15 million patients by 2050.[1] While AF can be highly symptomatic, the risks associated with the arrhythmia determine long-term outcome. AF increases mortality 1.5 fold in men and 1.9 fold in women and confers an approximate 4% yearly risk for stroke and systemic embolism of approximately 4 % per year.[2-3] Many new therapies and strategies for comprehensive AF risk management are being developed. Many of these offer the potential for greater stroke risk reduction with fewer bleeding complications.

Predicting Thromboembolic Risk in Atrial Fibrillation

Stroke is the most important and feared sequalae of AF. AF increases stroke risk 5-fold across the spectrum of patients. However, the stroke risk from AF is not equal in all patients. It is important to differentiate low risk patients who will not benefit from oral anticoagulation from intermediate and high-risk patients who likely will. There are four strong independent clinical risk factors for stroke in AF patients: prior stroke or transient ischemic attack (TIA) [5% risk per year], advanced age, hypertension, and diabetes.[3] Left ventricular (LV) dysfunction or history of congestive heart failure has also been associated with increasing stroke risk.[4] More limited data have shown other clinical risk factors linked to stroke risk in AF. These include: female gender, peripheral vascular disease, coronary artery disease, and history of prior myocardial infarction (MI).[5-6] Also left atrial appendage (LAA) clot, severe spontaneous echo contrast , a LAA emptying velocity < 20 cm/s, left ventricular dysfunction (EF < 40%), and aortic atheroma are echocardiographic features associated with thromboembolism.[7] Numerous inflammatory and hypercoaguable markers are elevated in AF. Elevated C-reactive protein (CRP) levels have been shown to be an independent predictor

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of stroke in AF.[8] Also, recent studies have shown that certain genetic variants (polymorphisms of chromosome 4q25 and 16q22) are associated with increased stroke risk.[9-10]

The $CHADS_2$ score is the cornerstone of stroke risk stratification in AF. It was initially formulated from the combination of prior risk stratification algorithms. The Atrial Fibrillation Investigators (AFI) scheme used a pooled analysis from the control groups of five trials, and the Stroke Prevention in Atrial Fibrillation (SPAF) classification was derived from a retrospective analysis of risk factors from aspirin treated cohorts of the SPAF trials. The $CHADS_2$ score assigns one point for congestive heart failure; one point for hypertension, one point for age > 75 years, one point for diabetes mellitus, and two points for history of prior stroke or TIA .[4] Currently, a score of zero is considered low risk, a score of 1 is intermediate risk and a score of 2-6 is considered to be high risk for developing a future stroke. The $CHADS_2$ score was prospectively validated in a cohort of Medicare beneficiaries.Its primary advantage is the simplicity of categorizing patients into different groups that warrant therapy to reduce stroke risk.

The newly published CHA_2DS_2-VASc score uses a larger spectrum of risk factors in an attempt to better indentify a low risk population that does not need any antithrombotic therapy. The new system modifies the original $CHADS_2$ score by assigning 2 points for age ≥ 75 years, and one point for age 65 years to 74 years, history of vascular disease (prior myocardial infarction (MI), peripheral arterial disease or aortic atheroma), and female gender (a score of zero is low risk, one is intermediate risk and 2-9 is high risk). This was initially validated against the European Heart Survey on AF, and recently in the Danish national patient registry. It showed a marginal improvement over the original $CHADS_2$ score in stroke predication. The main benefit of the $CHA2DS_2$-VASc score is that its low risk cohort had a very low rate of stroke and intermediate risk patients had a 0.6% to 1.45% per/year rate of stroke.[5,11] The CHA_2DS_2-VASc score is part of the 2010 sp(ESC) guidelines on management of AF. [12]

Modern implantable cardiac devices have the ability to detect arrhythmia and monitor AF burden. The TRENDS study suggested that a threshold duration of 5.5 hours of atrial fibrillation per month conferred an increased stroke risk for that given month.[13] Data from two studies combining the degree of AF burden detected from dual chamber pacemakers with $CHADS_2$ and CHA_2DS_2-VASc scores showed improved accuracy of stroke risk prediction. This potentially allows for more precision with prescribing oral anticoagulation (OAC).[14,15] The IMPACT study will examine whether early detection and treatment of AF with remote device monitoring can reduce stroke rates. Another potential strategy for select patients would be to only prescribe OAC at times when AF burden would predict a higher embolic rate.

Managing AF patients also includes assessment of their bleeding risk. Many of the same factors that predict increased bleeding risk also predict increased stroke risk, making it difficult discriminate in which patients the risk of bleeding outweighs the risk of stroke. The HAS-BLED criteria have been developed to assess bleeding risk. One point is assigned for hypertension (SBP > 160 mm Hg), abnormal renal or liver function, stroke, bleeding history or predisposition, labile INR (therapeutic < 60% of the time), older age (> 65 years), or use of certain drugs (platelet inhibitors, nonsteroidal anti-inflammatory drugs [NSAIDs], or concomitant alcohol use). A score of 0 is considered low risk, 1-2 is intermediate risk, and >2 is high risk.[16] OAC can be reconsidered if the HAS-BLED score is greater than the $CHADS_2$ or CHA_2DS_2-VASc score. The HAS-BLED criteria also appear in the ESC guidelines on management of AF.[12]

Preventing Stroke in Atrial Fibrillation

OAC with warfarin is the foundation of stroke prevention in AF. OAC results in an approximate 60-70% reduction of stroke, with an average absolute 3% reduction of thromboembolic events.[13] This effect has been consistent across multiple trials and different populations. Treatment with warfarin in AF patients is associated with an increase in major bleeding episodes (0.3-0.5% for absolute increase for major bleeding and 0.2% increase in intracranial hemorrhage.).[17] The net benefit of warfarin also extends to elderly patients (>75 years), which was shown in the BAFTA trials comparing aspirin (ASA) to Coumadin.[18] All major guidelines recommend OAC with a goal INR of 2-3 for patients with

a $CHADS_2$ score of 2 or greater.

Managing the risks and benefits of OAC in intermediate risk patients ($CHADS_2$ score of 1) is challenging.. Guidelines have historically offered the choice of warfarin or ASA for intermediate risk patients. Data from the early OAC trials for AF and cohort data suggested that the bleeding risk on warfarin cancelled the benefit from reduction in ischemic stroke in intermediate risk patients .[19] Contemporary data suggest that intermediate risk patients may benefit from warfarin. In the Active W trial, patients with $CHADS_2$ score of 1 had a reduction of ischemic stroke from 1.25%/year in the ASA-clopidogrel arm vs. 0.43%/year in the warfarin arm.[20] Data from a Korean cohort of $CHADS_2$ score of 1 patients showed a 20.9% stroke rate in the no therapy cohort, 10.7% in the antiplatelet group, and 4.2% in the warfarin cohort.[21] Also, analysis of a French cohort of intermediate risk AF patients showed a 8.4% event rate in warfarin arm and 17.9% in the non-warfarin arm.[22] The primary event driving the outcome in this study was death and not stroke. Both trials showed a low incidence of major bleeding, which did not negate the benefit of OAC. Data from a cohort of patients that received coronary stents showed that patients with a $CHADS_2$ score less than or equal to 1 had a beneficial stroke reduction with OAC .[23] There was a trend toward increased bleeding in the patients that received OAC. The spACCP and ESC guidelines for AF suggest that OAC be considered for intermediate risk
patients.

Guidelines include aspirin for treatment of patient with low to intermediate risk AF patients. A meta-analysis showed that aspirin resulted in a 20% relative risk reduction for stroke in the AF population.[24] The data for aspirin's benefit in AF stroke reduction is with 325 mg, and not from lower doses.[25] Recent data suggest the aspirin may only have a small beneficial role in AF. In the BAFTA trial, warfarin was superior to ASA in elderly patients, and was not associated with an increased risk of major bleeding.[18] The WASPO trial showed a higher rate of adverse events with ASA than with warfarin.[26] A Japanese trial showed no benefit of ASA (dose 150-200 mg) vs. control in the prevention of stroke in AF. There was also a trend toward increased major bleeding episodes 1.7% vs. 0.4% for placebo (p=0.10).[25] The 1.7% bleeding rate is similar to the warfarin arms of BAFTA and ACTIVE W. Furthermore, the addition of aspirin to warfarin has been shown to increase bleeding rates without the benefit of thromboembolism reduction. Newer guidelines have shifted toward the use of OAC in intermediate risk AF patients.

Recent trials have shown clopidogrel's role in AF stroke prevention, and it was recently added to the 2011 update to the ACC/AHA/HRS AF management guidelines. The ACTIVE A trial showed ASA plus clopidogrel was superior ASA alone in reducing major vascular events (6.8% per year vs. 7.6% per year) for patients deemed unable to take warfarin. This result was due to a reduction in strokes in the clopidogrel plus ASA arm (2.4% per year vs. 3.3% per year).[27] There was an increased risk major bleeding episodes (2.0% vs. 1.3%). The Active W trial showed that treatment with clopidogrel plus ASA was inferior to warfarin in the prevention vascular events (3.93% to 5.60%, p=0.0003.) Furthermore, the combination of clopidogrel plus ASA was associated with an increased risk of bleeding episodes (15.4% vs. 13.2%, p<0.001).[28]

Another key to risk reduction in AF is adequate monitoring of anticoagulation, maintaining patients in the target therapeutic range (INR 2.0-3.0). Data suggest that incremental stroke reduction benefit starts to plateau at an INR of 1.8-2.0, and an increased risk for intracranial hemorrhage and major bleeding begins to significantly increase with INR > 3.0-3.5.[29] Increasing the amount of time in therapeutic range (TTR) has been shown to improve patient outcomes. Recent data have shown that patients who spent more than 70% of the time with an INR between 2.0-3.0 had a significantly reduced rate of stroke and mortality, and those who spent < 30% with an INR between 2.0-3.0 had a trend toward worse outcome compared with control patients not taking warfarin.[30] Specialized warfarin clinics have been shown to improve control of INRs, and while home INR testing slightly improved INR control; it did not improve outcomes.[31] Pharmacogenetic assisted management of warfarin may help enhance warfarin control, especially during initiation of warfarin when adverse events are most common .[32]

New Anticoagulants for Treatment of Atrial

Fibrillation

Dabigatran (Pradaxa) is a new oral anticoagulant that has been approved by the FDA (150 mg bid dose, 75mg bid for creatinine clearance 15-30ml/min) for management of stroke risk in AF. Dabigatran is an oral direct thrombin (IIa) inhibitor (DTI) that blocks thrombin mediated generation of fibrin from fibrinogen and prevents the thrombin-mediated activation of factors V, VIII, XI, and XIII. Dabigatran is renally excreted (80%), and has a half-life of 12-17 hours.[33] It had been extensively studied in the prevention of venous thromboembolism (VTE) before the RE-LY trial demonstrated its efficacy in prevention of stroke in AF. The RE-LY trial randomized patients with AF and risk factors for stroke risk to warfarin or Dabigatran (110 mg or 150 mg bid). The primary outcome was stroke or systemic thromboembolism. The trial showed that Dabigatran 110 mg was noninferior to warfarin (event rate 1.53% per year vs. 1.69 per year, p <0.001 for noninferiority). Dabigatran 150 mg was superior to warfarin (event rate 1.11% P <0.001 for superiority). The dabigatran 110 mg group had a significantly lower risk of major bleeding than warfarin (3.36% vs. 2.71%, p=0.003), and the higher dose of dabigatran (150 mg) had a similar major bleeding rate (3.1%). Dabigatran significantly reduced intracranial hemorrhage (0.7% warfarin, 0.3% dabigatran 150 mg, and 0.2% dabigatran 110 mg). There was a trend toward lower mortality in the dabigatran treated patients. There was a small increase in the incidence of myocardial infarction that reached marginal significance with dabigatran 150 mg (0.5% vs. 0.7% p=0.048).[33]

Rivaroxaban (Xarelto) is the first of many oral direct factor Xa inhibitors in development. Factor Xa is at the confluence of the intrinsic and extrinsic pathways and promotes the conversion of prothrombin (factor II) to thrombin (factor IIa). It is currently approved in the US for prevention of deep venous thrombosis in patients undergoing knee or hip replacement. The Rocket-AF trial randomized rivaroxaban 20 mg daily (15 mg for a creatinine clearance 30-49 ml/min) against dose adjusted warfarin in patients with > 2 risk factors for stroke or a history of thromboembolism. The trial was double-blinded and the average $CHADS_2$ score was 3.5. Rivaroxaban was shown to be noninferior to warfarin with an event rate 1.71% per year (rivaroxaban) vs. 2.16% per year (warfarin) (p<0.001). A prespecified secondary on-treatment analysis showed rivaroxaban to be superior warfarin (event rate 1.70% per year vs. 2.15% per year p= 0.015). Major bleeding and adverse events were similar between groups. Intracranial hemorrhage (0.49% vs. 0.74% (p= 0.0149)) and fatal bleeding (0.24% vs. 0.48%, p=0.003) was significantly lower in the rivaroxaban group.[34]

Apixaban is another direct factor Xa inhibitor. It is CYP3A4 metabolized (75%) and renally excreted (25%). Two recent trials demonstrated its efficacy in AF stroke prevention. In AVERROES, apixaban 5 mg twice daily was compared to ASA (81 -364 mg) for prevention of stroke in AF patient deemed not candidates for warfarin therapy. The average $CHADS_2$ score was 2.1. The primary outcome was the incidence of stroke or systemic embolic event. The trial was stopped early due to the efficacy of the study drug. The primary event rate was 4.0% per year on ASA and 1.7% per year on apixaban (p=0.000004). Major hemorrhage was 1.2% per year on ASA and 1.5% per year on apixaban (p=0.330, ICH was 0.4% per year on apixaban and 0.3% per year in the ASA group (p=0.79). There was a trend toward decreased mortality with apixaban compared with ASA (3.4% vs. 4.4%, p 0.07).[35] In the ARISTOTLE trial, patients with AF and at least one stroke risk factor were randomized to apixaban 5mg bid or warfarin therapy. The primary outcome was a composite of ischemic or hemorrhagic stroke or systemic embolism. The primary event rate was 1.27% per year in the apixaban group versus 1.60% per year in the warfarin group (p<0.001 for noninferiority; p=0.01 for superiority). The rate of major bleeding was 2.13% per year in the apixaban group vs. 3.09% per year in the warfarin group (P<0.001), and the all cause mortality rate was 3.52% for apixaban and 3.94% for warfarin (P=0.047). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (P<0.001).[36]

There are many other new anticoagulants in early development. AZD0837 is a direct thrombin inhibitor in phase II development. Edoxaban is an oral direct Xa inhibitor that will be studied against warfarin for AF stroke prevention in the ongoing phase III ENGAGE TIMI 48 trial.[37] Betrixaban is also a Xa inhibitor that is almost completely eliminated in bile and is in phase II development.[37]

It is being developed with a Factor Xa reversal agent PRT064445.[38] Tecafarin is a novel Vitamin K antagonist that is not metabolized by the cytochrome P450 system, reducing drug interactions and dosing variability associated with warfarin.

Factor Xa inhibitors and direct thrombin inhibitors (DTIs) do not need routine monitoring since they offer reliable anticoagulation with a wide therapeutic window. DTIs and Xa inhibitors prolong PT and aPTT, but the values do not correlate with a specific drug level; however, these tests can show drug activity [39, 40] A thrombin clotting time (TT) is very sensitive for detecting DTI activity, but standardized reagents must be used to precisely monitor DTI effect. A Hemoclot Thrombin inhibitor assay (Hyphen BioMed, Neuville-sur-Oise, France) is a standardized TT assay that allows for a direct assessment of DTI activity and level. The ecarin clotting time (ECT) measures thrombin generation, thus directly measuring DTI effect.[39] Factor Xa inhibitor levels can be measured with a one-step heparin clotting time (HepTest, American Diagnostica, Stamford CT) or a prothrombinase-induced clotting time with short incubation periods. [40] However, these tests are mostly research tools currently with limited widespread commercial availability. In cases of overdose, or life threatening bleeding there are no specific antidotes for DTIs or Xa inhibitors. Activated charcoal can be given to inhibit absorption, and hemodialysis can remove dabigatran from the blood. Recombinant factor VII (rFVIIa; NovoSeven) has been shown in some reports to be able to reverse the effects of dabigatran; however, it may take several doses, depending on the clearance of dabigatran. Prothrombin complex concentrate can reverse the effect of rivaroxaban in healthy volunteers. [41] Specific reversal agents for DTI's and factor Xa inhibitors are being developed.

Non-Anticoagulant Strategies to Reduce Stroke Risk in Atrial Fibrillation

Hypertension is a key risk factor for the development of AF and thromboembolism in AF. Management of systolic hypertension has been shown to significantly reduce the rate of stroke in patients with AF. This has been particularly shown with angiotensin receptor blockers and angiotensin converting enzyme inhibitors. [42-43]

Since the left atrial appendage (LAA) has been implicated in up to 90% of strokes in AF, LAA occlusion has been proposed as an alternative to anticoagulation for patients with AF. [44] Outcomes data with surgical LAA occlusion are limited and frequently (30-50%) the occlusion is incomplete due to the variable nature of LAA anatomy and technique used. [44] Multiple percutaneous devices for LAA closure are in advanced stages of clinical development. In the PROTECT-AF study, the Watchman device for LAA occlusion was compared to warfarin. The device patients took warfarin for at least 45 days post implant. The Watchman device was noninferior to warfarin in the prevention of all strokes (hemorrhagic or ischemic). There was a significant increase in adverse events, but most were due to procedural related pericardial effusion.[45] An FDA panel recommended approval of the Watchman, and a second phase III randomized trial is underway. The PLAATO device has been studied in patients who are not candidates for warfarin. The 5-year follow-up data showed a 3.8% yearly rate of stroke, which was lower than the 6.6% stroke risk predicted by the $CHADS_2$ score for the cohort.[46] Both devices had high success rates with LAA closure as assessed by transesophageal echocardiography. [45, 46]

Maintaining sinus rhythm may also reduce stroke risk. Data from the SPAF trials showed that paroxysmal and persistent AF had similar stroke rates (3.2% paroxysmal per/year vs. 3.3% with persistent AF). Recent data from the ximelegatran trials SPORTIF III and SPORTIF V showed a stroke rate of 1.73% per year for persistent AF and a 0.93% per year for paroxysmal AF (p= 0.037).[47] Also, recent data from a meta-analysis of trials for dronedarone showed a stroke rate of 1.2% in the dronedarone treated group and 1.8% in the placebo group (p= 0.027%). [48] After successful atrial fibrillation ablation, patient who maintain sinus rhythm have a very low risk of stroke with cessation of OAC. [49] This includes patients with $CHADS_2$ score of 2 or greater. However, the data are retrospective and nonrandomized. Currently, the major guidelines for AF recommend continuing anticoagulation for all AF patients with a high risk for stroke regardless of whether the ablation was successful.

Atrial fibrillation is growing public health problem, and stroke is the most important cause of morbidity and mortality in AF. Proper risk stratification can identify the patients most likely to benefit from anticoagulation. Addition of data from implantable cardiac devices and identification of new risk factors for stroke in AF can lead to further refinement in calculating stroke risk in AF. This will help in properly directing therapy for AF patients while minimizing adverse events. While OAC with warfarin has been the mainstay of therapy in AF, many new anticoagulants and device therapies offers the potential for greater stroke reductions with a lower incidence of bleeding for patients with AF.

Conclusions

Atrial fibrillation is growing public health problem, and stroke is the most important cause of morbidity and mortality in AF. Proper risk stratification can identify the patients most likely to benefit from anticoagulation. Addition of data from implantable cardiac devices and identification of new risk factors for stroke in AF can lead to further refinement in calculating stroke risk in AF. This will help in properly directing therapy for AF patients while minimizing adverse events. While OAC with warfarin has been the mainstay of therapy in AF, many new anticoagulants and device therapies offers the potential for greater stroke reductions with a lower incidence of bleeding for patients with AF.

Disclosures

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