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Prevention of Stroke in Patients With Atrial Fibrillation

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Abstract

The presence of atrial fibrillation (AF) increases the risk of stroke, especially in patients with risk factors as outlined by the CHADS2 and CHA2DS2-VASc scoring systems. Although warfarin can reduce stroke rates by over 65%, only 55% of patients, in the USA, who should be on warfarin for AF and stroke prevention are taking the drug due to the need of INR monitoring, difficulties in maintaining a therapeutic INR in the therapeutic range and dietary and drug interactions. Dabigatran, an oral direct thrombin inhibitor and rivaroxaban and apixaban, factor Xa inhibitors, have demonstrated efficacy in reducing stroke in large clinical trials. These novel anticoagulants will change the therapeutic landscape since patients will be able to prevent stroke with a lower risk of intracranial hemorrhage and without the need for INR monitoring and less drug-dietary interactions.

Introduction

Atrial fibrillation (AF) is a common disease affecting up to 5.1 million individuals in the USA.[1–3] This number is expected to increase up to 15 million by 2050.[4,5] Currently, as many as 1% of the general population and 12% of those over 85 years of age have AF. The annual incidence of stroke in patients with AF is 5% to 12% and the presence of AF increases stroke risk five-fold.[6–9] In spite of this growing problem, less than 50% of eligible patients, in the USA, receive indicated antithrombotic therapy, and more than 50,000 preventable strokes each year are due to failure to use appropriate antithrombotic therapy in AF.[10]

AF and Stroke:

AF is present in as many as 15 % of all ischemic stroke patients. Although men are more likely to develop AF, women are more likely to have AF related stroke. Strokes in AF patients have an increased morbidity and mortality with a 50% one year mortality.11 Strokes typically present without a prior warning TIA. In addition, one third of stroke patients have the diagnosis of AF made after the stroke occurs. In stroke patients, AF prevalence increases with age from 6.5% in those in their fifties to 30.7% in those in their eighties. There is a slight ethnic variation with 29% of whites having AF in their first ischemic stroke vs. 18% of African-Americans and 14% of Hispanics.[12]

Ischemic strokes in AF patients tend to be more severe, secondary to emboli affecting larger cerebral arteries, resulting in worse neurological deficits and higher mortality.[12] One month mortality after an ischemic stroke is 3.4% in patients without AF vs. 11.3% in patients with AF.[12] The severity of the neurological deficits is related to a higher

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infarct volume in patients with AF (52 cc vs. 16 cc in non-AF patients) and higher incidence of parenchymal hemorrhagic transformation (29% vs. 5% in non-AF patients).13 In addition to the larger strokes, AF results in a high micro-embolic burden, which is evident in 29% of patients with stroke and 10% in patients with asymptomatic lone atrial fibrillation.14 During CT scanning, 14% of AF patients have silent brain infarctions found. This indicates a higher risk of having a symptomatic stroke in the following year (8%, 14%, 14% and 100% for patients with 0, 1, 2 and 3 or more silent infarctions respectively). Although patients with AF may suffer a stroke due to other causes, cardio-embolism remains the leading mechanism, causing 70% of strokes in patients with AF.

Risk Factors for Stroke in Patients With AF

Patients with AF who have history of stroke or-TIA, mitral stenosis or prosthetic heart valves are at very high risk for having a subsequent stroke.
On the other hand, patients older than 75 years, those with history of hypertension, diabetes or heart failure/impaired left ventricular systolic functionhave a moderately increased risk.[15,16] Multiplerisk stratification systems exist.[17] In patients with non-valvular AF those risk factors have been utilitiesin forming the CHADS2 scoring system (Table1). This scoring system gives two points to the high risk associated with having prior stroke/ TIA and one point for each of the moderate risk factors: age>75 years, hypertension, diabetes and heart failure. Patients, who are stratified as having CHADS2 score of 6, have an 18.2% risk of suffering a stroke in the following year. Even in patients with a CHADS2 score of 0 ("low risk"), there is a 1.9% risk of suffering a stroke in the following year.18 Recently a new scoring system has been developed, CHA2DS2-VASc, which adds additional known risk factors to the CHADS2 system (Table 2): vascular disease(myocardial infarction, peripheral artery disease and aortic atherosclerotic disease), female gender and age ≥65 years (also increasing the risk points to two for patient's ≥75 years). Based on this scoring system, a 68-year-old female with a history of myocardial infarction and hypertension has a CHADS2 score of 1 but a CHA2DS2-VASc score of 4, with about a 4% annual risk of stroke. It shouldbe emphasized that CHADS2 and CHA2DS2-VAScscoring systems apply to patients with non-valvular atrial fibrillation and that many other risk fac factors (like hyperthyroidism) were not included.

Stroke Prevention in Patients With AF

Current guidelines recommend using anticoagulation with warfarin for stroke prevention for patients with a CHADS2 score of ≥2 and aspirin only or no therapy for patients with a score of 0.1,2 Inpatients with a CHADS2 score of 1, therapeutic anticoagulation is recommended; however, aspirin is also recommended as an acceptable alternative.

In addition to warfarin and aspirin, several other pharmacologic therapies have been used for stroke prevention in patients with AF, including unfractionated heparin, low molecular weight heparin, clopidogrel, direct thrombin inhibitors and Factor Xa inhibitors. The latter two have the most impressive efficacy data for reducing the risk of stroke in high risk AF patients.

Warfarin

Warfarin is an effective anticoagulant by inhibiting the development of vitamin K-dependent factors in the coagulation cascade. The recommended therapeutic range for stroke prevention in patients with AF is an INR of .[2-3] This is based on the observation that an INR<2 sharply increases the risk of thromboembolism and with an INR>3 -3.5, the risk of intracranial hemorrhage (ICH) sharply increases.19

Warfarin has been in use for over 60 years and iseffective if the INR is kept in therapeutic range. It is relatively inexpensive and it is easy to reverse.

Multiple large studies have compared warfarin to aspirin or placebo. The relative risk reduction of stroke vs. placebo is 71% and vs. aspirin is 50%, which are both statistically significant. Conversely, warfarin increases the risk for major bleeding . Warfarin requires frequent monitoring to keep the INR in the therapeutic range and has significant interactions with many medications and foods. These limitations result in patient and healthcare provider reluctance to use warfarin. Overall, 55% of patientsthat are eligible for warfarin therapy receive it and appropriate warfarin

use drops to only 35% of patient's ≥85 years. In primary care population of patients that are candidates for warfarin therapy per guidelines and with no contraindications, only 15% have therapeutic INR. In addition, 65% did not receive warfarin and 6% received warfarin but had subtheraputic INR and 14% had supratheraputic INR. In the anticoagulation clinic population only 32% had therapeutic INR, while 40% had subtheraputic INR, 7% had supratheraputic INR and 21% were lost due to infrequent follow-up. The most frequent reasons for physicians not to use warfarin were concern about the risk of bleeding, assuming a low risk of embolism and patient refusal.[20,21]

The risk of ICH in patients receiving warfarin therapy is thought to be in the range of 1-2% with some reports as low as 0.5% and others as high as 4%. HASBLED is a new scoring system to predict the bleeding risk in anticoagulated patients with AF.[22] The risk factors included in the scoring are Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/ Alcohol Concomitantly. Hypertension, stroke and advanced age are also risk factors for ischemic stroke. This illustrates the importance of individualized decision making in this subset of patients that are at high risk for thrombotic and bleedings events.

Aspirin and Clopidogrel

Aspirin has been compared to placebo in multiple trials (AFASAK I, SPAF I, EAFT, ESPS II, LASAF and UK-TIA). In general, aspirin offers little protection from stroke compared to placebo and when compared to warfarin aspirin was inferior. Recently, in AVERROES, primary outcome events (stroke or systemic embolism) were lower with apixaban(1.6% per year) versus (3.7% per year) among those assigned to aspirin (HR 0.45; 95% confidence interval [CI], 0.32 to 0.62; P<0.001).[23] Of interest, there were only 44 cases of major bleeding (1.4% per year) in the apixaban group and 39 (1.2% per year) in the aspirin group (HR 1.13; 95% CI, 0.74 to 1.75; P = 0.57). In addition, there were 11 cases of intracranial bleeding with apixaban and 13 with-aspirin. The risk of a first hospitalization for cardiovascular causes was reduced with apixaban as compared with aspirin (12.6% per year vs. 15.9% per year, P<0.001). Recent data in 132,272 patients with non-valvular AF from Denmark reported that vitamin K antagonists consistently lowered the risk of thromboembolism compared to aspirin and no treatment, the combination of vitamin K antagonists and aspirin did not yield any additional benefits. Treatment with either of these drugs alone or in combination increased bleeding rates compared to no treatment and concluded that aspirin has no role in reducing stroke in such patients.24 Thus, aspirin has very little role in preventing embolic stroke in AF patients. However, the drug is commonly used in lower risk patients instead of therapeutic anticoagulation. This approach has little data to support efficacy yet still is associated with adverse events such as bleeding.

ACTIVE-W compared warfarin (target INR 2-3) vs. aspirin (75-100mg/day) plus clopidogrel 75 mg/day in 6706 patients over and median 1.28 years of follow-up paying attention to the primary end points of stroke, systemic embolus, myocardial infarction and vascular death.[25] The trial was stopped early due to the superiority of warfarin (RR=1.44 (1.18-1.76); P=.0003). ACTIVE-A compared aspirin (75-100 mg/day) plus clopidogrel 75mg/day vs. aspirin alone in 7554 patients over a median of 3.6 years of follow-up looking at the same primary end points.[26] The trial showed that aspirin and clopidogrel was superior to aspirin alone in preventing thromboembolism (RR=0.89 (95% CI,0.81–0.98; P=.01). This reduction of thromboembolic events came at the cost of increased bleeding (major bleeding RR=1.57 (1.29-1.92); P<0.001). The mean CHADS2 score in both active trials was 2.0. The results from the ACTIVE trials were incorporated in the 2010 American Heart Association and American Stroke Associated guidelines. For patients unable to take oral anticoagulants aspirin is recommended (Class I; Level of Evidence A). However, the combination of clopidogrel plus aspirin was not recommended for patients with a hemorrhagic contraindication to warfarin since it carries a risk of bleeding similar-to that of warfarin (Class III; Level of Evidence B).

New Oral Anticoagulants

The new oral anticoagulants include the direct-thrombin inhibitor, dabigatran, and the Factor Xa inhibitors rivaroxaban, apixaban, betrixaban and edoxaban (Table 3)

Dabigatran

Dabigatran is a direct oral thrombin inhibitor that is commercially approved for the prevention of-stroke and systemic embolism in patients with nonvalvular AF. It has a half-life of 14-17 hours and is given twice daily. It is administered as the pro-drug, dabigatran etexilate, and rapidly converted to an active drug by hepatic enzymes and eventually, 80% of the absorbed drug is excreted renally.

Dabigatran was compared to warfarin in RELY trial using a PROBE design (Table 4).[27-29] RELY enrolled 18,113 patients, with a mean CHADS2 score of 2.1, for a median period of 2 years looking for a primary outcome of stroke or systemic embolization. Patients were enrolled into one of 3 arms: warfarin, dabigatran 110mg twice daily and dabigatran 150mg twice daily. The median time in the therapeutic range (TTR) for the warfarin group was 67%. It is important to note that certain patients were excluded from that trial so the results of the trial may not necessarily apply to them. They include patient who are pregnant, in labor and during delivery, nursing mothers, pediatric, with mechanical prosthetic valve, hemodynamically significant valve disease, severe disabling stroke within 6 months or any stroke within 14 days, contraindication to warfarin or creatinine clearance (CrCl) less than 30 ml/min. The trial showed that dabigatran 110mg twice daily was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin; however it had lower rates of major hemorrhage. Dabigatran 150mg twice daily was associated with a 35% lower rate of stroke and systemic embolism but similar rates of major hemorrhage compared to warfarin. An additional finding of importance was that the 150 mg dabigatran arm of the study had a 76% risk reduction in hemorrhagic stroke and a 25% risk in ischemic stroke compared to warfarin. Based on these findings, the FDA approved the 150mg twice daily dose for patients with CrCl > 30 ml/min and also approved a 75mg twice daily dose, based on blood level modeling, for patients with impaired renal function (CrCl >15 and <30 ml/min). Uncontrolled data, in 1255 RELY patients undergoing 1985 cardioversions, showed a very low stroke/systemic embolism rate in all 3 arms of the study with the lowest being 0.3% in the 150mg twice daily dabigatran arm of the study.[30]

Table 1 CHADS2 scoring

Risk Factor	Stroke
Cardiac Failure	1
HTN	1
Age ≥75 y	1
Diabetes	1
Stroke	2

Table 1 CHA2DS2-VASc

Risk Factor	Score
Cardiac Failure	1
HTN	1
Age ≥75 y	2
Diabetes	1
Stroke	2
Vasc dz (MI, PAD, aortic atherosclerosis)	1
Age 65-74 y	1
Sex category (female)	1

Dabigatran has the potential for interaction with drugs that inhibit or induce the P-glycoprotein-substrate transporter. P-glycoprotein inducers (e.g. rifampin) reduce exposure to dabigatran and should generally be avoided. P-glycoprotein inhibitors (e.g. ketoconazole, verapamil, amio darone, dronedarone, quinidine, clarithromycin) increase dabigatgran levels 1.2 to 1.9 fold but generally do not require dose adjustments of dabigatran. Recently there had been a recommendation to consider decreasing the dabigatran dose to 75mg twice daily when co-administered with dronedarone. Dabigatran causes no meaningful alteration in the pharmacokinetics of amiodarone, atorvastatin, clarithromycin, diclofenac, clopidogrel, digoxin, pantoprazole or ranitidine. About 9% of the dabigtran patients in RELY developeddyspepsia requiring drug discontinuation.

New Oral Factor Xa Inhibitors

Rivaroxaban

Rivaroxaban is an oral factor Xa inhibitor recently approved by the FDA for reduction of stroke risk in patients with non-valvular AF.31 Rivaroxaban has a half-life of 6-9 hours, is almost 100% bioavailableand is 36-45% excreted renally. Rivaroxaban is a CYP3A4 and P-Glycoprotein inhibitor substrate.

The ROCKET AF trial compared rivaroxaban to warfarin in 14,264 patients with nonvalvular atrial fibrillation who were at increased risk for stroke (Table 4).32 This study included high stroke risk patients with a mean CHADS2 score of 3.7, with 55% of patients having a prior stroke of TIA. In a double blind, double dummy study, once a day rivaroxaban (20 mg a day or a reduced dose of 15 mg a day in patients with CrCl of 30-49 cc/min) was compared to warfarin with a median TTR of 57%. By intention to treat analysis, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism (HR=0.88) and there was no significant between-group difference in the risk of major bleeding. By on therapy analysis, rivaroxaban was superior to warfarin (HR =0.79; p=0.015)in preventing stroke or systemic embolism. Similar to dabigatran, rivaroxaban reduced the frequency of hemorrhagicstrokes compared to warfarin by 41% (HR = 0.59).

Apixaban

Apixaban is not currently FDA approved for stroke prevention in AF. It has a half-life of 12 hours. It is 25-30% excreted renally. Apixaban is a CYP3A4 and P-Glycoprotein inhibitor substrate. The AVERROES trial compared apixaban (5 mg twice daily) and aspirin (81 to 324 mg per day) in 5599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable.23 This trial showed that apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage. The ARISTOTLE Trial compared apixaban (5 mg twice daily [2.5 mg twice daily in selected patients]) to warfarin in a double blind study of 18,201 patients with atrial fibrillation at risk for stroke (mean CHADS2 score of 2.1) (Table4).33 Apixaban was superior to warfarin in preventing stroke or systemic embolism (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority; P=0.01 for superiority). Apixaban also caused less bleeding, and resulted in lower mortality (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; P=0.047), and reduced hemorrhagicstroke by 49% compared to warfarin.33

Edoxaban

TEdoxaban is not currently FDA approved for stroke prevention in AF. It has a half-life of 6-12 hours. It is 35% excreted renally. Edoxaban is a CYP3A4 and a P-Glycoprotein inhibitor substrate.

The ENGAGE trial is a double blind trial comparing

Table 3 The new oral anticoagulants

Drug	Dabigatran	Rivaroxaban	Apixaban	Betrixaban	Edoxaban
Mechanism of action	Thrombin inhibitor	FXa inhibitor	FXa inhibitor	FXa inhibitor	FXa inhibitor
Half-life	14-17 h	6-9 h	12 h	19-24 h	6-12 h
Regimen	BID	QD, BID	BID	QD	QD
Peak to trough	~7x	12x (QD)	3-5x	~3x	~3x
Renal excretion of absorbed drug	~80%	36-45%	25-30%	~15%	35%
Potential for drug interactions	P-glycoprotein inhibitor	CYP3A4 substrate and P-glycoprotein inhibitor	CYP3A4 substrate and P-glycoprotein inhibitor	Not substrate for major CYPs	CYP3A4 substrate and P-glycoprotein inhibitor

60mg and 30mg a day of edoxaban to warfarin. ENGAGE is completely enrolled (n=16,500) and in follow-up. Results of this trial should be known by the fall of 2012.34

Currently there is no antidote to dabigatran or factor Xa inhibitor overdosing. In the event of hemorrhagic complications, providers should initiate appropriate clinical support, discontinue treatment and investigate the source of bleeding. Since thosedrugs are primarily excreted in the urine, it is important to maintain adequate diuresis. Because of its low protein binding dabigatran, but not factor Xa inhibitors, can be dialyzed with the removal of about 60% of drug over 2-3 hours. Providers can consider surgical hemostasis or the transfusion of fresh frozen plasma or red blood cells. There is some experimental evidence to support the role of activated prothrombin complex concentrates (eg, FEIBA), or recombinant Factor VIIa, or concentrates of coagulation factors II, IX, or X; however,their usefulness in clinical settings has not been established. Administration of platelet concentrates can be considered in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used. Measurement of aPTT or ECT may help guide therapy for dabigatran.

Conclusions

Patients with AF are at an increased risk of stroke even if attempts to maintain sinus rhythm are part of the patient's therapy. Providers should assess the risk of thromboemobolism and the risk of bleeding and choose the appropriate pharmacologic therapy. For patients at low risk of stroke, no therapy or aspirin is appropriate. However, for patients with risk factors for stroke, warfarin, dabigatran or one of the new oral factor Xa drugs should be used. Newer agents are associated with a lower risk of intracranial hemorrhage compared to warfarin.

References

Table 4 Comparison of the recent trials studying the new anticoagulants

	Rocket AF	ARISTOTLE	RELY
N	14,264	18,201	18,113
VKA naive	37%	57%	50%
Design	Randomized, double-blind, double-dummy study	Randomized, double-blind, double-dummy study	PROBE design
Treatment	Rivaroxaban 1 dose (with dose adaptation for moderate renal impairment)	Apixaban 1 dose (with dose adaptation for selected patients)	Dabigatran 2 doses
Regimen	Once daily	Twice daily	Twice daily
Primary outcome	Efficacy: Composite of all-cause stroke and non-CNS systemic embolism Safety: Composite of major and clinically relevant non-major bleeding events	Efficacy: Composite of allcause stroke and non-CNS systemic embolism Safety: Composite of major and clinically relevant non-major bleeding events	Efficacy: Composite of all-cause stroke and non-CNS systemic embolism Safety: Composite of major and clinically relevant non-major bleeding events
TTR (median)	58%	66%	67%
CHADS2 (mean)	3.7	2.1	2.1
Previous TIA/CVA	55%	19.5%	20%
Primary outcome HR	0.88	0.79*	0.66 ** (150 mg dose)
Hem CVA rate	0.59*	0.51**	0.24 **(150 mg dose)
Ischemic CVA: HR	0.99	0.92	0.75 *(150 mg dose)
Major Bleeding rate	3.6%	2.13%	3.1% (150 mg dose)

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