

Stroke Prevention in Atrial Fibrillation

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Abstract

Non-valvular atrial fibrillation is a common and from a neurological perspective the most significant cardiac arrhythmia with a growing world-wide incidence. It also carries a significant associated morbidity and mortality, with cardioembolic strokes arguably being the most disabling sequelae. This brief review will highlight the important studies and the latest treatment modalities available for stroke prevention in patients with non-valvular atrial fibrillation.

Introduction

Non-valvular atrial fibrillation is a common cardiac arrhythmia with serious neurological morbidity. Various studies have reported prevalence rates of atrial fibrillation (AF) of approximately 1% of the population.¹⁻⁴ Affecting mostly the elderly, with as many as 1 in 10 experiencing AF in their 80s,⁵ the incidence of AF has been increasing in recent decades. With the aging of the population, these patterns are expected to continue well into the 21st century, with a prediction of a 2.5-3 fold increase in the number of AF patients by 2050.^{3, 5-8} In addition, with the rise of other comorbidities (such as coronary artery disease, hypertension, diabetes), more successful cardiac interventions and longer survival with congested heart failure (CHF), the estimates of morbidity and mortality of AF based on historical data may be failing to predict the true scope of the world-wide burden of AF.

Atrial Fibrillation and Risk of Stroke

Atrial fibrillation predisposes to thrombus formation, usually in the left atrial appendage, with the resulting cardioembolism producing both

cerebral and systemic emboli, and cerebral infarct arguably being its most serious sequelae. While advancing age, hypertension, diabetes and prior stroke or TIA overlap as risk factors for stroke sufferers with and without AF, the stroke rates in patients with atrial fibrillation are several times higher than their age and risk-factor matched controls.⁹ The attributable stroke rates due to atrial fibrillation skyrocket from 1.5% at age 50-59 years to 23.5% at age 80-89 years.¹⁰ Stroke is currently the third-leading cause of mortality and the premier cause of disability in the U.S and several studies have demonstrated that strokes in patients with AF tend to be more disabling than in patients without AF.^{11, 12} While the overall risk of stroke in patients with non-valvular AF is 3-4% per year, the range for a particular patient may vary widely (as much as twenty-fold) based on patient's age and clinical risk factors.^{13, 14} A systemic review of seven studies by the Stroke in Atrial Fibrillation Working Group conducted in 2007 identified several consistent risk factors for stroke including prior stroke or TIA (RR 2.5, 95%CI (1.8 3.5)), increasing age (RR 1.5 per decade, 1.3 1.7), hypertension (RR 2.0, 1.6 2.5), and diabetes mellitus (RR 1.7, 1.4 to 2.0).¹³ Other factors like female sex, history of heart failure or coronary artery disease were found to be less re-

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Table 1

CHADS₂ Stroke Risk Stratification Scheme for Patients with Non-Valvular AF

	RISK FACTORS	SCORE
C	Recent congestive heart failure	1
H	Hypertension	1
A	Age ≥75 years	1
D	Diabetes mellitus	1
S ₂	History of stroke or TIA	2

liable predictors in this review, although several studies have supported the importance of these risk factors, but whether or how they affect the likelihood of future stroke clearly requires further investigation.¹⁵⁻²² In clinical practice, patients with atrial fibrillation often have many of the above co-morbidities and teasing out the exact cause of stroke can be hard in an individual patient. For instance, aortic arch atheroma or low ejection fraction which are relatively rare but well-established conditions which cause stroke, they often co-exist with AF and may present competing mechanisms for embolic phenomena.

Stroke Risk Stratification Models

A simple and accurate stratification of stroke risk in AF has been the holy grail of numerous studies¹⁴ with a variety of stratification scales developed, leading to varying subgroupings and potentially conflicting treatment recommendations.⁹ Traditionally, three of the most prominent risk stratification systems are the CHADS₂ (Congestive heart failure, Hypertension, Age, Diabetes, Stroke/TIA) risk assessment for non-valvular AF, the American College of Chest Physician Guidelines and the American College of Cardiology/American Heart Association/European Society of Cardiology Guidelines.^{1, 23-25} CHADS₂ score, the most frequently-used, is a point system with one point assigned to presence of Congestive Heart Failure (C), Hypertension (H), Age ≥ 75 (A) and Diabetes (D) and two points to previous Stroke or TIA (S₂). A total score ranges from 0 to 6 [See Table 1], corresponding to the classical categories of low, intermediate and high risk. Annual stroke risks were determined to be less than 2% (Total score of 0, low risk), 2-4% (score of 1 or 2, intermediate risk) and greater than 4% up to 20% (scores of 3-6, high risk) [see Table 2].²³ A later revision of the CHADS₂ score categorized the high risk group

as scores 2-6 and shrunk the intermediate group to those with a score of 1.

The recommendations currently favor no anti-thrombotic or anticoagulation therapy for patients with no risk factors (lone atrial fibrillation), either aspirin or warfarin for a CHADS₂ score of one (Classic CHADS₂ offered either therapy for CHADS₂ scores of 1 or 2) and anticoagulation being favored for scores 2-6. The CHADS₂ score has the advantage of being easily administered, simple, well-validated and requiring no extensive radiological or serological testing to administer and is good at identifying low risk subjects. This score is accessible and easy to use for the many physicians involved in the treatment and care of AF patients. It also has limitations: it places a significant portion of patients into the clinically-confusing intermediate risk group and in stroke patients with AF does not distinguish between the different etiologies of previous strokes. CHADS₂ scoring system also dichotomizes the patients' age instead of treating it as a more continuous risk factor and does not account for evidence of systemic thromboembolism. It does not clearly define the diagnosis of CHF, and relies on historical risk factors, failing to take into account other stroke risk factors (female sex, low ejection fraction, peripheral vascular disease, et).²⁶ These limitations make this stratification less accurate and potentially not nimble enough to account for the complicated interplay between all the risk factors that lead to cardioembolism and strokes in atrial fibrillation. The predictive ability of the CHADS₂ score (c statistic hovering around 0.6 with 1 being a perfect predictive value and 0.5 pure guesswork) is not ideal, perhaps reflecting some of its limitations; however, no other scheme fares significantly better.^{27, 28} Recently, some modifications to the classic CHADS₂ scale to incorporate some additional risk factors or the reweighing of the existing components have been proposed, with improvement in its predictive power (c statistic 0.68-0.72).²⁹

Table 2

Classic CHADS₂ Score and Annual Stroke Risk for Patients With Non-Valvular AF

TOTAL CHADS ₂ SCORE	ANNUAL STROKE RISK	STROKE RISK CATEGORY
0	< 2 %	LOW
1 or 2	2 – 4 %	INTERMEDIATE
3 to 6	4 – 20 %	HIGH

Several of the above limitations of the risk scoring systems in AF have been addressed in recent guidelines.^{25, 30} In 2006, National Institute for Health and Clinical Excellence (NICE), evidence was provided for previous stroke or TIA, being elderly (≥ 75 years), structural heart disease, hypertension and previous MI as independent risk factors for stroke in patients with AF. Evidence was less strong for heart failure and diabetes. The presence of peripheral artery disease, valve disease, impaired left ventricular function; aortic plaque and carotid artery disease were also incorporated into the stratification models. Important potential risk factors such as being female or having thyroid disease were not included in this risk stratification. The patients were sub-divided into three groups: high (previous ischemic stroke or TIA or thromboembolic event, age ≥ 75 (with hypertension diabetes or vascular disease) or clinical evidence of valve disease or heart failure or impaired left ventricular function on echo), moderate risk (age ≥ 65 with no high risk factors or age < 75 with hypertension, diabetes or vascular disease) or low risk (age < 65 with no moderate or high risk factors). Similar to the CHADS₂ score, high risk group should be placed on anticoagulation, low risk on anti-platelet therapy and moderate group could be treated with either. The NICE guidelines rely on echocardiography, a wider array of risk factors and a step-wise stratification of age, presumably leading to a more accurate stratification scheme. The NICE and the Birmingham 2006 criteria were used to construct a modified Birmingham 2009 schema, which was expressed as the CHA₂DS₂-VASc acronym.³¹ The risk factors of Congestive heart failure/left ventricle dysfunction, Hypertension, Age 65-74, Diabetes mellitus, Vascular disease (prior MI, PAD or aortic plaque) and female Sex were each given a score of 1. Age ≥ 75 and prior Stroke, TIA or systemic Thromboembolism was each given a score of 2. This stratification combines the simplicity of CHADS₂ with the more comprehensive stroke risk pool of Birmingham 2006 and NICE criteria. Moreover, it classifies only 15.1% of patients into the potentially clinically-confusing intermediate category and 9.2% were classified as low-risk with no thromboembolic events recorded for this group. The C-statistic at 0.606 was comparable to other schema. Using this approach, it seems, a clinician will find most of his atrial fibrillation patients will need anticoagulation, with a small portion that will be in the ambiguous intermediate

group; and the ones who do not need anti-coagulation seem to be safe on anti-platelet agents and have very low risk of thromboembolic events. As an example, CHADS₂ would classify a 66 year-old man with AF and hypertension and MI and a 60 year-old man with AF and HTN as both having a score of 1, with either antiplatelets and anticoagulation as potential treatment choices. The future stroke risk between the two is likely not the same, a difference noted by the CHA₂DS₂-VASc score, with the same patients receiving scores of 3 and 1 respectively, leading to disparate management recommendations.

A recent systemic review of 18 studies was conducted assessing stroke risk factors in AF, risk stratification and cost effectiveness.³² Previous stroke or TIA, age over 75, hypertension, previous MI and structural heart disease were identified as predictive stroke risk factors. Left ventricular dysfunction by echo was determined to be a risk factor for stroke, while a clinical diagnosis of heart failure was a less clear predictive entity. Coronary and peripheral artery^{33, 34} diseases and complex aortic plaque were noted to contribute to stroke risk in varying degrees. Echocardiography was shown to be useful in identifying left atrial dilatation and left ventricular dysfunction in cases where the patient's stroke risk was unclear by clinical criteria alone.

European Society of Cardiology guidelines, just published this summer, adopt a more comprehensive approach of Birmingham 2009 and other recent schema while avoiding the descriptive ("low", "moderate" and "high") characterizations of stroke risk from the older classifications.²⁵ The authors believe that these qualitative terms are confusing and poor predictors for the risk occurrence of stroke, and prefer to treat the risk spectrum as a continuum. The risk factors are divided into major (prior stroke or TIA, thromboembolism and older age (≥ 75 years), with the presence of mitral stenosis or prosthetic heart valves also placing patients at high risk) and clinically relevant non-major (heart failure, especially with left ventricle function of $\leq 40\%$, hypertension, diabetes, female sex, age 65-74, and vascular disease (aortic plaque, PAD or prior MI)). A presence of any single major risk factor or two clinically relevant non-major risk factors would necessitate anti-coagulation. These recommendations add

several steps to weed out patients with CHADS₂ score of 1 or 0 who possess additional stroke risk factors and place them in the more beneficial anticoagulation therapy. Even for patients with one non-major risk factor, although both treatment options are offered, anticoagulation is preferred. Whether this classification offers risk stratification for optimal treatment superior to previous classification systems in patients with AF will need to be validated. With new thrombin inhibitors which are gaining wider acceptance as oral anticoagulants for AF, the risk-benefit balance of CHADS₂ and other risk stratification models' therapeutic recommendations will need to be re-evaluated.

Atrial Fibrillation Treatment for Stroke Prevention

Warfarin, Aspirin, Clopidogrel

A series of trials in the past quarter century were conducted to determine the best therapy for prevention of cardioembolic strokes in patients with nonvalvular atrial fibrillation.³⁵⁻⁴¹ The initial study was the Copenhagen AFASAK study, published in 1989, which consisted of 1007 outpatients with chronic non-rheumatic atrial fibrillation, randomized to three arms: warfarin (INR 2.8-4.2), Aspirin 75mg or Placebo. The primary and secondary points for the 2-year duration of the study were cerebral or systemic embolism and death respectively.

The adverse events on warfarin were less than a third as likely (1.5%) compared to aspirin (6.0%) or placebo (6.25%).³⁵ In 1990, The Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) compared 212 warfarin-treated patients with low INR of 1.2-1.5 to 208 patients in the control group (no anticoagulation, but the patients could choose to take aspirin) with the average follow up of 2.2 years. There were 2 strokes in the warfarin group (0.4% per year) and 13 strokes in the control group (3% per year) for a reduction of stroke of 86% when taking warfarin. The death rates were also lower in the warfarin (2.25%) compared to control (5.97%) with equal amounts of fatal hemorrhages, but a higher rate of minor hemorrhages in the warfarin group [36]. The first of Stroke Prevention in Atrial Fibrillation Studies (SPAF I), published in 1991, included 1330 participants followed for a

mean of 1.3 years. The primary outcomes (strokes and systemic embolisms) occurred in 2.3% of warfarin-treated patients versus 7.4% in the placebo arm for a 67% reduction of risk. The warfarin-ineligible aspirin-treated patients had 3.6% events compared to 6.3% of placebo for a reduction of risk of 42%. The risk of bleeding was virtually the same in all 3 arms, ranging from 1.4-1.6% [37]. European Atrial Fibrillation Trial (EAFT), published in 1993, included 1007 patients (average age 73) randomized to warfarin (INR 2.5-4), Aspirin 300mg or placebo for secondary prevention of repeat TIA or strokes and followed for an average of 2.3 years. The annual rate of outcome events (vascular death, myocardial infarction, strokes or systemic embolism) in warfarin-eligible patients was 8% in those taking the anticoagulant and 17% assigned to the placebo group. Aspirin provided a more modest benefit, with 15% of annual outcome events, compared to 19% in those on placebo. The bleeding rates were slightly higher on warfarin (2.8%) compared with 0.9% on aspirin, with no intracranial bleeds identified in either group.⁴⁰ A more recent study, the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA), assessed the optimal treatment for a more elderly population. Published in 2007, it enrolled 973 patients (mean age 81.5) randomly assigned to warfarin (INR 2-3) or aspirin 75mg and followed for an average of 2.7 year; it found the rate of events (ischemic or hemorrhagic strokes, or clinically significant arterial emboli) was half in warfarin compared to aspirin with an annual risk of extracranial hemorrhage higher in aspirin (1.6%) vs warfarin (1.4%). These findings were significant, suggesting that elderly patients can benefit from anticoagulation therapy in a relatively safe manner; a finding contrary to the common belief that "it is just too dangerous to anti-coagulate" the elderly.⁴¹ SPAF II and III were published in the mid 1990s with each of these trials suggesting superiority of anticoagulation therapy over aspirin and placebo/controls.^{42, 43}

A meta-analysis of 16 studies encompassing 9874 patients was performed in 1999.⁴⁴ The pooled analysis showed that dose-adjusted warfarin reduced stroke by 62% (95% CI 48%-72%) compared to placebo, with an absolute risk reduction of 2.7% per year for primary prevention and 8.4% for secondary prevention. The risk of intracranial hemorrhage was 0.3% a year with adjusted-dose warfarin and 0.1% with placebo. In the same meta-analysis,

aspirin had a reduction of stroke of 22% (95% CI 2% - 38%) with an absolute reduction of 1.5% per year for primary prevention and 2.5% for secondary prevention. The comparison of dose-adjusted warfarin to aspirin showed the former reducing stroke by 36% (95% CI 14%-52%) compared to the latter but also having a higher rate of intracranial hemorrhages with a relative risk of 2.1 (95% CI 1.0-4.6) with no statistically significant difference in overall mortality.⁴⁴ A later meta-analysis by the same group, conducted in 2007 of 28,044 patients with a mean age of 71 years and encompassing 29 studies showed dose-adjusted warfarin to reduce stroke of 64% (95% CI 49%-74%) compared to placebo while antiplatelet therapy provided a more modest reduction of 22% (95% CI 6%-35%).⁴⁵ [See Table 3]. Adjusted-dose warfarin was again proven more effective compared to aspirin providing a 39% (95% CI 22%-52%) relative risk reduction. Anticoagulation provided an absolute risk reduction in all strokes of 2.7% per year. The number needed to treat (NNT) to prevent one stroke was 37 for primary prevention and 12 for secondary prevention.⁴⁵ This review found only modest increases in major hemorrhages during anticoagulation compared to placebo or anti-platelets therapy; however, many participants took warfarin before the start of the trials and their mean age was in the 70s. Thus, these results may under-estimate the risk of bleeding in warfarin-naïve and older patients.

Given the above evidence of the superiority of warfarin, what about patients who are not suitable for anticoagulation with warfarin? Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-A) trial randomized 7554 patients who were ineligible for warfarin to either clopidogrel or a placebo and followed them over several years (median 3.6 year follow-up): 3.3% of those on aspirin and placebo and 2.2% on aspirin and clopidogrel suffered a stroke.⁴⁶ This

showed clopidogrel and aspirin offering extra protection with relative risk reduction of 0.72 (95% CI 0.62-0.83; $P < 0.001$) compared to aspirin alone. However, dual platelet therapy also conferred a greater risk of major bleeding (2.0% per year) compared to aspirin alone (1.3% per year). Patients who were eligible for warfarin were enrolled into the other arm of the trial, ACTIVE-W, comparing warfarin directly to combination of aspirin and clopidogrel.⁴⁷ The study was stopped early due to the clear superiority of warfarin over combination therapy with a relative risk of primary outcomes were 1.44 (95% CI 1.18-1.76) in dual antiplatelet therapy compared to anti-coagulation. Another Active W sub-study examined the rate of strokes or other non-cerebral emboli in paroxysmal vs sustained atrial fibrillation.⁴⁸ The annualized risk of stroke or systemic embolism was 2.0 in paroxysmal AF compared with 2.2 in sustained AF with a relative risk of 0.87 (95% CI 0.59-1.30, $p = 0.496$). After adjusting for confounding baseline variables, the relative risk was 0.94 (95% CI 0.63-1.40). Similar results were found in Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial which randomized patient to rhythm-control and rate-control arms. Over 4000 patients were enrolled, but the results showed nearly identical stroke risks in both groups with most events occurring after warfarin was stopped or the INR became sub-therapeutic.⁴⁹ These studies suggest that the risk of embolism remains high with perceived rhythm control and anticoagulation should be continued based solely on the underlying risk factors for stroke and bleeding complications.

Surgical Procedures: Closure of Left arterial Appendage

Surgical procedures have been considered for prevention of cardioembolism from non-valvular atrial fibrillation, based on the knowledge that the majority of thrombi form in the left atrial appendage. Currently, the two main left atrial appendage closure devices being studied are the PLAATO system and the Watchman device. Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) study enrolled 180 patients with non-valvular atrial fibrillation and contraindications to warfarin who underwent a device implantation with a

Table 3

Stroke Prevention in Patients With AF: A meta-analysis of 28,044 patients in 29 studies

	No of Trials	No of Patients	RRR (95% Confidence Intervals)
Warfarin vs. Placebo	6	2900	64% (49-74%)
Warfarin vs. Aspirin	12	12,963	Warfarin vs. Aspirin
Antiplatelets vs. Placebo	8	4,876	Antiplatelets vs. Placebo

good rate of success 90% (95% CI 83.1-92.9%) and also a significant amount of morbidity (6 cardiac tamponades (3.3%) and one embolisation of the device into the aorta (0.6%)) and mortality (2 patients died within 24 hours (1.1%)).⁵⁰ The trial had a relatively short follow-up of 129 patient-years during which 3 strokes (2.3% per year) occurred and was terminated prematurely for financial reasons. The patient selection was slightly different for PROTECT AF where investigators selected 707 patients eligible for warfarin and randomized them to closure (463 patients) or to the control group of anticoagulation with warfarin (244 patients). The patients were followed for 1065 patient-years monitoring for the primary endpoint of stroke, systemic embolism or cardiovascular death.⁵¹ The event rate was 3% for the intervention group and 4.95% for the controls with the rate ratio of 0.62 (95% CI 0.35-1.25) meeting the study's non-inferiority parameters. The interventional arm had a relatively high rate of complications with almost 5% experiencing serious pericardiac effusion, requiring drainage and 3.5% experiencing major bleeding, requiring transfusion. Some of the shortcomings of the trial included a relatively short follow-up, the interventional arm patients continuing the warfarin for several months after the implantation of the device and the INR goal being achieved only 66% of the time in the control group— all aspects that need to be addressed in further studies. With an improved periprocedural safety record and a carefully selected subgroup of patients, these devices may prove a viable and effective alternative for patients with very high risk for bleeding complications.

Other Medication: Statins, ACE-I, ARBs

In the past decade, two meta-analysis looked at the role of statins, ACE-inhibitors and ARBs in preventing AF. Statins are thought to act by decreasing inflammation, thrombosis and fibrosis, with 6 studies of 3557 patients showing a 61% reduction in the incidence of recurrent AF.⁵² ACE-inhibitors and ARBs effect the activation of the RAS system and may be potent inhibitors of electrical and structural cardiac remodeling and decrease atrial conduction times; they reduced the risk of new-onset atrial fibrillation by 28% in the meta-analysis, overall.⁵³ More recent data from Angiotensin II-antagonist in Paroxys-

mal Atrial Fibrillation (ANTIPAF) trial, presented at the European Cardiology Society meeting in August, 2010 had contradictory results.⁵⁴ It randomized 425 patients with paroxysmal atrial fibrillation to receive olmesartan or a placebo and followed them for a year. No difference in overall AF burden (the primary endpoint) nor time to first AF recurrence, symptomatic AF recurrence, onset of persistent AF, number of strokes, clinic or hospital visits (secondary endpoints) between an ARB or a placebo was found. The results suggest that ARBs may be more effective in primary preventions or longer follow-up might be needed to elucidate their effects as secondary prevention agents. Clearly, more comprehensive studies are needed before these drugs are recommended for patients with atrial fibrillation.

Risk of Bleeding and Bleeding Risk Scales

While warfarin has been proven to be an effective treatment for atrial fibrillation; its use has been curtailed by the risk and fear of bleeding complications. In the past decade it has been established that the optimal INR goal for patients with atrial fibrillation is 2.5 with 2.0 to 3.0 being the range. If it is below the range, there is an increased risk of ischemic stroke; if above it, the risk of hemorrhage goes up.^{55,56} A systematic review of risk factors for anticoagulation-related complications in patients with atrial fibrillation from 9 studies was conducted with numerous potential risk factors for bleeding being identified.⁵⁷ For increasing age, female gender, uncontrolled hypertension and a history of cerebrovascular disease or thromboembolism the evidence was inconclusive. For polypharmacy, history of MI or ischemic cardiac disease, the evidence was found to be more convincing, with polypharmacy showing the most robust results. In a separate study, increasing age was found to be a factor for intracranial hemorrhage in AF patients, regardless of warfarin use.⁵⁸ As mentioned above, BAFTA showed convincing evidence of the safety of anticoagulation in the elderly. These results have to be interpreted with caution, however.

The patients with higher CHADS₂ scores were excluded from this study and 80% were taking anti-thrombotic therapy, thus constituting a possible survivor effect. It seems that age has been established as a risk factor for increased incidence of ischemic strokes, atrial fibrillation and hemor-

rhagic strokes, thus posing a clinical conundrum with the population most likely to benefit is also most likely to suffer potentially devastating bleeding side effects.

Elderly and feeble patients with atrial fibrillation are more prone to falling and it is this fact that has been stated as a reason to keep them off anti-coagulation. A study found that patients on warfarin who were at high-risk for falling suffered more than twice the intracranial hemorrhage compared to other participants in the study, mostly due to four-fold increase in traumatic hemorrhage.⁵⁹ The 30-day mortality after an intracranial hemorrhage was significantly higher in patients on warfarin (51.8%) vs. those than who were not (33.6%). However, the relative risk reduction of anticoagulation was 25% for patients who were at high risk of falls when their CHADS₂ score was 2 or above. There was no overall reduction in risk in patients who had a CHADS₂ score of 0 or 1. The results showed that patients with a high risk of stroke still benefit from anti-coagulation, despite the increase in mortality and morbidity due to increased bleeding. Precautions such as regular exercise, bone-strengthening regimen and walking aids should logically be implemented to minimize their risk of falling. Another study using a Markov decision analytic model to determine the preferred treatment approach, demonstrated warfarin therapy, regardless of age, was preferred (12.90 quality-adjusted life-years per patient, vs 11.17 quality-adjusted life-years for aspirin and 10.15 for no therapy at all).⁶⁰ It was found that a person has to fall 295 times in a year before warfarin is no longer considered the optimal therapy. A later review found that other risk factors such as alcoholism, thrombocytopenia, non-compliance with monitoring show surprisingly little supporting and even conflicting evidence about their effect on risk of bleeding.⁶¹

Several bleeding score stratifications have also been proposed.⁶²⁻⁶⁴ A composite bleeding stratification score with the acronym HEMORRHAGES (Hepatic or renal disease, Ethanol abuse, Malignancy, Older (than 75 years of age), Reduced platelet count or function, Re-bleeding risk, Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk and Stroke) with each risk factor worth one point was proposed.⁶⁵ In a reg-

istry of 3791 Medicare patients, the risk of hemorrhage was 1.9 (95% CI 0.6-4.4) per 100 point-years for a HEMORRHAGES score of 0 and 12.3 (95% CI 5.8-23.1) for a HEMORRHAGES score of 5 or greater. The score had a C statistic of 0.67. More recently, a more simplified and user-friendly hemorrhagic stratification has been proposed, the HAS-BLED which is an acronym for Hypertension, Abnormal renal or liver function (1 point each), Stroke, Bleeding, Labile INRs, Elderly (age >65) and Drugs or alcohol (1 point each).⁶⁶ This score has a C-statistic of 0.72 overall and even higher values for antiplatelet therapy alone (0.91) or no antithrombotic therapy at all (0.85). The authors determined that for the vast majority of AF patients, the risk of bleeding outweighs any potential benefits of anticoagulation when the HAS-BLED score is higher than their CHADS₂ score. If validated by other studies, this relatively simple and easy-to-administer bleeding stratification system could introduce a tested and validated system for quantifying a patient's bleeding risk – a complement, and not a replacement, to the treating physician's clinical judgment.

Warfarin Utilization

How is anticoagulation utilized in patients with low, moderate and high risk for stroke in atrial fibrillation? A retrospective review encompassing 171, 393 patients found that warfarin was used in 40.1% of low risk, 43.5% of moderate risk and only 42.1% of high risk patients.⁶⁷ Warfarin utilization was nearly identical across risk-groups with a majority of high risk patients not getting the proper treatments and almost half of the low risk getting a treatment that would offer them little benefit and a disproportionate risk. Only a third of patients received uninterrupted anticoagulation for the 6 months after the treatment was started, implying that an even-smaller percentage of high risk patients stay on the optimal regimen. Other studies show comparable levels of anticoagulation usage among atrial fibrillation patients in the clinical practice.⁶⁸⁻⁷¹ These troubling real-world statistics indicate the need for greater education of physicians and patients alike about the guideline recommendations, the true risk of stroke and bleeding complications and the optimization of warfarin administration and monitoring or the widespread use of newer, simpler and more user-friendly anticoagulants.

New Anticoagulants for Stroke Prevention in Patients with AF

While the trials of the past several decades have proven the efficacy of warfarin, why has the actual use of the drug been less than ideal, with half the qualifying patients not being on optimal therapy?^{72, 73} Some of the barriers to better compliance include variability in metabolism due to numerous drug interactions, diets rich in vitamin K, genetic variations requiring frequent, costly and inconvenient coagulation monitoring, slow onset of action and a narrow therapeutic window with possibly devastating consequences of over or under dosing the medication.⁷⁴ Over the past several years, new compounds have been in development, which aim to improve on the side effect and pharmacokinetic profile of warfarin and achieve a more rapid onset of action and clearance of the drug from the system and avoid costly, time-consuming monitoring, while maintaining the drug's great efficacy. These medications include a more stable Vitamin K antagonist (ATI-5923), direct thrombin inhibitors (Ximelagatran and Dabigatran), Factor Xa inhibitors (Apixaban, Rivaroxaban, Idraparinux, etc) and Factor IXa inhibitors (TTP889)⁷⁵ [See Table 4].

ATI-5923, a vitamin K antagonist, is more stable than warfarin as it is not metabolized by the CYP2C9 system and has a longer half-life of 136 hours; it is currently undergoing a phase 3 trial.⁷⁶ Factor Xa inhibitors, of which Apixaban and Ri-

varoxaban are the furthest in clinical development, have a relatively high oral bioavailability, utilize the renal system for some to all of their clearance and potentially, as a class, have minor food and drug interactions, with CYP3A4 inhibitors for Apixaban and Rivaroxaban being a notable exception.⁷⁷ Idraparinux's phase 3 study (Amadeus) was stopped early secondary to increased bleeding, although another trial is ongoing. Ximelagatran, a direct thrombin inhibitor, has a half-life of 5 hours, is excreted by the kidneys and has minimal food and drug interactions; however, in phase 2 clinical trials,^{78, 79} while showing similar efficacy and better hemorrhagic side effects than warfarin, it also exhibited liver toxicity with 3 fatalities and was not approved for the market.^{75, 80} The follow-up compound, AZD-0837 has no similar safety issues so far and is undergoing two phase II trials for atrial fibrillation with preliminary results showing it has similar bleeding rates to warfarin, but relatively more side effects, most of which are gastrointestinal.^{81, 82} A more thorough review of the new anticoagulants for stroke and other cardiovascular diseases has been recently published by Ahrens et al.⁸³

Dabigatran

The other direct thrombin inhibitor is dabigatran, which has no food and minimal drug interactions (notably quinidine and amiodarone), has no apparent liver toxicity, with rapid onset of action of 1-2 hours, a 12-17 hour half-life with a predomi-

Table 4

New Anticoagulants for Stroke prevention in Patients with AF

Class	Compound	Phase of Clinical Trial
Stable Vitamin K antagonist	ATI-5923	Ongoing Phase III trial
Direct Thrombin Inhibitors	Ximelagatran	Two Phase II trials terminated due to liver toxicity
	Dabigatran	Phase III trial (RE-LY) completed
	AZD-0837	Two Phase II and a Safety trial completed.
Factor Xa inhibitors	Apixaban	Two Ongoing Phase III trials
	Rivaroxaban	Two Ongoing Phase III trials
	Betrixaban	Phase II trial completed
	Edoxaban	Phase II trial for completed
	Idraparinux	One Phase III trial stopped early due to increased bleeding. One Phase III trial ongoing
	SSR126517E	Ongoing Phase III Trial
	YM150	Ongoing Phase III Trial
Factor IXa inhibitors	TTP889	One Phase II Trial for venous thromboembolism, no active AF trials

nately renal excretion, and no need for blood monitoring.⁸⁴ The phase 3 trial, comparing dabigatran with warfarin, Dabigatran versus Warfarin in Patients with Atrial Fibrillation, the (RE-LY) was recently published.⁸⁵ The study enrolled 18,113 patients, who were randomized to dabigatran in two doses of 110 and 150mg twice a day or adjusted-dose warfarin and followed for a median time of 2 years, monitoring for stroke or systemic embolism as the primary outcome. Rates of these events were 1.69 per year in warfarin group (a low rate compared to other studies) and 1.11% for 150 mg of dabigatran (relative risk 0.66 (95% CI 0.53-0.82)) and 1.53% for 110mg dosing (relative risk 0.91 (95% CI 0.74-1.11)). The rate of life-threatening, intracranial, major and minor bleeding were statistically significantly lower in both dabigatran doses than in warfarin, with the lower dose exhibiting the lowest number of hemorrhagic events. Higher dose dabigatran patients did have a higher rate of heart attacks compared to warfarin (relative risk 1.38 (95% CI (1.00-1.91))). The increased cardiac risk and the potential for yet-undiscovered liver toxicity will require longer-term monitoring. Some of the possible concerns about dabigatran (cost of the name brand, no reversibility, no serological testing to monitor its effect, and unclear pharmacokinetics in those with kidney impairment) were addressed in a recent editorial.⁸⁶ If approved by the FDA, it will provide a welcome alternative to warfarin and may help deliver optimal treatment to many more of our patients.

Conclusions

In the past few decades, the incidence of non-valvular atrial fibrillation and the resulting cardioembolic stroke has increased significantly and will continue to increase due to increased longevity, improved detection methods and the concomitant rise of associated risk factors and co-morbidities. We have also made great progress in learning the pathophysiology and natural course of the disease, its risk factors and its complications and in discovering different and increasingly effective treatments, with many exciting developments ahead. The risk factors for stroke and for possible hemorrhagic complications have been determined and stratified in various validated schema. The new anticoagulant therapies hold a great promise for better treatment with fewer complications

in patients with AF. Continuing education of the public and the medical community regarding the latest developments in the treatment of atrial fibrillation will ensure that our patients are getting the optimal treatment of this common condition.

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