Atrial Fibrillation: Current Management

Invited Editorial
A great leap forward in the management of atrial fibrillation - F. W. A. Verheugt 167

Lead Article
Atrial fibrillation: current status and challenges - K. A. A. Fox 171

Expert Answers to Three Key Questions
Which drugs and devices can we use for protection against thromboembolic stroke? - A. J. Camm 189
How do we balance risk and benefit in a population at risk of both stroke and bleeding? - P. Kirchhof 197
Is warfarin obsolete in the era of new anticoagulants? - K. W. Mahaffey 206

Fascinoma Cardiologica
Art and the Heart: Peter Harris, the scientist, the clinician, and the artist— the Complete Man - T. J. C. Ruigrok, C. Anand, I. S. Anand, R. Ferrari 215

Summaries of Ten Seminal Papers - M. Dweck 221
Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation - E. M. Hylek and others
Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks - M. I. Aguilar, R. Hart
A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study - C. Pappone and others
Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation - E. M. Hylek and others
Dabigatran versus warfarin in patients with atrial fibrillation - S. J. Connolly and others
Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED … score - G. Y. Lip and others
Rivaroxaban versus warfarin in nonvalvular atrial fibrillation - M. R. Patel and others
Apixaban versus warfarin in patients with atrial fibrillation - C. B. Granger and others
Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study - L. Fröberg

Bibliography of One Hundred Key Papers 233
Atrial fibrillation is the most common chronic cardiac arrhythmia in clinical cardiology. It affects about 1% of the population, and of individuals over the age of 80, about 10% suffer from this type of rhythm disturbance. Due to the loss of atrial kick, left ventricular cardiac function is diminished, resulting in a propensity to heart failure, fatigue, and disability. The presence of palpitations can be very disturbing for younger patients and may hamper them in their physical and professional activities. Finally, the diminished blood flow through the heart, especially the left atrium, may lead to thrombosis in the left atrium and left atrial appendage, resulting in subsequent systemic embolization. Although many of the characteristic risks and consequences of atrial fibrillation have been known for decades, little progress has been made in the management of the disease until the past 10 years.

In this issue of Dialogues in Cardiovascular Medicine, Keith A. A. Fox, who also doubles as Guest Editor, reviews the current status and challenges in the field of atrial fibrillation in his Lead Article, while three world experts look at more specific developments. All four authors point out the huge leap forward in the prevention of stroke in patients with atrial fibrillation made possible thanks to the advent of the new oral anticoagulants. They emphasize that these drugs have a fast onset and fast offset of action and need only once- or twice-daily dosing without further monitoring, and seem ideal both for patients on warfarin and for new patients with atrial fibrillation who are at risk for stroke.

First, atrial fibrillation should be reduced. A. John Camm looks at which drugs and devices are best effective in the protection against thromboembolic stroke. Correction of the heart rhythm either pharmacologically or by electrical cardioversion has not improved clinical outcome. Pharmacological management of atrial fibrillation can be helpful in slowing the heart rate, but restoring sinus rhythm is hardly successful over

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time and may even be deleterious.\textsuperscript{1,2} Since hypertension is the most common cause of atrial fibrillation, it should be detected and properly treated so as to prevent atrial fibrillation and the most common other complications of hypertension like heart failure, myocardial infarction, ischemic stroke, and intracranial hemorrhage. This can be achieved through better pharmacological treatment. Renal artery denervation has been recently developed with hopeful results in the reduction of systolic and diastolic blood pressure in patients with hypertension refractory to multidrug treatment.\textsuperscript{4} In patients with sick sinus syndrome, pacemaker therapy may reduce the progression to atrial fibrillation. This can be even better achieved with dual chamber pacing as established in the MOST (MOde Selection Trial)\textsuperscript{5} and CTOPP (Canadian Trial Of Physiologic Pacing)\textsuperscript{6} trials. Finally, atrial fibrillation can be abolished electrically by pulmonary vein ablation. Unfortunately, large randomized controlled studies are not available to support such a strategy for left atrial ablation. The large CABANA trial (Catheter ABlation vs ANtiarrhythmic drug therapy for Atrial fibrillation)\textsuperscript{7} is currently ongoing. Mechanical prevention of stroke can be achieved by left atrial appendage occlusion with the WATCHMAN\textsuperscript{®} device. The WATCHMAN study is the only randomized trial with an unexpectedly high stroke rate in the warfarin arm.\textsuperscript{8} Clearly, further studies are necessary to prove that left atrial ablation may cure atrial fibrillation in a large number of patients with acceptable cost and safety, and left atrial appendage occlusion needs large-scale evaluation as well. Needless to say, these trials should be carried out on a background of stroke prevention with the new oral anticoagulants.

Paulus Kirchhof addresses the question of how to balance risk and benefit in a population at risk for both stroke and bleeding. Prevention of thromboembolism and stroke can be achieved by the use of oral anticoagulation using vitamin K antagonists. Although this is very successful,\textsuperscript{9} the therapy is laborious and associated with severe bleeding in up to 3\% of patients per year.\textsuperscript{10} Recently, new oral anticoagulants have been developed, tested, and introduced in clinical practice. They are at least as effective as warfarin, and by the same token they are much safer, especially with respect to the occurrence of intracranial bleeding.\textsuperscript{11}

So have the vitamin K antagonists become obsolete, and can we do away with them? As shown by Kenneth W. Mahaffey this is clearly the option, especially in countries with no extensive network of thrombosis clinics. But for many patients who are stable on oral anticoagulants without apparent bleeding or strong fluctuations of the International Normalized Ratio (INR), a farewell to the thrombosis clinics will be difficult. Most of them feel comfortable seeing nurses and doctors regularly in these clinics and they even make friends among their fellow patients. Furthermore, the switch from warfarin to the new oral anticoagulants has only been studied in three large trials in terms of efficacy and safety,\textsuperscript{12-14} but not in the real world. Finally, no antidote with proven efficacy is available, so that the long-term safety of the new oral anticoagulants still has to be established.
In conclusion, many of the aspects of atrial fibrillation treatment have not changed significantly over the last decades. The only positive development that has been clearly tested and established is the introduction of the new oral anticoagulants. Yet, the question of whether these drugs represent a genuine leap forward will only be answered once these agents have been used extensively in large populations with atrial fibrillation. But other developments also seem hopeful (Table I). Large ongoing long-term registries like GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation) and GARFIELD (Global Anticoagulant Registry in the FIELD)\textsuperscript{15} may help us in the evaluation of these improvements in real life.

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Atrial fibrillation is a sinister often silent rhythm disturbance and a key cause of stroke and death, especially in older age and when combined with other risk factors. Worldwide, it is the silent epidemic of the elderly. In the minority of patients, interventional approaches are possible to restore sinus rhythm, including electrophysiological ablation of pulmonary veins. However, although they relieve symptoms they do not abrogate future stroke risk. Anticoagulation is highly effective in reducing the risk of stroke and systemic embolism, but controlling vitamin K antagonists is challenging. Many patients are untreated because of real or perceived bleeding risks and many patients discontinue treatment. The newer anticoagulants present a revolutionary change (oral direct thrombin inhibitors: dabigatran; factor-Xa inhibitors rixaroxaban, apixaban, endoxaban). They do not require monitoring and their management is not confounded by the many food and drug interactions of warfarin. Importantly, the newer agents are at least as effective as warfarin in preventing stroke (some are more effective) and have similar or lower risks of bleeding. The newer agents all reduce a key complication of vitamin K anticoagulation, intracranial hemorrhage. Widespread application of the newer agents presents challenges, but also major opportunities to improve outcome and quality of life.

Patient diagnosed with atrial fibrillation may be aware of an irregular heartbeat or may have presented with nonspecific symptoms of fatigue, breathlessness, or reduced exercise capacity, or may be entirely asymptomatic. Unfortunately, the first presentation may also be the most devastating complication, embolic stroke. Stroke is increased fivefold compared with an age-matched population without atrial fibrillation.

**What is atrial fibrillation and how does it present?**

“Is it just an irregular heartbeat doctor?”

Most individuals have experienced occasional irregularity of the heartbeat due to extrasystoles, so a more persistent irregularity of heart rhythm may not appear sinister and hence presentation may be delayed. However, atrial fibrillation is much more than an irregularity of heart rhythm, for several reasons: firstly it may be a marker of underlying heart disease including the impact of hypertension on the heart, ischemic heart disease, heart muscle disease, and endocrine disorders including hyperthyroidism and diabetes. Second, the rhythm disturbance may itself lead to impairment of cardiac function with reduced cardiac output, diminished exercise tolerance, and heart failure. Third, the hemodynamic and coagulation consequences of atrial fibrillation lead to thrombus formation, systemic emboli, and substantially increased risk of stroke (Figures 1 and 2, pages 173 and 174).

Atrial fibrillation is recognized by the patient or the doctor by an irregularity of the pulse rate both due to varying intervals between heart beats and varying pulse volumes (“irregularly irregular” pulse). On clinical examination, it may be confused with sinus rhythm complicated by multiple supraventricular or ventricular ectopic beats as these produce similar features in the peripheral pulse. Atrial fibrillation may be missed, clinically, if the pulse is only recorded for a short interval as there may be brief episodes where a beat-to-beat variation is only modest. In addition, the resting peripheral pulse
is a poor guide to the impact of atrial fibrillation on exercise performance. On exercise, heart rate rises disproportionately in atrial fibrillation, thus contributing to the reduced exercise capacity and fatigue experienced by the patient. The peripheral pulse is also deceptive as it records only heartbeats of sufficient amplitude to be propagated and palpable in a peripheral pulse. The true cardiac rate may be substantially higher (due to short interventricular intervals that lead to inadequate ventricular filling and beats of insufficient amplitude to be palpable at the periphery). So what is required for diagnosis? Simply, the electrocardiogram is diagnostic if atrial fibrillation is present. However, especially at the onset of the condition, atrial fibrillation may be intermittent and prolonged ambulatory recordings may be required to capture episodes of atrial fibrillation. As the thrombotic consequences of paroxysmal atrial fibrillation are similar to those of persistent atrial fibrillation, thorough investigation is fully warranted in those with symptoms of intermittent arrhythmia. In atrial fibrillation, the electrocardiogram records irregular ventricular depolarizations with apparently chaotic atrial contractions. Although the condition was initially thought to be due to multiple wavelets propagating in a random fashion throughout the atria, the mechanisms are now recognized to be more complex. These include focal discharge at rapid rates with heterogeneous conduction. There is also evidence of reentrant mechanisms within the atria. Rapid atrial activation can induce a process of electrical remodeling that makes restoration of sinus rhythm more difficult: “atrial fibrillation begets atrial fibrillation.” Intracellular calcium overload has been postulated in the initial mechanism of remodeling, resulting in shortening of the atrial refractory period. More prolonged atrial arrhythmias can downregulate calcium entry and result in de-differentiation of atrial myocytes toward a more fetal phenotype. Structural changes include interstitial fibrosis, further perpetuating the arrhythmia, and contributing to the conversion of paroxysmal atrial fibrillation to persistent atrial fibrillation. More recent evidence has demonstrated that atrial fibrillation may arise in tissue within the pulmonary veins in proximity to their connection with the left atrium. Ablation or electrical isolation of the pulmonary veins may result in effective treatment of paroxysmal atrial fibrillation (see Choice of Antithrombotic Management section). A surgical procedure can also be performed at the time of open heart or valve surgery to isolate the propagation of atrial fibrillation.

In summary, a seemingly benign irregularity of heart rhythm may be the harbinger of serious underlying cardiac disease, the cause of important symptomatic and
exercise intolerance, and the trigger for thrombosis, embolism, and stroke. It is inadequately recognized and inadequately diagnosed and is currently inadequately treated (see Choice of Antithrombotic Management section).

**WHY DOES ATRIAL FIBRILLATION OCCUR?**

*Why do I have this rhythm disturbance, doctor?*

Atrial fibrillation occurs with increasing frequency in older age and is the most common cardiac arrhythmia. Interstitial fibrosis contributes to heterogeneity of conduction and refractoriness within the atria, predisposing to atrial fibrillation. A variety of underlying conditions contribute to the development of atrial fibrillation (Figure 1). A common mechanism involves increased left atrial “stretch” either due to raised filling pressure or volume overload of the atria. Reduced left ventricular compliance is a consequence of hypertension, and structural heart disease and valvular regurgitation leads to volume overload. The structural changes in the atria facilitate development of atrial fibrillation, but the condition may originate at the junction of the atria with the pulmonary veins. Altered myocyte fiber orientation at the junction of the pulmonary veins and atria can occur as a consequence of pressure changes and may result in shortened refractory periods, impacting on the initiation and perpetuation of atrial tachyarrhythmias.

Various inherited cardiac conditions are associated with atrial fibrillation and these include both short and long QT syndromes and the Brugada syndrome. These are associated with supraventricular arrhythmias and with atrial fibrillation. Inherited cardiac conditions, including hypertrophic cardiomyopathy and familial forms of ventricular preexcitation and abnormal left ventricular hypertrophy, may be associated with gene mutations, including of the PRKAG gene. Other inherited forms of atrial fibrillation are associated with mutations of genes coding for atrial natriuretic peptide, loss of function mutations in the cardiac sodium channel gene SCN5A, or gain of function in the cardiac potassium channel. It is likely that discovery of further mutations will contribute to our understanding of the pathogenesis of this condition.

Therapies aimed at preventing atrial fibrillation (for example, by reducing blood pressure with angiotensin receptor blockers) have been disappointing, but the failures of “upstream” approaches to prevent the condition may be the consequence of inadequate treatment duration and the inability to reverse the structural changes within the atria once they have been initiated.

In patients with a normal atrioventricular conduction system, the ventricles are protected from the very high atrial rates by the His-Purkinje system acting as a “gate-keeper.” Intrinsic refractoriness of the atrioventricular (AV) node and concealed conduction limit the number of electrical impulses that leave the AV node toward the ventricle. However, fluctuations in sympathetic and parasympathetic tone, especially during exercise, influence the frequency of conduction to the ventricles and hence the ventricular rate. Digitalis is effective in slowing ventricular rates by an increase in parasympathetic tone and is effective in controlling heart rate at rest. However, it is poor at controlling the increase in heart rate on exercise. Conversely, β-blockers and nondihydropyridine calcium antagonists reduce the ventricular rate both during exercise and at rest (see Choice of Antithrombotic Management section).

In patients with inherited preexcitation syndromes, fast and potentially life-threatening ventricular rates may occur because of the bypassing of the normal “gate-keeper” function of the AV node. In such patients, the use of drugs that slow atrioventricular nodal conduction, without prolonging atrial accessory pathway refractory time (for example with verapamil, digitalis, and...
diltiazem), can all accelerate conduction via the accessory pathway, with risk of life-threatening arrhythmias. The acute loss of coordinated atrial and ventricular contraction— as seen in the onset of atrial fibrillation— reduces cardiac input by between 5% and 15% and this effect is more pronounced in patients with reduced ventricular compliance (for example, those with hypertrophy and hypertension).

Persistently elevated ventricular rates above approximately 120 to 130 beats per minute may produce a ventricular tachycardiomyopathy, but this is potentially reversible by restoring heart rate and preventing further dilatation of the atria.5

EPIDEMIOLOGY AND NATURAL HISTORY
“... but lots of people have this heart irregularity?”

The prevalence of atrial fibrillation has been estimated at between 1% and 2% of the population and is linked to increasing life expectancy. However, the influence of contributing conditions like diabetes and obesity may increase the prevalence beyond that attributable to the changes in demographics.6-7 Although atrial fibrillation is uncommon in younger individuals (less than 0.5% in those below 40 to 50 years of age, the lifetime risk of developing atrial fibrillation is 1 in 4 of those who have reached the age of 40.8 By 80 years of age, more than 10% of the population have atrial fibrillation. Men are more commonly affected than women and it is estimated that more than 6 million people within the European community suffer from this arrhythmia.

COMPLICATIONS OF ATRIAL FIBRILLATION
“... is it dangerous doctor?”

Stroke is a devastating consequence of atrial fibrillation, and approximately 1 in 5 of all strokes are due to underlying atrial fibrillation. However, this may be an underestimate due to undiagnosed paroxysmal atrial fibrillation and the contribution of emboli to “cryptogenic strokes.”9,10 Importantly, paroxysmal atrial fibrillation carries the same risk of stroke as permanent or persistent atrial fibrillation.11,12

Death rates are increased twofold in those with atrial fibrillation independent of other known predictors of mortality.9,13 Importantly, this death rate is reduced by anticoagulant therapy (see below).

Approximately one third of all hospitalizations due to rhythm disturbances are the consequence of atrial fibrillation, and the arrhythmia complicates other hospitalizations, including those for acute coronary syndrome, heart failure, and thromboembolism.

Vascular dementia and cognitive dysfunction may be the consequences of atrial fibrillation, and it has been postulated that asymptomatic embolic events may contribute to cognitive decline in patients with atrial fibrillation despite the absence of recognized stroke.10

Reduced exercise capacity and reduced quality of life are the most common presentations of patients with atrial fibrillation, and the lack of functional reserve is manifest by increased heart rate on exercise.

Heart failure is an important complication of atrial fibrillation and New York Heart Association (NYHA) class II-IV heart failure is found in about one third of patients with atrial fibrillation.14,15 Conversely, more than one third of patients that present with heart fail-

Figure 2. Schematic to illustrate the most common clinical features and complications of atrial fibrillation.

“Silent” atrial fibrillation describes the condition in the absence of symptoms. The heart failure may be a consequence of the atrial fibrillation and, conversely, heart failure can lead to increased back pressure in the atria, volume overload, and the development of atrial fibrillation. In consequence, there are major clinical and health economic impacts (Figure 2).
CLASSIFICATION OF ATRIAL FIBRILLATION AND INITIAL INVESTIGATION

“… but I only have this irregularity occasionally doctor?”

The classification of atrial fibrillation is potentially confusing.

- When atrial fibrillation is first recognized, irrespective of its duration this is classified as **first diagnosed atrial fibrillation**.
- **Paroxysmal atrial fibrillation** consists of episodes of atrial fibrillation that are self-terminating usually within about 2 days, but can last for up to 7 days. The longer the episodes last, the lesser the likelihood of conversion spontaneously to sinus rhythm.
- **Persistent atrial fibrillation** is present when the episode lasts more than 7 days or requires termination by electrical or pharmacological cardioversion.
- **Permanent atrial fibrillation** exists where the arrhythmia continues and a rhythm control strategy has not been adopted or has failed.

Assessment of the patient with atrial fibrillation requires evaluation of underlying risk factors including diabetes, hypertension, valvular heart disease, and myocardial disease. If the patient is hemodynamically compromised by the rapid ventricular rate (with heart failure) then the management of heart rate and heart failure is an urgent priority. The initial assessment of a patient with atrial fibrillation includes echocardiography to detect ventricular, valvular, and other structural or congenital heart disease, thyroid function tests, full blood count, and renal function, and a fasting glucose measurement for diabetes. In patients with suspected coronary artery disease or regional mechanical dysfunction, further investigation of myocardial ischemia may be indicated.

MANAGEMENT OF ATRIAL FIBRILLATION: CONTROLLING HEART RATE AND RHYTHM

“Doctor if you correct this irregularity, will I be fine?”

Patients with acute or decompensated heart failure and atrial fibrillation require urgent assessment of the underlying cause of the heart failure and the potential for cardioversion to sinus rhythm.

It is critical that all patients with atrial fibrillation should be evaluated for their stroke risk and their bleeding risk. Where the time of onset of atrial fibrillation is accurately known, and is less than 48 hours duration, such patients may be cardioverted with parenteral anticoagulation and this is associated with very low risk of stroke. If the duration of atrial fibrillation is uncertain, or longer than 48 hours, transesophageal echocardiography may be used to detect intracardiac thrombus (which would preclude cardioversion because of the risks of emboli). Transthoracic echocardiography provides valuable information on cardiac structure and function, including contributory factors for the cause of the atrial fibrillation.

Patients may present with stroke or transient ischemic attack (TIA) as the first manifestation of their atrial fibrillation and they require emergency investigation using computed tomography. For those with thrombotic or embolic stroke, emergency evaluation for revascularization or thrombolysis is of paramount importance (full consideration of revascularization is beyond the scope of this article).

In those without acute hemodynamic compromise, the key focus is on rate and rhythm management and anticoagulation. In the absence of acute heart failure, oral administration of β-blockers or nondihydropyridine calcium antagonists can be used to control the heart rate response. In selected patients with impaired ventricular function, specific antiarrhythmic agents may be required (for example, amiodarone). Urgent cardioversion may be appropriate depending upon the echocardiographic findings.

Electrical cardioversion requires anesthesia, but is more effective than pharmacological cardioversion and is indicated in patients with atrial fibrillation compromised hemodynamically or with heart failure (depending upon the underlying structural abnormalities). In patients who are not acutely symptomatic, pharmacological cardioversion may be initiated by administration of a bolus antiarrhythmic drug (for example, flecainide, propafenone, amiodarone). β-Blockers are effective in rate control, but cardioversion rates are low and digoxin is not effective for the termination of atrial fibrillation. The main risks of cardioversion are associated with thromboembolic events (approximately 1% to 2% risk), but this is reduced by appropriate anticoagulation. If the onset of atrial fibrillation is known and is within 48 hours, then the risks of thromboembolic events are very low with cardioversion.

Guidelines recommend the use of intravenous flecainide or propafenone for pharmacological cardioversion when there is no structural heart disease. In patients...
with recent-onset atrial fibrillation and structural heart disease, intravenous amiodarone is recommended. Single oral administration of flecainide or propafenone ("the pill-in-the-pocket approach") may be used in patients with no significant structural heart disease and provided this treatment has proven to be safe during previous testing in hospital.

In the longer-term management of rate and rhythm, consideration is given to the underlying conditions and the extent to which the patient is symptomatic from episodes of atrial fibrillation. Randomized trials have compared rhythm versus rate control strategies in patients with atrial fibrillation, but have found no difference in all-cause mortality, and no difference in stroke rate in the comparison of the strategies. Rhythm control (cardioversion/ablation) is less successful in those with longer duration atrial fibrillation, those of older age, and those with severe associated cardiovascular conditions including dilatation of the left atrium.

Similarly, the trials assessing quality of life have found no difference in quality of life with rhythm control compared with rate control strategies. This is despite the fact that quality of life is significantly impaired in those with atrial fibrillation. The ATHENA trial (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation/atrial flutter) assessed the efficacy of dronedarone in preventing cardiovascular hospitalization or death in patients with atrial fibrillation or atrial flutter and the findings indicate a reduction in hospitalisation. Dronedarone is not approved for the treatment of permanent atrial fibrillation, but it reduces heart rate during atrial fibrillation relapses in those with paroxysmal atrial fibrillation. Dronedarone should not be used in patients with advanced heart failure (NYHA class II-IV), especially heart failure precipitating hospitalisation. Amiodarone is an effective rate control drug and is usually well tolerated in hemodynamically compromised patients, but for chronic treatment it has a potentially serious side effect profile including thyroid dysfunction, bradycardia, and eye and lung complications.

Left atrial catheter ablation is reserved for patients who remain symptomatic despite optimal medical therapy including rate and rhythm control. It is usually undertaken in patients with symptomatic paroxysmal atrial fibrillation, resistant to at least one antiarrhythmic drug. Ablation procedures involve pulmonary vein isolation and circumferential pulmonary vein ablation (performed as catheter procedures). A meta-analysis has found that catheter ablation has a 77% success rate for the treatment of atrial fibrillation, whereas medical treatment has a 52% success rate. Currently, only a small minority of all patients with atrial fibrillation are managed with ablation procedures (<5%) and many older patients have contraindications to the procedure or are less likely to respond because of structural changes and the duration of atrial fibrillation.

Surgical ablation is reserved for those undergoing open chest valvular or coronary revascularization procedures, freedom from atrial fibrillation is reported in 75% or more of patients following the procedure.

**ANTICOAGULATION IN ATRIAL FIBRILLATION**

"Doctor, will I get a stroke?"

Although the aim of rate and rhythm management for patients with atrial fibrillation is symptom relief, there is no evidence that these treatments impact on the rates of stroke or death. In contrast, anticoagulation is
Effective and critically important in reducing risks of stroke and embolization. For each patient the balance of stroke risk and bleeding risks must be considered prior to commencing anticoagulation. Based upon systematic reviews, the key risk factors for subsequent stroke are prior stroke or TIA or systemic embolism, advanced age, hypertension, diabetes, and structural heart disease (Table I). In addition, moderate-to-severe LV systolic dysfunction is a predictor of stroke as is the presence of thrombus in the left atrium (on transesophageal echo) and detection of complex atheromatous plaques in the aorta (both of the latter increase the risk of stroke by more than twofold). In addition, the appearance of echocontrast is an indicator of thrombotic risk with a 3.5-fold increase in stroke risk, linked also to low left atrial velocities on echocardiography.

**Stroke risk in atrial fibrillation**

The most frequent thromboembolic complication in patients with atrial fibrillation is ischemic stroke, and patients with atrial fibrillation have a risk of stroke that is increased fivefold compared with an age-adjusted population.\(^{19}\) According to a community-based stroke study, there are about 4.5 strokes per 100 patients per annum in patients left untreated.\(^{19}\) These strokes are more likely to be severe and are often fatal.

**Prediction of stroke risk**

Recent systematic reviews have identified a number of key risk factors for stroke and these include prior stroke/TIA/thromboembolism, older age, hypertension, diabetes, and structural heart disease.\(^{20,21}\) The simplest risk scoring system is the CHADS\(_2\) score (Table I) with Congestive heart failure, Hypertension, Age over 75, and Diabetes each contributing 1 point and prior Stroke contributing 2 points.\(^{16}\) Although useful, the accuracy of predicting stroke with the CHADS\(_2\) score is only moderate with a C statistic of 0.58.\(^{16}\) A more refined risk score has been developed, the CHA\(_2\)DS\(_2\)-VASc score. The components consist of congestive heart failure, hypertension, age over 75 (double score), diabetes, stroke (double score), vascular disease, age 65 to 74, female sex.\(^{22}\) Although more complex, this scoring system is more accurate than the CHADS\(_2\) score, especially for identifying those at very low stroke risk.

**Bleeding risk and anticoagulation**

“Doctor, isn’t that rat poison … and will I bleed?”

Unfortunately, many of the same factors that predict increased risk of stroke also predict risk of bleeding. Based on an observational cohort of 3978 European subjects from the EuroHeart Survey a bleeding risk score has been derived HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR [International Normalized Ratio], Elderly [age over 65], Drugs or alcohol concomitantly) (Table II).\(^{23}\) Although more accurate than the other published risk scores for bleeding, its predictive accuracy is not strong (Figure 3, page 178).\(^{24}\)

**Risk factors for stroke and for bleeding; treatment strategy**

The first step in deciding on whether antithrombotic therapy is indicated is to assess the stroke risk (CHADS\(_2\) score and CHA\(_2\)DS\(_2\)-VASc score [Vascular disease; Age 65-74 y; Sex category]) and the bleeding risk (HAS-BLED score) in the context of the individual patient’s circumstances, including the influence of other conditions that may influence anticoagulation or antithrombotic therapy and other medications, and importantly, the patient’s perspective (Tables I and II; Figures 1 and 2).

The treatment strategy in a patient with atrial fibrillation is shown in Table III (page 178). Table IV (page 178) gives a simplified strategy. Importantly, patients with paroxysmal atrial fibrillation have a similar risk of stroke to those with persistent or permanent atrial fibrillation and so should be managed in exactly the same way with regard to anticoagulation.

Younger patients (less than 60 years of age) with atrial fibrillation in the absence of any risk factors “lone atrial fibrillation” are at very low risk of stroke of approxi-
One important point to note is that, in practice, several adverse situations may interfere with effective treatment of atrial fibrillation. Table V lists four such critically important deficiencies in the anticoagulation management of patients with atrial fibrillation.

In the absence of bleeding contraindications:

- Atrial fibrillation with no CHA2DS2-VASc risk factors (score 0), no antithrombotic therapy (guidelines include the possibility of using aspirin in this group, but this confers bleeding risk without clear evidence of benefit)

- For one clinically relevant major risk factor (i.e., CHA2DS2-VASc score of 1) either anticoagulation or aspirin 75-325 mg daily could be used, but oral anticoagulation is preferred

- For those with one major risk factor or two or more clinically relevant non-major risk factors (in other words a CHA2DS2-VASc score of 2 or more), then oral anticoagulation is recommended

A registry program conducted in the United States, the NABOR program (National Anticoagulation Benchmark and Outcomes Report), demonstrated that overall, 21.7% of patients with atrial fibrillation received no treatment, 25% received aspirin, 20% received aspirin plus warfarin, and one third received warfarin alone. When the patients were categorized according to their risk of stroke, then the proportion of the high-risk group treated with warfarin or with aspirin was no greater than for the overall group of patients.25

Figure 3. Receiver-operating characteristic curves of the bleeding risk schemes for the three outcomes.

The accuracy for predicting bleeding is only modest. The HAS-BLED score performed better for the primary end point of any clinically relevant bleeding compared with HEMORRHAGES (c-index: 0.6 vs 0.5; P=0.003) and ATRIA (0.6 vs 0.5; P=0.062).

Abbreviations: ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol; HEMORRHAGES, Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk, and Stroke.

The EuroHeart Survey has examined use of vitamin K antagonists in patients with atrial fibrillation and at risk of stroke, and although a higher proportion of patients in the high-risk group were treated with vitamin K antagonist, there remains an important shortfall in anticoagulation.

In studies conducted in elderly patients in the United States, it was found that patients were in the therapeutic range (INR 2-3) only 58% of the time. In addition, major hemorrhage rates were 7.2% and intracranial hemorrhage rates 2.5% with the rates 2.7 times higher in those in patients over 80 years of age. Importantly, 28% of patients discontinued anticoagulation after 1 year (because of difficulties in control or bleeding).

To establish a diagnosis of atrial fibrillation an electrocardiogram is required, often triggered by clinical symptoms such as palpitations or dyspnea or awareness of an irregular heart rhythm. Systematic and more prolonged heart rhythm monitoring is justified in symptomatic patients and recommended by guidelines. In addition, patients with recurrent syncope and patients with potential indications for anticoagulation (like cryptogenic stroke) should undergo prolonged monitoring to detect occult atrial fibrillation. In selected patients, a small recorder device can be implanted under local anesthesia and interrogated remotely to establish whether or not symptoms correlate with an arrhythmia and whether the arrhythmia is atrial fibrillation.

In the patient with documented atrial fibrillation, a decision also needs to be made about whether rate control or rhythm control management should be adopted. As discussed above (see rate and rhythm management section), rhythm control can confer symptomatic benefit, but there is no evidence that it confers a reduction in stroke or reduces death and other outcome events. Rhythm control may be indicated for patients that are significantly symptomatic from atrial fibrillation, provided that the structural characteristics of the heart are such that they can sustain sinus rhythm after cardioversion or ablation. Importantly, a patient should not discontinue anticoagulation after cardioversion or electrical ablation because thrombotic and embolic risks continue. Further evidence is needed, over the longer term, to establish whether such patients may discontinue anticoagulation subsequently.

In selected patients, ablation procedures are indicated (see Management of Atrial Fibrillation section) and some patients may be suitable for an atrial appendage occlusion device. If a patient has a high bleeding risk and thrombus in the atrium, the possibility exists to introduce an “umbrella-like” device to prevent embolization of the thrombus from the atrium. Currently, this is limited to specialist centers, but the application may become more widespread as the devices become more straightforward to use and the evidence base grows.

**CHOICE OF ANTITHROMBOTIC MANAGEMENT**

**Antiplatelet therapy versus control**

“Doctor, can I manage with aspirin…?”

A total of 4876 patients have been randomized in controlled studies of antiplatelet therapy (most commonly aspirin) compared with placebo to reduce the risk of thromboembolism in patients with atrial fibrillation. Aspirin alone, compared with placebo, or no treatment, was associated with a nonsignificant 19% (95% confidence interval [CI], -1% to -35%) reduction in the incidence of stroke. In the primary prevention trials, the absolute reduction was approximately 0.8% per year, but 2.5% per year in the secondary prevention trials. Aspirin was associated with the 13% (95% CI, -18% to -36%) reduction in disabling stroke and a 29% reduction (95% CI, -6% to -53%) in nondisabling strokes. Considering all trials with a reference placebo arm or control arm, then the meta-analysis indicates that antiplatelet therapy reduces the risk of stroke by about 22% (95% CI, -6% to -35%). The dose of aspirin differs considerably among the studies, ranging from 50 mg to 1300 mg with no clear evidence of heterogeneity of benefit. However, low-dose aspirin (less than 100 mg) has lower rates of bleeding than higher-dose aspirin, and therefore if aspirin is used it is reasonable to use doses in the lower range (75 to 100 mg daily).

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**Table V. Deficiencies in anticoagulation treatment of patients with atrial fibrillation.**

The EuroHeart Survey has examined use of vitamin K antagonists in patients with atrial fibrillation and at risk of stroke, and although a higher proportion of patients in the high-risk group were treated with vitamin K antagonist, there remains an important shortfall in anticoagulation.

In studies conducted in elderly patients in the United States, it was found that patients were in the therapeutic range (INR 2-3) only 58% of the time. In addition, major hemorrhage rates were 7.2% and intracranial hemorrhage rates 2.5% with the rates 2.7 times higher in those in patients over 80 years of age. Importantly, 28% of patients discontinued anticoagulation after 1 year (because of difficulties in control or bleeding).
Many of the patients with atrial fibrillation also have underlying vascular disease, and it is interesting that the magnitude of risk reduction is broadly similar to that seen when aspirin is given for patients with arterial vascular disease (about 18%).

The risks of antithrombotic therapy in patients with lone atrial fibrillation are very low (in the absence of major or non major clinically relevant risk factors) as revealed in the Japanese Atrial Fibrillation Stroke Study where patients were randomized to aspirin in a dose of 150 to 200 mg per day and a control group without antiplatelet therapy or anticoagulation. Interestingly, the primary outcome events were higher in the aspirin-treated patients (3.1% per year) than the control group (2.4% per year), and the treatment increased major bleeding (1.6% versus 0.4% in controls). Thus, no therapy rather than aspirin or anticoagulation is an appropriate choice in those with very low risk of stroke and in the absence of major or non major clinically relevant risk factors. In patients with risk factors for stroke, the evidence does suggest that aspirin is superior to control, but it is associated with more bleeding, and recent trial data suggest that this bleeding risk may be as high as seen with anticoagulation (see AVERROES trial [Apixaban versus Acetylsalicylic Acid to Prevent Strokes]).

**Comparison of anticoagulant therapy using vitamin K antagonists and antiplatelet therapy**

Overall, nine studies have been conducted and these clearly demonstrate that vitamin K antagonists are superior to antiplatelet therapy. The risk reduction is approximately 39%.

In the BAFTA trial (Birmingham Atrial Fibrillation Treatment of the Aged) vitamin K antagonist treatment with a target INR of 2 to 3 was superior to aspirin 75 mg per day in reducing fatal or disabling stroke or systemic arterial embolism and there was no difference in the risk of major hemorrhage between warfarin and aspirin. However, the reduction in stroke and systemic embolism was 52%. Nevertheless, there is a risk of intracranial hemorrhage, and considering all trials together the risk of intracranial hemorrhage is about 0.2% per year greater with warfarin than with aspirin. The ACTIVE W trial (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events—Warfarin) trial tested warfarin anticoagulation against the combination of clopidogrel and aspirin. There was a 40% reduction in outcome events with warfarin (95% CI, 18%-56%) with no difference in bleeding events between the arms. In the arm of the trial where aspirin alone was compared with aspirin plus clopidogrel there was an 11% reduction in outcome events, but major bleeding was increased (2% versus 1.3%). Interestingly, half of the patients entered into the trial were thought to be unsuitable for vitamin K antagonist therapy and 23% had a risk factor for bleeding at the trial entry. The important implication is that dual antiplatelet therapy is not safer than anticoagulant treatment and even single antiplatelet therapy may have a similar bleeding risk to oral anticoagulant therapy.

**Challenges of anticoagulation with vitamin K antagonists**

Prescribing guidelines in the UK and US list more than 50 drug interactions for warfarin and these include commonly used agents including many of the antibiotics, the anti-inflammatory agents, statins, antiarrhythmic agents, and alcohol (http://www.nhssb.n-i.nhs.uk/prescribing). Similarly, there are many food substances that interfere with warfarin metabolism, such as kale, spinach, turnip, collards, Swiss chard, parsley, mustard greens, Brussels sprouts, endive lettuce, romaine lettuce, and a number of other food substances used widely in far eastern countries (National Institute for Health (NIH) Task Force http://ods.od.nih.gov/pubs/factsheets/coumadin1.pdf).

Thus, the search for novel anticoagulants has taken place in the face of a substantial unmet need and the difficulties in maintaining stable and predictable anticoagulation with vitamin K antagonists. Nevertheless, there is clear evidence that warfarin is superior to antiplatelet therapy and substantially superior to no treatment. Despite its limitations, anticoagulation with warfarin reduces the risk of stroke by approximately 60% and compared with no treatment this therapy will continue to be used worldwide until the newer anticoagulants become available and affordable.

Maintenance of a stable INR is also influenced by the pharmacogenetics of vitamin K antagonist therapy, particularly the cytochrome P450 2C9 gene and the vitamin K epoxide reductase complex 1 gene. These genotypes influence warfarin dose requirements. The NIH in the US has recommended consideration of gene testing therapy for those undergoing anticoagulation with vitamin K treatment, but this is impractical in the majority of clinical settings and has not been shown to be cost effective. No trials have demonstrated that genetic testing improves hard outcome events.
In an attempt to prove compliance, self-monitoring systems have been devised to allow sufficiently able patients, or their carers, to test anticoagulation levels and improve vitamin K antagonist management (in association with advice from an anticoagulation clinic).

**POTENTIAL ADVANTAGES OF THE NEWER ANTICOAGULANTS**

"Doctor, should I take one of the new anticoagulants instead of warfarin?"

The newer oral anticoagulants fall into two categories, direct thrombin antagonists and factor Xa inhibitors (Figure 4). They have several important features (Table VI).

**Ximelagatran and the SPORTIF trials**

The first of the agents was ximelagatran, but it was withdrawn in 2006 on account of liver toxicity, having demonstrated similar efficacy to warfarin in the SPORTIF III and V trials (Stroke Prevention using the ORal direct Thrombin Inhibitor ximelagatran in patients with nonvalvular atrial Fibrillation).16

**Dabigatran and the RE-LY trial**

In the open RE-LY trial (Randomized Evaluation of Long-term anticoagulation therapyP), with blinded adjudication of end points, dabigatran was compared with warfarin in two doses of 110 mg or 150 mg, both administered twice daily. It was a noninferiority design and the trial was open with respect to warfarin or dabigatran, but the comparison of the two study doses was blinded. Dabigatran is a direct antithrombin inhibitor and is a prodrug and has a bioavailability of about 6%. Its half-life is 12 to 14 hours and renal clearance is 80%. There are interactions with platelet glycoproteins, but in common with the other newer anticoagulants, it does not have the drug interactions of warfarin. The low bioavailability of only 6% and the high renal clearance need to be taken into consideration, in patients where absorption may fluctuate and especially in those where

**Table VI. Major features of the new oral anticoagulants.**

- They avoid the need for anticoagulant monitoring and are given orally once daily or twice daily in a fixed dose
- They have reduced rates of stroke and systemic embolism (or similar rates with some agents)
- They have reduced rates of intracranial hemorrhage and fatal intracerebral bleeding (with all of the new oral anticoagulants)
- They have similar rates of major bleeding (or lower for some agents and dosages)
- They have stable and predictable metabolism without the drug and food interactions of warfarin
renal function is borderline or may deteriorate over time. The dabigatran 110-mg bid dose was demonstrated to be noninferior to warfarin for the prevention of stroke and systemic embolism (primary end point 1.5% per year versus 1.7% per year for warfarin) and there was a significant lower rate of major hemorrhage compared with warfarin (yearly event rate 2.7% versus 3.4%) (Figure 5).32,33

The dabigatran 150-mg bid dose was superior to warfarin in preventing stroke in all systemic embolism (yearly event rate 1.1% versus 1.7%) and it had a similar rate of major hemorrhage as warfarin (yearly event rate 3.1% versus 3.4%) (Figure 5).32

Both dabigatran doses were associated with significantly lower rates of intracranial hemorrhage compared with warfarin (yearly event rates 0.23% and 0.30% with dabigatran 110 mg and 150 mg bid compared with 0.74% with warfarin) (Figure 6).32,33

Gastrointestinal major bleeding was higher than with warfarin for the 150-mg bid dose (1.9% versus 1.0%), but was similar to warfarin in the lower dose of dabigatran (1.1% versus 1.0%). In the original report, the frequency of myocardial infarction was higher for dabigatran than for warfarin (risk ratio [RR], approximately 1.35; confidence interval [CI], 1.0-1.91), but in a subsequent communication there was adjustment for baseline risk, and this difference was no longer statistically significant. The composite of shorter- and longer-term trials with dabigatran has also suggested a modest excess of myocardial infarction (RR, 1.31; CI, 1.03-1.67), but it must be recognized that trials are heterogeneous and this rate of myocardial infarction is much lower than the rate of stroke in these trials. Most side effects were similar for dabigatran and warfarin except for dyspepsia, which was twice as frequent with dabigatran (11.8% with the 110-mg dose versus 5.8% with warfarin).

In summary, the lower dose of dabigatran had similar efficacy to warfarin and improved rates of bleeding, while the higher dose had superior efficacy, but similar rates of bleeding.

**Rivaroxaban and the ROCKET AF trial**

The ROCKET AF trial (Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation) tested oral once-daily rivaroxaban against dose-adjusted warfarin in a double-blind, double-dummy design.34 Patients received 20 mg of rivaroxaban once daily except among those with creatinine clearance of 30 to 49 mL per minute where the dose was 15 mg once daily. By design, this was a higher-risk cohort of patients and unlike the RE-LY trial and the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation)
where the CHADS2 score was approximately 2.1, it was 3.5 in the ROCKET AF trial. In ROCKET AF, the patients had a high frequency of coexisting conditions with more than half (55%) having previous stroke or TIA or systemic embolism, 62% had congestive heart failure, 90% had hypertension, 40% had diabetes, and 17% previous myocardial infarction. The primary efficacy end point of stroke or systemic embolism was reduced, while the patients were on treatment (hazard ratio [HR], 0.79; 95% CI, 0.66-0.96), but in the intention-to-treat analysis, which included approximately 20% of the time off treatment, the difference was no longer significant (Figure 5). It can be concluded that the new treatment was at least as effective as warfarin, and more effective while they received double-blind treatment. Major bleeding was no different and major and nonclinically relevant non major bleeding were also no different between rivaroxaban and warfarin (Figure 6). Fatal bleeding and intracranial bleeding were less common with rivaroxaban, but there was an increase in transfusion (1.7% versus 1.3%) and an increased hemoglobin drop of 2 or more grams (2.8% versus 2.3%). In a separate publication of the patients with moderate renal dysfunction where the lower dose of rivaroxaban was used, the overall results were consistent with the main trial. Similarly, in those with prior stroke or TIA and those without prior stroke or TIA, the results were consistent. In summary, rivaroxaban was at least as effective as warfarin, with similar rates of major bleeding, but lower rates of intracranial and fatal bleeding.

**Apixaban and the ARISTOTLE and AVERROES trials**

Apixaban is a similar direct anti-Xa agent to rivaroxaban and it was administered as a twice-daily tablet in the AVERROES trial and in the ARISTOTLE trial. In AVERROES, it was compared against aspirin for patients who were unsuitable or thought to be unsuitable for vitamin K antagonist treatment. Interestingly, the CHADS2 score of this population was 2.1, which is very similar to that of the trial population randomized to apixaban versus warfarin. The findings of the AVERROES trial were very clear and there was an approximate halving of the frequency of stroke or systemic embolism with apixaban (RR, 0.46; 95% CI, 0.33-0.64). It is also of interest that the rates of major bleeding were no greater for apixaban than for aspirin (RR, 1.14; 95% CI, 0.74-1.75). Minor bleeding was more frequent with apixaban than aspirin (RR, 1.27; CI, 1.01-1.61). The ARISTOTLE trial was similar in design to the ROCKET AF trial as a double-blind, double-dummy design with 18,201 patients. The risk profile was lower than for the ROCKET AF trial (CHADS2 score 2.1). Apixaban was administered at 5 mg orally twice daily, but 2.5 mg bid in selected patients. The results showed a HR of 0.79 with 95% CI, 0.66-0.95, so the trial met its criteria for noninferiority, and also for superiority, compared with warfarin (Figure 5). In both ARISTOTLE and ROCKET AF there was no excess of myocardial infarction with a new agent. A key finding from ARISTOTLE was the reduction in major bleeding (HR, 0.69; 95% CI, 0.60-0.80), and as for the other agents there was a reduction in intracranial bleeding. Gastrointestinal bleeding was similar to that of warfarin (Figure 6).

In summary, apixaban is superior to aspirin in those unsuitable or thought to be unsuitable for vitamin K antagonist therapy and is superior to warfarin based upon the ARISTOTLE trial, and with reduced rates of major bleeding. It is anticipated to be approved for clinical use.

**Summary of the newer anticoagulants**

In summary, the newer oral anticoagulants share several features: they do not require anticoagulant monitoring; they result in lower rates of stroke and systemic embolism (at least for some agents and dosages), they have reduced rates of intracranial bleeding, they are easier to administer with a fixed dose and no requirement for anticoagulation monitoring, and they are free of the drug and food interactions of vitamin K antagonists. However, there are also a number of challenges: currently there are no specific antidotes to the newer oral anticoagulants; the evidence for their use is limited to the trial populations studied; the health economic evaluations suggest cost effectiveness, but it will be challenging to meet the higher drug costs of the newer agents.

Although the newer agents do not have specific antagonists, they clear from the system more rapidly than warfarin, and standard management of bleeding events was sufficient for almost all of the bleeding events in the trials. Caution must be exercised in those with, or at risk of, renal dysfunction, especially for agents with higher renal clearance (eg, dabigatran), and patient education is required to ensure that individuals conscientiously maintain the drug therapy.

**CONCLUSIONS**

Atrial fibrillation is poorly recognized and poorly treated. There are major challenges in detecting atrial fibrillation among older patients and those with parox-
ysmal atrial fibrillation. Atrial fibrillation often coexists with complex comorbidity and factors that contribute to both stroke risk and bleeding risk. Evaluation of the risks and benefits of antiarrhythmic therapy and of anticoagulation therapy is of critical importance in the management of this condition. Novel approaches have been devised to treat the rhythm disturbance, which include percutaneous and surgical ablation procedures. As yet, these do not have evidence of improved outcome, although they do improve symptoms. The scope for applying such procedures to the vast majority of frail and older patients is limited and the success rates are much lower in such patients. Thus, there is the need for better rate control, especially on exercise, and better management of anticoagulation. Although warfarin is very successful compared with no treatment and is more effective than antiplatelet therapy, it is challenging to control and is complicated by interactions with other drugs and with many dietary factors. In consequence, INR control is in the therapeutic range only about half the time with vitamin K antagonists and more than 25% of patients discontinue the vitamin K antagonists within 1 year of commencing. This exposes untreated or poorly treated patients to a future stroke risk that is approximately fivefold higher than age-matched anticoagulated patients. The rates of major hemorrhage seen in trials are substantially lower than those seen in clinical practice, perhaps because of the better control administered within trials.

The novel anticoagulants present opportunities for improved outcomes, reduced rates of stroke and intracranial hemorrhage (and in some cases reduced major bleeding), and substantially improved tolerability and convenience. They also present the opportunity to treat a greater proportion of patients with atrial fibrillation; those that currently remain untreated, those that discontinue treatment, and those that are poorly controlled. The health economic challenges are considerable, and depending upon the health care system these may be borne by the individual or by the health care provider or insurance system. Nevertheless, the prospects for improved outcome with lower rates of stroke and lower rates of complications present a bright future for patients with atrial fibrillation, despite the increase in prevalence of this condition.

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Dabigatran versus warfarin in patients with atrial fibrillation.

Rivaroxaban versus warfarin in nonvalvular atrial fibrillation.

Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment.

Apixaban in patients with atrial fibrillation.

Apixaban versus warfarin in patients with atrial fibrillation.
Which drugs and devices can we use for protection against thromboembolic stroke?

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Drugs for stroke prevention in atrial fibrillation (AF) are oral anticoagulants (vitamin K antagonists or the newer anticoagulants) and antiplatelet agents, alone or in combination. Antiarrhythmic drugs have generally proved ineffective in terms of antithrombotic value. “Devices” include implantable objects (left atrial appendage occluder, pacemaker, or implantable cardioverter-defibrillator), or involve ablation. Most patients with AF and thromboembolic risk should be treated with an oral anticoagulant. Left atrial appendage occlusion or closure is for those with a high bleeding risk or unsuccessful anticoagulation. No thromboembolic protection is needed in the absence of thromboembolic risk factors. In successfully ablated patients with significant underlying cardiovascular disease, AF is likely to recur and they should not abandon formal treatment with proven anticoagulant therapy until more convincing data support this policy.

DRUGS

Several types of drug might reduce thromboembolic events in AF. Those which have been investigated in detail include antiplatelet agents, anticoagulant drugs, and antiarrhythmic drugs.

Antiplatelet agents

There is small, but still disputed, advantageous effect of aspirin on stroke in patients with AF. Meta-analysis shows 18% reduction in stroke and transient ischemic attack (TIA), but it is not statistically significant. Of more importance is the obvious internal inconsistency within the largest of the trials that report a comparison between aspirin and placebo (SPAF, Stroke Prevention in Atrial Fibrillation). The single trial composite result obtained by combining the disparate results obtained when aspirin was compared with warfarin or placebo with the results from the group randomized only to aspirin versus placebo gives rise to great concern about the validity of the results. Other trials have clearly documented that aspirin is associated with as much bleeding as that seen with warfarin, especially in the elderly. Thus, aspirin monotherapy for stroke prevention is not clearly effective, but obviously carries some hazard. Progressively, it is being phased out as an appropriate therapy for thromboprophylaxis in AF. Other antiplatelet agents are also of little value in this context.

A combination of antiplatelet agents (aspirin and clopidogrel) has also been evaluated against both aspirin and warfarin in a suite of trials known as ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events). The ACTIVE W trial (W, for warfarin) was halted prematurely when it was clear that the combination of antiplatelet drugs was clearly less effective than warfarin in reducing major cardiovascular events including stroke (relative risk [RR], 1.44; 95% confidence interval [CI], 1.18-1.76, \( P=0.0003 \)). ACTIVE A (A, for aspirin) ran its full course and demonstrated a significant, but small, reduction in the primary composite end point of major cardiovascular events (RR, 0.89; CI, 0.81 to 0.98; \( P=0.01 \)), and a significant 28% reduction in stroke (RR, 0.72; CI, 0.62 to 0.83; \( P<0.001 \)), but an increase in bleeding (RR, 1.57;
95% CI, 1.29 to 1.92, \( P < 0.001).\) The net benefit of the combined therapy compared with aspirin was in favor of the combination,\(^7\) giving rise to the view that aspirin plus clopidogrel was useful for those patients at high risk of thromboembolism who were unable to take vitamin K antagonists (VKAs), especially when the reason was other than bleeding.\(^8\) However, the advent of new oral anticoagulant drugs (NOACs) has alleviated many of the problems associated with VKAs and has reduced the need for combined antplatelet therapy for this indication.

**Anticoagulant drugs**

Warfarin/Coumadin and other VKAs reduce the risk of stroke by 62% and the risk of mortality by 26% in patients with AF.\(^9\) Despite these impressive benefits, the drugs have not been universally well used. Many patients and some doctors are suspicious of a drug that was first used, and is still used as a rodent poison. Only about half of the patients that should be anticoagulated (annual thromboembolic risk of about 2% or more) are prescribed and continue to take VKAs, and only 50% of these patients are therapeutically anticoagulated. This situation has arisen because of concerns related to bleeding, drug and food interactions, and the need for frequent blood tests to monitor and adjust the dose of VKAs.

Recently, a series of direct thrombin inhibitors and direct and indirect factor Xa inhibitors (NOACs) have been investigated as potential alternatives for VKAs. These drugs do not have food-drug interactions and have so few drug-drug interactions that they may be used in fixed dosages without the need to monitor their anticoagulant effect. Of these drugs, dabigatran (150 mg bid) and apixaban (5 mg bid) proved superior to dose-adjusted warfarin, and dabigatran (110 mg bid) and rivaroxaban (20 mg od) were noninferior to dose-adjusted treatment with VKAs in large trials with stroke and systemic embolus as the primary end point.\(^10-12\) Intracranial hemorrhage was significantly less with all the NOACs, thromboembolic stroke was less with dabigatran, and major bleeding was less with apixaban and dabigatran 110 mg bid (Figure 1).\(^5,6,10-15\) Recent guidelines have either regarded NOACs as alternatives, or recommend them in preference to VKAs.\(^16,17\) Because of the reduced risk of intracranial hemorrhage with NOACs, most guidelines have begun to extend the recommendation for anticoagulation to AF patients with an annual stroke risk of 1% to 2%. Clinical experience is still limited with NOACs, but there are already many reports of major bleeding with dabigatran, largely in patients with poor renal function and where the drug has been used off-label. Some are concerned that there are no fast-acting “antidotes” to the anticoagulant effect of these drugs and that easy assessment of the status of anticoagulation cannot be assessed in most hospitals.

**Antiarrhythmic drugs**

No antiarrhythmic drug has a direct anticoagulant action. However, if thrombosis is dependent on the duration of AF or its overall burden, or

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if embolism is provoked by a change in rhythm from AF to sinus rhythm, an antiarrhythmic approach may indirectly reduce the likelihood of stroke or systemic embolism. This had not been demonstrated with any antiarrhythmic agent until dronedarone was compared against placebo in a large population of patients with recurrent AF and a significant risk of stroke. In the ATHENA (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation/atrial flutter) trial stroke was reduced from 1.8% per year to 1.2% per year (HR, 0.66; CI, 0.46 to 0.96; P=0.027).18 Therefore it seems that if dronedarone is truly effective at reducing stroke in patients with recurrent AF its antiarrhythmic action must be largely responsible.

**DEVICES**

A device may be inserted into the left atrial appendage (LAA) to effectively occlude its orifice and endothelialize to provide protection against clot formation. A pacemaker or ICD can be used to prevent or interrupt ongoing AF, to reduce the burden of AF, and theoretically to reduce the likelihood of stroke. Left atrial (LA) catheter ablation may effectively eliminate AF for many years in a significant proportion of patients and thus render them less likely to suffer stroke.

**Left atrial appendage, closure or excision**

Most thrombi associated with AF, especially in patients without rheumatic or prosthetic heart valves, are thought to form in the LAA. For this reason surgical excision or closure of the LAA has been practiced empirically for many years. More recently occlusion devices have been designed which can be inserted percutaneously using transseptal puncture to gain access to the LA. Two of these devices are now commer-

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**Figure 1. Efficacy and safety of oral anticoagulants.**

**Category**

- W vs placebo
- W vs Wlow-dose
- W vs aspirin
- W vs aspirin+clopidogrel
- W vs ximelagatran
- W vs dabigatran 110
- W vs rivaroxaban
- W vs dabigatran 150
- W vs apixaban 5

**Relative hazard ratio (95% CI)**

- W vs dabigatran 110
- W vs rivaroxaban
- W vs dabigatran 150
- W vs apixaban 5

**Abbreviation:** w, warfarin.
cially available in Europe (WATCH-MAN and Amplatzer Plug), and several others are being investigated. Results compared with standard anticoagulation are available from one moderately large randomized clinical trial, PROTECT-AF (WATCHMAN LAA system for embolic PROTECTion in patients with Atrial Fibrillation).20 and preliminary results from a smaller observational ASAP (AcetylSalicylicAcid Plavix) study in patients in whom a VKA was contraindicated are also available. Results indicate that the WATCHMAN device is not inferior to warfarin in terms of stroke prevention and that, apart from periprocedural complications, safety end points are at least comparable to those encountered with VKA therapy. Procedure-related complications were far fewer in the second half of the PROTECT-AF study and in the continued access program, indicating that not only the net benefit of device placement might be even better than seen in PROTECT-AF, but also that careful training is required before new centers and operators embark on this procedure. ASAP showed that the WATCHMAN device substantially outperformed the expected benefit from no therapy or antiplatelet treatment (stroke rate per 100 patient years: 1.7% vs 7.3% and 5%, respectively) in patients for whom anticoagulants could not be prescribed.

Other studies and registries with this and other devices are under way. Studies comparing LAA occlusion against NOAC therapy are urgently needed. The use of this type of device is gaining popularity, but the most appropriate indications have not yet been defined. Broadly, those with a high risk of bleeding who have a significant risk of thromboembolic stroke are the most likely candidates (Figure 2).21

**Left atrial ablation**

In 2006, a moderately sized observational study demonstrated in 755 AF patients, 56% of whom had ≥1 risk factor for stroke, that the risk of a thromboembolism after LA radiofrequency ablation was 1.1% over a follow-up of up to 30 months in nonanticoagulated patients. This was not significantly different to the Framingham population. It was concluded that discontinuation of anticoagulant therapy appeared to be safe after successful LA ablation.22 The Intermountain AF Study reported results following ablation in 4212 patients compared with 16 848 patients with AF who did not undergo ablation and the same number of normal controls without AF. They were followed for more than 3 years and the postablation AF patients were only anticoagulated if their CHADS2 score was >2 (CHADS2: Congestive heart failure, Hypertension, Age over 75, Diabetes, and prior Stroke). Stroke rates were similar in the post-ablation AF patients and the control patients without AF, but it was significantly higher in the AF patients who were treated conventionally without undergoing ablation (HR, 1.68, \(P<0.0001\)). However, the three groups were not well matched.23

Many more retrospective studies have now been published (Table I),22,24–28 all suggesting that postablation patients are less vulnerable to thromboembolic events.24,28 However, the most compelling is a propensity-matched analysis involving 3194 patients with AF treated by LA ablation and 6028 patients with AF treated with antiarrhythmic drugs, from which 801 pairs were derived. There was a significant reduction (HR, \(0.60; CI, 0.43-0.84; P=0.005\)) in those suffering stroke or TIA over a 27-month period.28

There has not yet been any prospective randomized trial of LA ablation therapy alone versus standard treatment with VKAs or NOACs. Longer term follow-up after LA ablation,29 especially in patients with significant underlying heart disease (ie, those also most at risk of stroke), are now showing that AF is likely to recur in most. Guidelines therefore continue to insist that, irrespective of the rhythm achieved by LA ablation, the standard approach to anticoagulation should continue.16,17,21

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**Figure 2. When to consider a left atrial appendage (LAA) occlusion device—balance of thromboembolic and bleeding risk.**

![Figure 2. When to consider a left atrial appendage (LAA) occlusion device—balance of thromboembolic and bleeding risk.](image-url)

**Thromboembolic risk**

- Major bleeding event on anticoagulant
- Bleeding risk

**Bleeding risk**

- 3–4% patients
- 1–2% patients

**3–4% patients**

**1–2% patients**

![Diagram showing the balance of thromboembolic and bleeding risk.](image-url)
Pacemakers

There is little doubt that AF is less in patients with sick sinus syndrome who are treated with dual chamber pacemakers compared with those who are treated with single-chamber ventricular pacemakers. For example, in MOST (MODE Selection Trial), atrial fibrillation was reduced by 21% in the dual chamber pacing cohort compared with ventricular demand pacing (HR 0.79, 95%CI 0.66 to 0.94, P=0.008).30 and in CTOPP (Canadian Trial Of Physiological Pacing) the development of "chronic" AF was reduced 27.1%, (P=0.016).31 It is more controversial whether dual chamber pacing is similarly helpful in patients with atrioventricular block.32 Although pacemaker algorithms have been designed to incorporate overdrive pacing to prevent bradycardia and reduce the density of atrial premature beats, these have been of little value in reducing the burden of AF and they have not been evaluated for stroke prophylaxis.

ICDs can detect and convert AF. They are not routinely programmed to do this automatically because patients are generally conscious during episodes of AF and an endocardial shock is painful. However, devices specific for this purpose are now being reconsidered. There is a theoretical benefit, but no study has been conducted to document this.

**DISCUSSION**

If oral anticoagulants were effective therapies, and not associated with the risk of bleeding, not subject to major interactions with food or other drugs, and if patient adherence to therapy were assured, there would be no need to consider “device-based” therapies, which have none of these problems in the long term. NOACs have eliminated or reduced some of the disadvantages seen with VKAs, but they are still...
heavily dependent on patient adherence, and major bleeding is not eliminated, although it is reduced.

The choice between drug or device for thromboembolic protection in AF may seem to be a simple debate, but fundamental questions about the mechanism of thrombogenesis associated with AF are involved. Two basic questions must be addressed:

• Is AF merely a marker of increased thrombogenicity or is it essential to the mechanism of thrombus formation?
• What proportion of thrombi associated with AF form outside the left atrial appendage?

The risk factors for stroke in patients with AF are also risk factors for stroke in sinus rhythm. It is far from clear that any reduction in the burden of AF using an antiarrhythmic drug, a pacemaker/ICD, or LA catheter ablation will eliminate or significantly reduce the risk of thromboembolism. ASSERT (ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial) demonstrated that a 6-minute episode of "AF" is sufficient to identify patient at 2.5-fold the risk of subsequent stroke compared with similar patients without an arrhythmic episode that is so short that it seems very unlikely to be mechanistically involved in thrombus formation. A detailed analysis of data from the TRENDS (not an acronym) study (continuous monitoring with implanted pacemaker) showed that although a period of AF >6 hours identified patients at thromboembolic risk, stroke often occurred well before or well after such episodes were recorded, again casting doubt on the mechanistic relevance of the arrhythmia itself. If AF is only a marker of thromboembolic risk, then its elimination will not eradicate the stroke risk, and other modalities of treatment, such as anticoagulant drug therapy, will continue to be needed.

The blind-ended sack known as the left atrial appendage is thought to be the site of thrombus formation in a fibrillating LA. However, this is not always the case as thrombus can form on any damaged endothelium from the pulmonary veins to the aortic valve. Atherosclerotic plaque from the ascending aorta to the cerebral arteries can embolize to cause a stroke or TIA. LAA occlusion cannot prevent all of these events.

It is technically possible to occlude, excise, or close the LAA such that thrombus formation could not occur at this site. These procedures are technically feasible, at some cost related to their invasive nature. However, periprocedural complications can be greatly reduced by appropriate training. Surgeons have routinely excised the LAA, but we still await a randomized trial to demonstrate the value of this procedure. Several devices for LAA occlusion are now commercially available in Europe, and a second trial of occlusion on this occasion against NOACs (or a mixture of NOACs and VKAs) is needed to confirm the encouraging results seen with PROTECT-AF.

Until more evidence is available, it is wise to confine LAA occlusion/excision solutions to those patients who have a high bleeding risk (eg, a major bleed on standard anticoagulant therapy) and a high thromboembolic risk (eg, an ischemic stroke while treated with optimum anticoagulation). This case is obviously at the extreme of those for whom standard therapy with oral anticoagulation is contraindicated. There are other indications for LAA occlusion when oral anticoagulants cannot be used, but this therapy should certainly not yet be considered a legitimate alternative to standard oral anticoagulation.

CONCLUSION

The majority of patients with AF and thromboembolic risk should be treated with an oral anticoagulant. A well-controlled dose-adjusted VKA is satisfactory for many. NOACs may be a preferred alternative in general, but particularly for any who have difficulty with VKA therapy. Some with a high risk of bleeding risk, or who have failed optimum oral anticoagulation therapy, will be candidates for left atrial appendage occlusion or closure. Patients with no thromboembolic risk after left atrial ablation will not need thromboembolic protection, but others with some small risk may forgo anticoagulation in the expectation that their arrhythmia has been abolished, but this carries some risk. For those with significant underlying cardiovascular disease it is likely that their AF will eventually recur and that their risk of stroke will remain substantial: they should not abandon treatment with proven therapy, ie, oral anticoagulants.

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How do we balance risk and benefit in a population at risk of both stroke and bleeding?

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At least one in five strokes is due to atrial fibrillation, plus an unknown number of strokes caused by “silent,” undiagnosed paroxysmal atrial fibrillation. Oral anticoagulation, either with vitamin K antagonists or with one of the new oral anticoagulants, prevents approximately 2/3 of strokes in atrial fibrillation. While the net clinical benefit of oral anticoagulation has been shown in many trials, there is a small, but significant, risk of severe bleeding, including intracranial hemorrhage, induced by oral anticoagulant therapy. This article discusses several areas of concern, such as withholding of anticoagulant therapy in patients not at risk for stroke, reducing bleeding risk by choosing the most appropriate type of anticoagulant, and treating reversible risk factors for bleeding, and tries to outline strategies and practicalities to resolve these issues in clinical practice.

Keywords: atrial fibrillation; hemorrhage; oral anticoagulant; risk factor; stroke

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Antithrombotic therapy in atrial fibrillation has been reshaped dramatically in the last decades: continuous, conceptually lifelong anticoagulant therapy is the current standard of care to prevent strokes in almost all patients with atrial fibrillation. Only a bit over 20 years ago, the first “game-changing” evidence favoring oral anticoagulant therapy for stroke prevention over antiplatelet therapy was published. Today, we have ample evidence from large-scale clinical databases demonstrating that most patients with atrial fibrillation are at high risk for stroke. Furthermore, anticoagulant therapy using vitamin K antagonists seems to confer a net clinical benefit by preventing strokes. This beneficial effect is achieved while inducing a small, but relevant, risk of severe hemorrhage, including life-threatening events such as intracranial hemorrhage. In fact, fears to cause such major adverse events, although they are less frequent than preventable strokes, is one of the main reasons for the persistent underuse of anticoagulant therapy in atrial fibrillation patients who are at risk for stroke and in need for such therapy. This underuse of oral anticoagulant therapy appears to continue despite unanimous guideline recommendations to use oral anticoagulant therapy in most patients with atrial fibrillation. There is a clear need for better implementation to increase the use of anticoagulation. In fact, the desire to reduce the number of severe bleeding events to a minimum remains valid, and techniques to avoid some bleeding events may support more widespread use of anticoagulants. The ideal anticoagulant would prevent thrombus formation in the atria without causing bleeding events in other organs. Short of such a magic bullet, there are three major strategies to reduce bleeding in patients with atrial fibrillation which will be discussed in this article:

- Withholding of anticoagulant therapy.
- Choosing the safest effective therapy.
- Reducing factors that can cause bleeding events.

WITHHOLDING ANTICOAGULANT THERAPY

Anticoagulant therapy has a clear net clinical benefit in patients at risk for stroke. All current guidelines concur in recommending oral anticoagulation for patients with atrial fibrillation and two or more stroke risk factors, and indeed also to consider it in patients with only one of those stroke risk factors.

Patients not needing oral anticoagulation

The higher the stroke risk, the higher the absolute benefit of oral anticoagulant therapy seems to be. Con-
versely, patients without risk factors for stroke are at such a low risk for stroke that anticoagulant therapy does not appear to be needed. Consequently, the current European Society of Cardiology (ESC) guidelines recommend not to use any anti-thrombotic therapy, based on the observation that even the use of a low dose of aspirin already increases bleeding risk markedly, while the effectiveness of aspirin to prevent strokes is remarkably low. This recommendation discourages a potentially hazardous therapy with limited evidence for efficacy in patients with “lone” atrial fibrillation at low risk for stroke. The Canadian and American guidelines also discourage the use of oral anticoagulation in these patients, but recommend aspirin for some atrial fibrillation patients at lower risk of stroke (Table 1).

While it seems obvious from the available clinical data and for common sense to withhold anticoagulant therapy from patients who are not at risk for stroke, there is a persistent tendency toward “over-anticoagulation” in atrial fibrillation patients at low risk for stroke.

Grey zone at lower end of stroke risk

In some patients at the low end of the risk spectrum, there are no conclusive data for optimal antithrombotic therapy. In patients at slightly increased risk for stroke, eg, patients of one of the new oral anticoagulants, apixaban, over aspirin in a cohort in which most patients were at low stroke risk. The other guidelines may be more concerned with the known protective effect of aspirin in patients with coronary artery disease (CAD) and stroke. In patients at relatively low risk of stroke, there is still an evidence gap to inform on the optimal anticoagulant therapy, and individual assessment, eg, considering the extent of disease severity, will help to guide decisions in such patients.

Table 1. Recommended antithrombotic therapy for atrial fibrillation patients following the American, Canadian, and European guidelines based on stroke risk.

<table>
<thead>
<tr>
<th>ACCP/AHA/HRS</th>
<th>CCS</th>
<th>ESC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 high risk factor (prior stroke, age ≥75 years)</td>
<td>NOAC or VKA</td>
<td>NOAC preferred to VKA</td>
</tr>
<tr>
<td>2 or more risk factors</td>
<td>NOAC or VKA or ASA</td>
<td>If age &gt;65 NOAC preferred to VKA</td>
</tr>
<tr>
<td>1 risk factor</td>
<td>NOAC or VKA or ASA</td>
<td>If female or vascular disease ASA</td>
</tr>
<tr>
<td>No risk factors</td>
<td>ASA</td>
<td>Nothing</td>
</tr>
</tbody>
</table>

Withholding an anticoagulant may be warranted in patients who have survived an intracranial hemorrhage whose cause cannot be mended. These rare events—0.4% to 0.8%, per year in recent controlled trials—pose therapeutic challenges that call for an individualized decision based on a multidisciplinary assessment: the decision for or against anticoagulant therapy should consider the individual stroke risk and the risk of recurrent intracranial bleeding, which will be influenced by the type of bleeding, the clinical circumstances of the bleeding event (such as International Normalized Ratio [INR] levels or drug dosing at the time of the bleed, or triggers of the event such as a trauma), but also integrate information from cerebral imaging and possibly genetic factors to estimate the individual likelihood of a repeat event. Many major bleeding events, such as a gastric bleed due to an ulcer, but also an intracranial bleed due to an aneurysm which can be clipped or operated, have a reversible cause and do not require to withhold anticoagulant therapy in the long term. Withholding an anticoagulant for a short time to manage the bleed is often needed and justified.
Can oral anticoagulant therapy ever be stopped in atrial fibrillation patients?

Historically, traceable up into antithrombotic treatment applied in the AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management), some patients with atrial fibrillation were considered “cured” or at least “free of atrial fibrillation” when sinus rhythm was restored and its persistence had been measured by several Holter ECG recordings. We know now that atrial fibrillation recurs in almost all patients in the long term, although the time between episodes can vary, and that discontinuation of anticoagulant therapy confers adverse outcomes. We also know that the risk for bleeding is highest in the first year after initiation of anticoagulant therapy, and that, conversely, the risk of bleeding is markedly lower in patients who survived an initial period of anticoagulation without major problems. Furthermore, the protective effect of oral anticoagulant therapy does not seem to change over therapy time. Hence, the decision for anticoagulant therapy is conceptually a lifelong decision, unless complications of therapy occur. A short-term withdrawal of oral anticoagulation is often justified for elective surgical procedures. Patients undergoing vascular procedures such as coronary stent placement or catheter ablation, in contrast, seem to benefit from uninterrupted anticoagulation.

CHOOSING THE SAFEST EFFECTIVE THERAPY

Optimal delivery of vitamin K antagonist therapy

Until very few years ago, vitamin K antagonists were the only medication for oral anticoagulation, and outside of controlled trials they are the only therapy that has proven its effectiveness in “everyday” clinical practice as evidenced in registries and other large cohorts. Vitamin K antagonists have a narrow therapeutic range and require a constant level of anticoagulation, measured as an INR of 2 to 3, to be safe and effective. Patients who are treated in centers that do not achieve such a therapeutic INR for most of the time in their patients have higher stroke rates while on anticoagulant therapy. Dedicated anticoagulant clinics and devices that allow point-of-care or patient self-assessment of the anticoagulation intensity on vitamin K antagonists may improve vitamin K antagonist therapy. Maintaining a constant INR by careful dose adjustment of vitamin K antagonist dose, control of confounders such as vitamin K intake, and considering the genetic determination of the required maintenance dose are helpful to optimize effectiveness and safety in patients receiving vitamin K antagonists.

New oral anticoagulants: a safer alternative to vitamin K antagonists?

The clinical development of oral, fixed-dose direct thrombin and factor Xa inhibitors, and the recent approval of dabigatran and rivaroxaban by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), has broadened the therapeutic options for oral anticoagulant therapy. These new oral anticoagulants or “NOACs” are all at least as effective as vitamin K antagonists—all were compared against warfarin—in preventing strokes in atrial fibrillation.

All three newer substances for which published information from large trials is available, apixaban, dabigatran, and rivaroxaban, show a lower rate of intracranial hemorrhages compared with warfarin in the respective controlled trials. Apixaban and dabigatran in the higher of the two doses tested also appear to prevent all-cause strokes better than warfarin. The publication of the trial results and the approval of dabigatran and rivaroxaban, with apixaban being in the late stages of the approval process, have changed the guidelines. The Canadian and European guidelines recommend to prefer NOACs over vitamin K antagonists provided that they are used within the approved label of the drugs (Table 1). The Canadian and European guidelines have chosen to recommend the approved substances dabigatran and rivaroxaban, but also apixaban, assuming that the approval of the latter medication for clinical use is to be expected shortly.

The preference of NOACs over vitamin K antagonist therapy put forward by the ESC, the American College of Chest Physicians for dabigatran, has been justified by the better safety of the NOACs in respect to clinically relevant major bleeding events and especially intracranial hemorrhages. The American College of Chest Physicians only considered dabigatran on the grounds of the approval status at the time of writing of the guidelines, and also bases its preference of dabigatran over vitamin K antagonists on the grounds that dabigatran prevents ischemic strokes better than warfarin. Time will tell whether the compelling beneficial outcomes seen in controlled trials of the novel anticoagulants translate into a clinical benefit in real-world practice.
Approved and tested dosing of NOA Cs

In Europe, all new oral anticoagulants are available in different doses: Dabigatran was tested in two different doses, of which the lower dose (110 mg bid) was equally effective in preventing strokes compared to warfarin, but caused less bleeding events, while the higher dose (150 mg bid) prevented strokes better than warfarin at a similar rate of major bleeding events, while intracranial and deadly bleeds were still lower on dabigatran. The European label defines an adjustment of dabigatran dosing based on patient age (Table II). Of note, the FDA only approved the higher dose, while in Canada both doses are available to choose from. Both rivaroxaban and apixaban were tested in a single dose, but per trial protocol required a reduced dose in patients with chronic kidney disease (Table II), without any appreciable effect on outcomes.47

In this context, it is worth to note that the new anticoagulants have been used in their lower dose in Japan, and that the INR target in Japan is lower than in the rest of the world (INR 1.5-2.5).

As the anticoagulant effect of the NOA Cs is not measured in patient blood, regular intake of the medication is imperative to assure a therapeutic effect. The short biological half-life of all three NOA Cs (5 to 20 hours) suggests that each forgotten dose will cause a short period without stroke protection, while intake of more than the recommended pills will result in rapid overdosing. Implementation of regular medication intake in clinical practice—outside of pill count and regular trial visits—will be needed to assure safe and effective NOAC therapy.

Antiplatelet therapy in atrial fibrillation patients

Guidelines concur in stating that antiplatelet therapy, including a combination therapy of aspirin and clopidogrel, is inferior to oral anticoagulation therapy to prevent strokes in atrial fibrillation. Comparisons of aspirin therapy with warfarin and apixaban not only demonstrate the well-established inferiority of antiplatelet therapy compared to oral anticoagulation, but also show that the bleeding risk with aspirin alone is not much different from the bleeding risk on oral anticoagulants.28,29 In summary, there is really no good place for antiplatelet therapy to prevent strokes in atrial fibrillation patients. The only exception may be patients who, after repetitive explanation of benefit and risk, refuse any therapy with an oral anticoagulant (vitamin K antagonists or one of the new anticoagulants). These could be treated with a combination of clopidogrel and aspirin, which, again, has inferior effectiveness and similar bleeding risk compared to vitamin K antagonist therapy.48 Better education of such patients should emphasize the benefits of oral anticoagulants, though.

Table II. Dosing of new oral anticoagulants in the controlled atrial fibrillation trials and per European approval.

<table>
<thead>
<tr>
<th>Medication (generic name)</th>
<th>Dosing evaluated in trials</th>
<th>Approved European dosing</th>
<th>Approved US dosing</th>
<th>Approved Canadian dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>110 mg bid, 150 mg bid</td>
<td>150 mg bid, consider 110 mg bid in patients &gt;75 years of age, use 110 mg bid in patients &gt;80 years of age</td>
<td>150 mg bid, 75 mg bid in dialysis patients</td>
<td>150 mg bid, 110 mg bid</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg od, 15 mg od in patients with reduced renal function</td>
<td>Not yet approved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>5 mg bid, 2.5 mg bid in patients with reduced renal function</td>
<td></td>
<td></td>
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</tbody>
</table>

How do we balance risk and benefit in a population at risk of both stroke and bleeding? - Kirchhof
apy" of clopidogrel, aspirin, and an oral anticoagulant in the RE-LY trial (Randomized Evaluation of Long-term anticoagulation therapy) did not show differences in bleeding rates whether they were on dabigatran (either dose) or vitamin K antagonist. Unfortunately, the data to support such a claim are scarce so far.

Patients who receive a stent and patients with a myocardial infarction require antiplatelet therapy to prevent stent thrombosis and reinfarction, while anticoagulant therapy needs to be maintained to prevent stroke. There is good evidence that anticoagulant therapy cannot prevent stent thrombosis or reinfarction, and some evidence that withdrawal of anticoagulant therapy after stent implantation increases death rates. Hence, “triple therapy” consisting of aspirin, clopidogrel, and a vitamin K antagonist, is needed in these situations. Unfortunately, there are no controlled trials on the optimal management of patients who are in need of both oral anticoagulation and antiplatelet therapy, leaving an evidence gap in this relatively large cohort of patients which is estimated to comprise 5% to 15% of all patients with atrial fibrillation. Recognizing the need for clinical guidance and the lack of controlled trial information, the European and Canadian guidelines have included recommendations for antithrombotic therapy in atrial fibrillation patients requiring a stent. Both the Canadian and the European guidelines recommend so-called “triple therapy” of aspirin, clopidogrel, and an oral anticoagulant for a short time after a myocardial infarction or placement of a stent. To minimize the risk of severe bleeds, both guideline sets require to limit the duration of triple therapy to the minimally required duration, usually 1 to 6 months. The ESC specifically recommends radial access for anticoagulated atrial fibrillation patients requiring an arterial vascular procedure to reduce the risk of access-site related bleeding complications.

### REDUCING FACTORS THAT CAN CAUSE BLEEDING EVENTS

Stroke risk factors and bleeding risk factors largely overlap. Bleeding risk is highest in those patients who are at highest risk for stroke. This can be appreciated when the risk factors for stroke and the bleeding risk factors in anticoagulated patients are tabulated and compared (Figure 1). Indeed, the CHADS2 score is one of the best clinical scores to predict bleeding risk. A few additional factors can predict bleeding without increasing stroke risk, namely:

- Concomitant medication with antiplatelet agents (see above).
- Alcohol abuse.
- Anemia.
- History of bleeding events (Figure 1).

For the appreciation of net clinical benefit, we should remind ourselves that the rate of strokes in atrial fibrillation is markedly higher than the rate of clinically relevant bleeding events. Hence, the patients at highest bleeding risk are also the patients that are in greatest need for anticoagulant therapy, and a high perceived bleeding risk should almost never result in withholding of anticoagulant therapy (except-
Also allow withholding anticoagulant therapy, while we are unlikely to enter any-thing close to this ideal world soon. There are, however, technological advances that may allow us to better identify when patients are at risk for stroke, and to pick out those at highest risk for bleeding. Magnetic resonance imaging of the brain and genetic tests may in the future help to identify patients at increased risk for intracerebral bleeds, eg, by detecting prior microbleeds. Assessment of the metabolome of an individual patient may allow to define which anticoagulant could be the best for a given patient. Long-term monitoring of cardiac rhythm has already shown to help identify patients with “silent,” clinically unrecognized atrial fibrillation who are still at risk for stroke. Large studies are under way to determine whether long-term monitoring of heart rhythm could in the future be used to limit “on-demand” anticoagulant therapy to periods when atrial fibrillation is present. While this is a theoretically attractive prospect, the current data suggest that withholding of anticoagulant therapy based on perceived restoration and maintenance of sinus rhythm is dangerous and will increase stroke risk. Last but not least, even on optimal anticoagulant therapy in controlled trials, the residual stroke rate is disappointingly high at around 1.5% per year. Hence, further interventions to reduce stroke in atrial fibrillation patients on optimal anticoagulation are needed. It is at least conceivable that safe delivery of rhythm control therapy, taking away the arrhythmia that causes cardio-embolic stroke, may help to prevent strokes “on top of anticoagulation” in the future. All of these technological approaches require formal testing in controlled trials prior to their clinical application.

**SUMMARY**

Anticoagulant therapy is a very effective way to prevent strokes in atrial fibrillation. Stroke risk outweighs the risk for bleeding in almost all patients with atrial fibrillation, and a perception of increased bleeding risk is rarely sufficient to justify withholding of anticoagulant therapy. Despite this proven efficacy, there is a persistent need to reduce bleeds induced by oral anticoagulation. The clinical availability of new, fixed-dose oral anticoagulants provides new treatment options in addition to the vitamin K antagonists that may help to reduce severe bleeding events in atrial fibrillation patients on oral anticoagulation. Antiplatelet agents are not suitable to prevent strokes in atrial fibrillation, but may be needed as a combination (“triple”) therapy in patients with atrial fibrillation who receive a coronary stent or suffer from a heart attack. Correction of treatable risk fac-

**Established measures**

- Control blood pressure adequately
- Minimize the use of antiplatelet drugs including over-the-counter nonsteroidal anti-inflammatory drugs
- Eliminate local sources of bleeding, eg, gastric or duodenal ulcers
- Reduce alcohol abuse, support abstinence in alcoholics
- Avoid comedication that increases the dose of anticoagulants, eg, via interference with hepatic elimination and metabolism

**Less validated measures**

- Avoid medications with a platelet-inhibiting function
- Treat underlying diseases such as heart failure, mitral valve disease, vascular disease or diabetes mellitus

**Table III. Clinical measures to reduce the risk of bleeding in anticoagulated patients.**

In an ideal world, we would know in whom a cardiac thrombus will soon form, and put those patients on anticoagulant therapy, while we would also identify those patients who will experience an intracranial bleed and withhold anticoagulant therapy just prior to the event in exactly those patients who will suffer from it. Such an ideal world would also allow withholding anticoagulant therapy in those who will not experience a stroke, which comprise the majority of atrial fibrillation patients. We are unlikely to enter any-

**Optimal management of bleeding risk factors**

In addition to choosing the best anticoagulant, several factors that increase bleeding risk are corrigible. Hypertension markedly increases the risk for severe and intracranial bleeds, and more so if blood pressure is not well controlled. Hence, all patients receiving anticoagulant therapy should also receive adequate blood pressure control therapy, and well-controlled blood pressure is an important contributor to maintain safe anticoagulant therapy. Furthermore, the use of substances that inhibit platelet function such as aspirin, but also other non-steroidal anti-inflammatory drugs should be limited to the minimal required amount. This also applies to the use of over-the-counter analgesic substances, although there are no controlled data that would link their use to bleeding, mainly due to the nature of their distribution.

**A GLIMPSE INTO THE LOOKING GLASS**

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**Table III. Clinical measures to reduce the risk of bleeding in anticoagulated patients.**

In an ideal world, we would know in whom a cardiac thrombus will soon form, and put those patients on anticoagulant therapy, while we would also identify those patients who will experience a stroke, which comprise the majority of atrial fibrillation patients. We are unlikely to enter any-

**Established measures**

- Control blood pressure adequately
- Minimize the use of antiplatelet drugs including over-the-counter nonsteroidal anti-inflammatory drugs
- Eliminate local sources of bleeding, eg, gastric or duodenal ulcers
- Reduce alcohol abuse, support abstinence in alcoholics
- Avoid comedication that increases the dose of anticoagulants, eg, via interference with hepatic elimination and metabolism

**Less validated measures**

- Avoid medications with a platelet-inhibiting function
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tors for bleeding is an important part of a well-delivered anticoagulation management. In the future, genetic testing, brain imaging, and possibly long-term monitoring for recurrent atrial fibrillation could help to tailor the optimal anticoagulant therapy for individual patients.

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Effect of home testing of international normalized ratio control on clinical events. 

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Tremendous advances have been made in anticoagulant therapy for atrial fibrillation (AF), which will have important implications for clinical care and patient outcomes in coming years. Traditionally, warfarin has been the prevailing treatment; however, the complexity of warfarin administration, which requires frequent dosage adjustment and anticoagulation monitoring, has led to the development and testing of new anticoagulant agents, such as rivaroxaban, dabigatran, and apixaban. These new agents are at least as good as, if not superior to, warfarin in reducing stroke and non–central nervous system embolism, and their safety profile is consistently either as good as or better than that of warfarin. This article discusses these new agents and warfarin and puts them in context with modern and future health care needs.

Is warfarin obsolete in the era of new anticoagulants?

Kenneth W. Mahaffey, MD
Duke Clinical Research Institute - Durham - NC - USA

Selected Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>AF</td>
<td>atrial fibrillation</td>
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<tr>
<td>aPPT</td>
<td>activated partial thromboplastin time</td>
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<tr>
<td>ARISTOTLE</td>
<td>Apixaban for Reduction In Stroke and Other Thromboembolic Events in atrial fibrillation</td>
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<tr>
<td>AVERROES</td>
<td>Apixaban Versus acetylsalicylic acid (ASA) to Reduce the Rate of Embolic Stroke</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>INR</td>
<td>international normalized ratio</td>
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<tr>
<td>RE-LY</td>
<td>Randomized Evaluation of Long-term anticoagulation therapy</td>
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<tr>
<td>ROCKET AF</td>
<td>Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for the prevention of stroke and Embolism Trial in Atrial Fibrillation</td>
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<tr>
<td>TTR</td>
<td>time in therapeutic range</td>
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issues. A safe, effective therapy with simple dosing and limited drug and food interactions that is cost effective would be an attractive alternative to warfarin in the management of patients with AF.

**NEW ADVANCES**

In the last several years, five pivotal trials comparing warfarin with three new oral anticoagulants in patients with AF have been completed (Table I). These five trials enrolled more than 55,000 patients in countries around the world. The data from these trials provide a strong foundation for making evidence-based clinical decisions regarding these new agents.

The AVERROES trial (Apixaban VERSus acetylsalicylic acid [ASA] to Reduce the Rate Of Embolic Stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment) was the only trial of the five that did not compare a novel anticoagulant with warfarin. Patients who were not candidates for warfarin were randomly assigned to 5 mg twice daily of apixaban or aspirin. The results showed that the apixaban group had significant reductions in stroke and non-central nervous system (CNS) embolism with bleeding patterns similar to the aspirin group.

The RE-LY (Randomized Evaluation of Long-term anticoagulation therapy) trial was an open-labeled trial of more than 18,000 patients randomly assigned to warfarin or one of two doses of dabigatran. The high dose of dabigatran was shown to be superior to warfarin in reducing stroke and non-CNS embolism, and it was shown to be noninferior for the primary safety outcome of bleeding. The low dose of dabigatran was noninferior to warfarin for the reduction of stroke and non-CNS embolism and was superior in reducing bleeding compared with warfarin.

The ROCKET AF trial (Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation) was a double-blind study of more than 14,000 patients randomized to rivaroxaban or warfarin. Rivaroxaban was shown to be noninferior to warfarin in the reduction of stroke and non-CNS embolism, with similar bleeding outcomes. A similar trial conducted in a Japanese population, J-ROCKET

Table II shows odd ratios of each novel anticoagulant compared with warfarin for key outcomes, includ-
Is warfarin obsolete in the era of new anticoagulants? - Mahaffey

Table III. Summary of ACC/AHA/ESC 2006 Guidelines and ACCF/AHA/HRS 2011 Focused Update.

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Recommended prophylaxis</th>
</tr>
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<tr>
<td>No risk factors</td>
<td>Aspirin 81-325 mg daily</td>
</tr>
<tr>
<td>One moderate risk factor</td>
<td>Aspirin 81-325 mg daily, or warfarin, alternative dabigatran (NVAF)</td>
</tr>
<tr>
<td>Any high risk factor or &gt;1 moderate risk factor</td>
<td>Warfarin, alternative dabigatran (NVAF)</td>
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Table III provides the general recommendations. Patients with no risk factors for stroke or non-CNS embolism should be treated with aspirin. Patients with one moderate risk factor should be treated with aspirin, warfarin, or alternatively, dabigatran. Patients with any high-risk factor or more than one moderate risk factor should be treated with warfarin or, alternatively, dabigatran.

Figure 1. Proportion of eligible atrial fibrillation patients receiving warfarin.

The squares represent individual studies, and the size of the square represents the weight given to each study in the meta-analysis. Error bars represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending upwards from 1 is the null value. None of these studies were randomized controlled trials. List of studies shows name of first author and year of publication.

non-CNS embolism in patients with AF, but it has not been incorporated into recent treatment guidelines. Apixaban has not yet been approved by the FDA or other regulatory agencies for the treatment of AF.

**A NEW ERA OF ANTICOAGULANT THERAPY FOR ATRIAL FIBRILLATION**

From these well-designed, well-executed clinical trials showing improved outcomes with new anticoagulants compared with warfarin, the totality of the evidence supports the need to embrace a new era of anticoagulant therapy for AF. Physicians should be looking for reasons to use these new therapies rather than reasons not to use them. In the United States, only about 50% of patients with AF with indications and eligibility for anticoagulants are being treated (Figure 1).1,13-17 The reasons have been well described and include risk of bleeding, inconvenience of anticoagulant monitoring, drug and food interactions, and other factors. Many patients with AF that are not being treated with warfarin are potential candidates for treatment with one of the new agents that do not require anticoagulation monitoring. In addition, patients already on warfarin should be considered for transition to one of the new anticoagulants. There is a common belief that patients already on warfarin with or without stable international normalized ratio (INR) values should remain on warfarin therapy, however, time in therapeutic range (TTR) with an INR of 2.0 to 3.0 is very challenging. A systematic review by Baker and colleagues showed that patients from community practices and coagulation clinics are in the therapeutic range only 50% to 55% of the time (Figure 2).1,13-17,19-21

Despite the enormous amount of data collected during these large global clinical trials, important clinical issues have been identified by physicians and patients as the new anticoagulants are incorporated into clinical practice. The common issues include the following:

- Whether patients with stable anticoagulation defined by TTR should remain on warfarin.
- Lack of a reversible agent for these new agents.
- No need to monitor and no clear strategy to assess anticoagulation status if necessary.
- Increased drug cost compared with vitamin K antagonism.
First, intuitively, patients with stable TTR would be more likely to have less benefit with a novel agent compared with warfarin. When analyses are performed across the three major trials (ROCKET AF, ARISTOLE, and RE-LY), no heterogeneity of the treatment effect with the new agents compared with warfarin is observed based on TTR using a center TTR analysis framework (Figure 3).

These data show a consistent treatment effect with rivaroxaban, dabigatran, or apixaban in the respective trials: across quartiles of center TTR, there is no statistically significant interaction for a treatment effect comparison of the new agents and warfarin despite the observation that event rates in the warfarin group are lower as the TTR improves, as would be expected.

Second, physicians and patients have expressed concern about the lack of an agent to reverse the new anticoagulants, particularly in emergency situations with major bleeding or invasive procedures or surgery. It is important to remember that the major trials of the new agents in more than 50,000 patients from clinical investigative sites around the world were performed without an available antidote. Despite the lack of an antidote, the safety profile defined by major or minor bleeding with these new anticoagulants is consistently either as good as or better than warfarin. Importantly again, the reduction in intracranial hemorrhage in all trials with the new anticoagulants compared with warfarin is a major benefit.

Due to the risk of major bleeding, having a safe and effective reversal agent or reversal strategy could be beneficial. Recent work has shown that prothrombin complex concentrates can reverse the novel anticoagulants. Current recommendations for the management of patients with major or life-threatening bleeding with these agents include routine measures such as volume resuscitation, surgical intervention as needed, and administration of blood products, factor concentrates, and prothrombin complex concentrates. Most of the major manufacturers of the novel anticoagulants are exploring options for the development of antidotes, and we will likely have available options in the future. Part of the success of the new anticoagulants is probably due to the much shorter half-lives (which are on the order of 5 to 14 hours, depending on agent and renal function) compared with warfarin.

Third, although patients and physicians have complained for years about the logistical challenge and inconvenience of anticoagulation monitoring with warfarin, it has now become common to express concern about not needing monitoring and not having a validated mechanism for monitoring. The clinician’s desire to monitor anticoagulants is common and has impacted the acceptance of low-molecular-weight anticoagulants.
heparin and glycoprotein IIb/IIIa inhibitors into clinical practice. The outcomes in all of the large AF trials were achieved without routine monitoring of the anticoagulant effect of the new agent. In clinical practice, the status of a patient on a new agent may need to be assessed, not monitored, during an acute bleeding episode, following blood product replacement with a goal of reversal, or before surgery or invasive procedures. The factor Xa inhibitors apixaban and rivaroxaban affect the prothrombin time (PT), factor Xa activity, and chromogenic factor Xa level to varying degrees—each can be measured using readily available or easily modifiable laboratory procedures. Neither drug has a meaningful effect on the activated partial thromboplastin time (aPTT). 26-28 The PT is relatively insensitive to dabigatran’s anticoagulant effect, the aPTT is moderately sensitive with a curvilinear response, and the thrombin time is highly sensitive to even low plasma concentrations. The ecarin clotting time may be useful because of its documented linear relationship with dabigatran plasma concentrations, but it is not widely available in hospital laboratories. 29 Although laboratory measures may provide information about the presence of an anticoagulant effect, correlations between ex vivo anticoagulation related to oral factor Xa and thrombin antagonists, and clinical outcomes require further evaluation.

Finally, a major concern is the cost of these agents. The actual drug prices for the new agents are more than for warfarin, but it has been well described that other costs are associated with warfarin administration in clinical practice. Cost-effectiveness analyses have not been published by the trial leaders of ROCK ET AF, RE-LY, or ARISTOTLE; however, a series of cost-effectiveness analyses have been performed using the published literature. 30-32 These analyses have used a variety of statistical methodologies and costs for dabigatran. The results show that fixed doses of dabigatran were cost effective using usual benchmarks and pricing estimates. Formal patient-level cost-effectiveness analyses need to be performed and published so that we can fully understand the health care expenditures that are associated with the use of the new agents compared with warfarin.

PATIENTS WITH AF WHO SHOULD STILL BE CONSIDERED FOR WARFARIN

Several important patient populations will continue to require warfarin anticoagulation for AF. Patients who were not eligible to be enrolled in the novel anticoagulant clinical trials, including those with renal disease (defined by a creatinine clearance of <30 mL/min), mechanic valve prosthesis, and valvular AF, should not be treated with one of the new anticoagulants since there are no data about safety or outcomes. Also, patients: (i) who have suffered adverse events while taking dabigatran or rivaroxaban, (ii) who still require anticoagulant therapy, and (iii) for whom the event is thought to be related to either agent should be transitioned to warfarin. Finally, patients who simply cannot afford the new agents should be treated with warfarin.

SUMMARY

Tremendous advances in the management of AF with anticoagulant therapy have been realized based on the results of major clinical trials comparing new agents with warfarin. These studies have shown us that the new agents are at least as good as, if not superior to, warfarin in reducing stroke and non-CNS embolism. All of the novel anticoagulants are superior to warfarin in reducing the incidence of intracranial hemorrhage, and there is similar or less bleeding with these agents. The large patient populations of these trials have provided a thorough evaluation of these agents across broad cohorts and clinical practice settings and provide confidence in their safety and efficacy.

We need to embrace the new era of anticoagulant therapy. Patients with AF at risk for stroke and non-CNS embolism and candidates for anticoagulant therapy should be considered for treatment with one of the new oral anticoagulants or transitioned from warfarin to one of these new anticoagulants. In the new era, it should be a goal to increase the proportion of candidate patients being treated with anticoagulation, and to transition those patients being treated with warfarin, an obsolete agent, to one of the new agents so that they can enjoy the benefits of better clinical outcomes.

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Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. 
On the occasion of Peter Harris’s retirement in 1988, Philip Poole-Wilson voiced the feelings of many when he said: “Some may wonder how it was that Peter had time to be the violinist, the painter, the traveller, and the humorist.”

For Peter, it was an elemental truth that the practice and appreciation of art and science have a common identity. In his reckoning, the source of all art and all true science lies in the need to know that what is impenetrable and incomprehensible exists in actuality, and will, with conscious questioning and probing, come to knowledge, with the most radiant beauty. He considered the act of living an exploration of the mystery and marvel of the structure and function of all there is; the harmony of intuition and imagination providing the impetus to enter with unbound, irreverent curiosity, observation, and contemplation into the realm of art and science: complements and continuums of the same reality. An influential international statesman in cardiology, Peter was at the forefront of the revolution in biomedical research that started more than half a century ago and paved the way for radical new treatments that are now taken for granted in most branches of medicine.

Corte del Papa, entrance from the Rio della Pietà. Watercolor from The Bricks of Venice. Original: 10x15 cm.

Starting with one room and a skeletal staff of a single technician and a secretary, over the years Peter’s laboratory in London became a focal center for the study of the underlying physiology and biochemistry of heart disease. The number of clinical cardiologists and scientists in vantage positions all around the world and in whose work and lives he still remained involved, bear witness to his research acumen and teaching abilities.

Peter used art to make clear his science. With dexterity he applied paint and brush to demonstrate his sense of beauty and exultation in research and discovery. His scientific papers were elucidated with drawings and paintings. The program booklet of the World Congress of the International Society for Heart Research held in London in 1983, of which he was the President and organizing secretary, exquisitely illustrated with his water colors was truly unique, it remains to date one of its kind.
Peter sought to bring a sense of refinement to everything within his reason and action. In fact, love for painting, music, literature, cooking, gardening, and all things creative had been bequeathed to him as part of his heritage.

His father was as well a gifted artist. In deference to his mother, to the very end he tended with warmth and dedication the roses he had transplanted at her death from her home to his garden in Islington, London, as too he cooked considered, delectable meals, in accordance to her recipes, for the pleasure of his friends.

THE POET

Poetry is but painting with a gift of speech; it was therefore only in character that the artist in Peter would not only have the facility of erudite prose, but also the sensibility of expression in poetry. An award-winning poem he wrote, that was published in 1984, is reproduced, see box. His delight in the play of words remained with him through life. In the last year before death claimed him, every night before retiring to bed, even when worn and weary by ill health, Peter summoned energy and inspiration to write a limerick or two for his granddaughter.

THE MUSICIAN

Peter strongly adhered to the dictum that without music life was a mistake. For him music gave charm and

Brother Francis

We remember your buttercups, elaborate as innocence, your words falling straight as apples.
It was morning Some simple leaves took their wayward course. Foxes yawned. Birds cocked their heads, beaded, knowing.

The eye of man is subtle as moving water. He sleeps now, his hand in the crutch of time. Candles flicker. Dogs bark your quiet ghost through the long night.
gaiety to everything, it washed away the trite of the mundane, and then in keeping with all else that defined him, it was the mosaic of the airwaves, the echo of the invisible world. Violin was his instrument of choice. Though, during his active working life, he had practiced and played when possible, on retirement, with more flexibility of time, he honed his skills and spent many evenings playing in company of Mr. Alessandro Molin, a violinist at the Fenice orchestra.

Along with having found humor to be the common language of the Universe, Peter was of the conviction that humor is what kept the wit sharpened and the intellect vibrant. It was also an asset he respected, an asset that he consciously nurtured and utilized to great effect. In addition to the joy it afforded those in his association, it fostered his deeply ingrained humility, never allowing him to take himself too seriously.

THE TRAVELLER

An intense enthusiasm for learning and adventure made Peter an inveterate traveller. For him the destination was never a foreign land, but the excitement of another way of seeing things. This together with his interest in pulmonary circulation led him to the Andes, Ladakh, and Tibet to research on animals and humans at high altitude. His study of the blood flow to the lungs of the yaks showed that they had adapted genetically to high altitude by eliminating the vasoconstrictor response to hypoxia. An examination of cross breeds with cows, the dzo and stol, revealed that this characteristic was transmitted as an autosomal trait. During the course of his travels, while the rational mind in him called for analysis of the information garnered,
the irresistible urge of the creative artist was to replicate all detail, intricacies and observation with drawing and color. Those who were so fortunate to be his travelling companions were in awe, as they were most grateful, upon receiving a superb painting of shared experience and scene.

VENICE

After his retirement, Peter moved to Venice to edit the journal Cardio-science. Venice offered him the opportunity to study in depth the architecture of the city and to further his appreciation of art and nurture his immense talent to paint. He lived in Venice for seven years with his wife Francesca in an apartment overlooking the Grand Canal near the Ca’ d’Oro, among other things wandering the streets with a ladder to enable a better vantage point to photograph his objects of examination and fascination. The Bricks of Venice, years in writing and investigation, is a memorial to his great love for Venice. As he says:

“My title is no parody of Ruskin’s masterpiece The Stones of Venice, but is offered in homage.” His introduction to the book further bears testimony to that.

“Scattered among the hidden corners of Venice, in private houses, on bell towers and under the eaves of churches, is a group of brick and tile designs dating back to the eleventh to fifteenth centuries. It needs the single-mindedness of a ferret to find many of them, hidden in the gloom of a narrow calle or secret courtyard. Ruskin knew and admired them; but even that indefatigable researcher did not find them all, and the breathtaking vision of The Stones of Venice is, naturally for the most part focused on Gothic stonework. It is surprising that here, in the most researched city in the world, such a treasury of medieval architecture could have been so ignored. The present book is the first to draw attention to the diversity and charm of this neglected side of Venice.

Publication may be timely. Apart from their intrinsic artistic and architectural interest, these unconsidered fragments are at danger from neglect, insensitive repair, even vandalism. Windows in the Campiello S Rocco that Ruskin described as ‘amongst the most ancient efforts of Gothic art in Venice’ have completely disappeared. Aware-
ness of their value may help draw the attention of the charitable organizations such as Venice in Peril to the possibility of preserving a unique heritage at a relatively low cost.

I have tried to keep my writing hand free from the cobwebs and dry brick dust that the title might lead one to expect, enlivening the text with many vignettes of personalities and life in medieval Venice. In addition, these little brick relics are part of the changing face of a living city that expresses its underlying economic and religious forces. To this end, many chapters are centered around mini-essays: brick making, the bricklayers, pavements, bell towers, but also the social hierarchy, a fashion in women’s footwear, the mendicant friars, defense architecture, air pollution.

Illustrations and text bear equal responsibilities, the two having been conceived together and fused from the beginning, text drawing the eye to relevant details and providing a background. The illustrations are designed both for accuracy and for aesthetic presentation. I have used a limited palette of earth colors to give cohesion and reinforce the sense of a work designed as a whole. Those watercolors also bring out the character of brick better than photos can.”

In addition to this book, *The Bricks of Venice*, in an endeavor to bring attention to the rich variety of angelic images, to describe their development, and to give a background to the religious beliefs of which they were an expression, Peter was in the process of completing a book on Angels before he died. He so believed that Venice was the ultimate city of angels: “not just those limited to churches, but the many that form an integral part of its streetsceny—witness to a life that is now largely lost on us.” Lamentably, Peter Harris was Vice-President of the European Society of Cardiology (1972-1976) and secretary in a critical period of its development (1976-1980). He was also President of the International Society for Heart Research (1981-1983). In 1986, the Society created the prestigious Peter Harris Award for Achievement in Research. After his retirement in 1988, he lived in Venice, London, and Longboat Key (Florida). “Prof.” as he was fondly known, succumbed to cancer in 2002.
Atrial Fibrillation: Current Management

Summaries of Ten Seminal Papers

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3. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAf Study
   C. Pappone and others. J Am Coll Cardiol. 2006

4. Major hemorrhage and tolerability of warfarin in the first year of therapy...
   E. M. Hylek and others. Circulation. 2007

5. Dabigatran versus warfarin in patients with atrial fibrillation

6. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation...
   G. Y. Lip and others. Chest. 2010

7. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED... score

8. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation

9. Apixaban versus warfarin in patients with atrial fibrillation

10. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study

Selection of seminal papers by
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Summaries of Ten Seminal Papers - Dweck

Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation


This seminal paper incorporated an elegant study design to reveal some key insights as to how therapeutic warfarin therapy might modify not only the incidence of stroke, but also the severity of these events. However, before tackling the intricacies of this interesting study it is useful to first consider some of the background issues against which it was first published. Back in 2003 (admittedly not so very long ago, but a lot has changed in that time), it was already well established that if you had atrial fibrillation (AF), not only were you more likely to suffer from a stroke, but the severity of that stroke was likely to be much worse. This did not offer patients with AF much cause for optimism. Warfarin had been shown to reduce the incidence of stroke, but little or no information was available as to whether it might impact on the severity of the stroke. Indeed, there were concerns that warfarin might even make the situation worse due to hemorrhagic transformation. Furthermore, it was increasingly being suggested that in certain patient subgroups a slightly less aggressive form of anticoagulation may be appropriate. Indeed, the American College of Cardiology and the American Heart Association had only just issued guidance suggesting that a lower target international normalized ratio (INR) (1.5 to 2.0) may be suitable in patients with AF over the age of 75. The study by Hylek and colleagues set out to investigate some of these important issues.

The authors conducted a large retrospective, observational study of 13,559 patients with nonvalvular atrial fibrillation. Patients (n= 592) who sustained an embolic stroke were identified and the severity of their stroke was graded (using the Rankin scale) and data were collected as to their 30-day mortality. Subsequently, the study investigated whether patients being on warfarin vs aspirin or no therapy impacted on the severity of the stroke and also whether the admission INR was of importance.

Patients on aspirin or no blood thinning medication sustained more severe strokes than those on therapeutic warfarin (INR 2.0 to 3.0) and had an increased mortality. Similarly, this was also true when comparing subjects with a subtherapeutic INR. Indeed, nearly two thirds of patients who had an embolic event while on warfarin had a subtherapeutic INR. Interestingly, there was no difference in stroke severity or mortality comparing patients with an INR <1.5 with those with values between 1.5 and 1.9. Finally, the authors also examined the effect of INR control on the incidence of intracerebral hemorrhage and discovered that the risk of such a bleed did not appear to be increased until the INR was over 4.0.

This paper therefore showed that warfarin therapy reduces not only the incidence of stroke related to atrial fibrillation, but also the severity of that stroke. Furthermore, it provided a strong rationale for a target INR of greater than 2.0 in preference to lower thresholds, with some reassurance that the risk of intracerebral hemorrhage was not associated with marginal elevations in the INR above 3.0.

Swedish voters reject adoption of the Euro; Edward Teller, father of the hydrogen bomb, dies at the age of 95; and Europe launches its first mission to the moon, the SMART-1 probe to provide a detailed study of the lunar surface
Patients and doctors alike are all too familiar with the problems associated with warfarin therapy. It is difficult to administer, interacts with a vast array of medications and food products, and has unpredictable pharmacokinetics. The result is that patients have to undergo regular blood testing: annoying for both them and their health care providers! Nevertheless, for many years warfarin has been the mainstay of stroke prediction across the world in patients with atrial fibrillation (AF). This Cochrane review provides the rationale and justification for this treatment approach and why for many years we have forgiven warfarin its many faults. Specifically, why it is often used in preference to aspirin, which itself has been shown to reduce the rate of stroke in atrial fibrillation by about a fifth.

The authors examined the results of 8 previously conducted randomized studies comparing the efficacy of warfarin versus antiplatelet therapy in patients with nonvalvular AF and no history of prior cerebrovascular accident. The period of follow-up was 1.9 years per patient and the primary outcome measure was all-cause stroke alongside a raft of secondary outcomes detailed below. Two previous meta-analyses had proved inconclusive and the results of the individual trials were not consistent.

The review indicated that warfarin reduced all-cause stroke (odds ratio [OR], 0.68; 95% confidence interval [CI], 0.54 to 0.85), ischemic strokes (OR, 0.53; 95% CI, 0.41 to 0.68) and systemic emboli (OR, 0.48; 95% CI, 0.25 to 0.90) by at least a third. While there was a trend to an improvement in myocardial infarction (OR, 0.69; 95% CI, 0.47 to 1.01) and disabling or fatal strokes (OR, 0.71; 95% CI, 0.59 to 1.04), there was no benefit with respect to vascular death (OR, 0.93; 95% CI, 0.75 to 1.15) or all-cause mortality (OR, 0.99; 95% CI, 0.83 to 1.18). As might be expected, the rate of intracranial hemorrhage was almost double in the warfarin group compared to aspirin (OR, 1.98; 95% CI, 1.20 to 3.28). However, somewhat unexpectedly, the rates of non-central nervous system bleeding were actually higher in the antiplatelet arm (OR, 1.90; 95% CI, 1.07 to 3.39). This is likely to have been driven by the largest study included in the meta-analysis that compared warfarin to dual antiplatelet therapy, a combination well known to have bloodthirsty tendencies! More recent trials have indicated that bleeding rates between aspirin and warfarin are in fact largely equivalent and that aspirin should not be recommended over warfarin on the basis of bleeding risk alone.

The rationale for warfarin therapy in patients with atrial fibrillation is therefore primarily related to its reduction of overall stroke rates by one third. While intracerebral hemorrhage rates are doubled, this is more than compensated for by a halving of ischemic events, which occur with greater frequency. Without doubt such a significant reduction in stroke should be considered as a major benefit to warfarin therapy, however it should be noted that these figures only translate in to an absolute reduction in stroke of about 1% per year over aspirin, and that patients treated with warfarin did not in fact live any longer.

The Russian city of Sochi is selected as the host city for the 2014 Winter Olympics, A new species of cephalopod, dubbed the “octosquid” is discovered off the coast of Hawai at a depth of 910 meters; and the Great Wall of China, Petra in Jordan, the Christ the Redeemer statue in Brazil, Machu Picchu in Peru, Mexico’s Chichen Itza Mayan site, the Colosseum in Rome, and the Taj Mahal in India, are the “New Seven Wonders of the World”
A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study


*J Am Coll Cardiol.* 2006;48:2340-2347

Is it possible to treat atrial fibrillation by effectively burning away the electrical pathways that underlie its etiology? At first glance this might seem like rather an aggressive approach to the treatment of atrial fibrillation. Nevertheless, this intrepid group of Italian investigators sought an answer to this very question.

Accumulating evidence had suggested that atrial fibrillation often arises within tissue in the pulmonary veins close to their insertion into the left atrium. Therefore, techniques had been developed in order to electrically separate this tissue from the body of the left atrium. Radiofrequency catheters are introduced into the left atrium and using the heat generated by a high-frequency alternating current in the catheter tip, a series of burns can be administered around the circumference of the pulmonary vein ostia. Initial reports had suggested that this might well prove an effective strategy, and these authors sought to compare it with medical therapy in the setting of a randomized control trial.

One hundred and ninety-eight patients with long-standing paroxysmal atrial fibrillation were enrolled and randomized in a non-blinded fashion to circumferential pulmonary vein ablation or antiarrhythmic medication (sotalol, flecainide, amiodarone, or a combination). Patients were followed up for 1 year and were provided with an event monitor. This yielded a rigorous assessment of their heart rhythm, indeed, patients were instructed to record their electrocardiogram three times a day and whenever they experienced any symptoms consistent with arrhythmia. The primary endpoint was freedom from a documented recurrent atrial tachycardia during the 12-month follow-up period.

The results were impressive. A dramatic decrease in recurrent arrhythmic events was observed, with 86% of the pulmonary vein ablation group free from events at 1 year compared with just 22% treated with antiarrhythmic medication. Furthermore, this translated into a 7-fold reduction in the subsequent number of hospital visits in the ablation group (24 versus 167 in the medical therapy group).

This study really highlighted two key findings. Firstly, that the medical therapy of paroxysmal atrial fibrillation is ineffective in maintaining sinus rhythm in most patients and that, given the adverse side effect profile of these drugs, alternative treatment strategies are required. Secondly, that contrast catheter pulmonary vein isolation holds promise as just such an alternative, proving highly successful in maintaining sinus rhythm at 1 year and doing so with very little in the way of complications.

While this encouraged many an electrophysiologist to reach for their ablation catheter, some key questions remained. Follow-up was short and it is unclear whether sinus rhythm can be maintained in the long-term or whether such procedures are merely a delaying tactic. Furthermore, the patients studied were generally young with few comorbidities, and further work is required to assess whether this form of treatment might also prove useful in the more elderly cohorts commonly seen in clinical practice. Finally, this study did not answer perhaps the key question, which is whether the apparent reduction in arrhythmic events observed with catheter ablation will ultimately translate into fewer cerebrovascular events and improved clinical outcomes. Nevertheless, on the basis of this and other studies, catheter ablation has become established as a useful treatment option for patients with atrial fibrillation, particularly in symptomatic patients when antiarrhythmic medication has failed.

500 people are reported drowned after a ferry travelling between the port of Kumai in Borneo and Semarang in Java sinks during a storm; Augusto Pinochet, Chilean president (1973-1990), dies aged 91 of a heart attack; and the European Union announces the introduction of a common EU-wide driving license in 2013
Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation


Circulation. 2007;115:2689-2696

Atrial fibrillation is a disease that increases in prevalence with age. Indeed, it can be observed in 10% of the population over the age of 80. However, the majority of clinical studies examining the efficacy of warfarin have been conducted in patients that are considerably younger. These seemed to suggest that warfarin was relatively well tolerated, with low rates of major hemorrhage. However, these findings did not align well with observational data illustrating that warfarin is relatively underprescribed in the general population, nor did it ring true with many clinicians dealing day in and day out with patients on this drug.

This key study therefore attempted to examine the real world experience of warfarin use among more elderly individuals (all were aged over 65). Unlike previous studies, it recruited patients at the time when warfarin therapy was instigated, so as to more accurately reflect warfarin tolerability and discontinuation rates. Follow-up was for 12 months, international normalized ratio (INR) levels were documented during this period, and the major clinical outcomes were major hemorrhage, time to discontinuation of warfarin, and physician reason for discontinuation.

In total, 472 subjects were recruited, over half were over 75, and one third were over 80. INR levels fluctuated considerably. Indeed overall, patients spent only 58% of their time on warfarin in the therapeutic range (INR 2.0-3.0) and were subtherapeutic in almost one third of the cases. As expected, the rates of bleeding were higher than previously reported, with 26 major hemorrhages documented, 9 of which were intracranial. Independent risk factors for a major bleed were age over 80, INR over 4.0 (despite patients only having spent 2% of their time with an INR in that range), and the first 90 days of therapy, indicating that if an adverse event is going to happen it tends to occur early.

As suspected, discontinuation rates were high, with over 25% having stopped the drug by the end of the year. In those under 80, this was due predominantly to reversion to sinus rhythm. However, in the over-80s, the story was different, with the high discontinuation rates related to concerns regarding patient safety in over four fifths of the cases. The majority of these concerns were related to episodes of bleeding, falls, medication noncompliance, and poorly controlled INR readings.

In summary, this study confirmed what many practicing doctors had observed in their clinical practice: that in real life warfarin is often difficult to administer and unpredictable. Patients spend much of their time with a subtherapeutic INR and therefore prone to the risk of stroke. Furthermore, the risk of major bleeding is relatively high, particularly in the elderly, leaving us with a difficult choice to make regarding warfarin in this group. While this study demonstrated that complication rates were higher, the elderly are also the patient group at highest risk of stroke and therefore have the most to gain from anticoagulation. The challenge was on to better define the risks and benefits of anticoagulation in an individual patient so that more appropriate recommendations as to the need for warfarin could be made.
Despite the clear disadvantages associated with warfarin, it has remained for many years the treatment of choice in atrial fibrillation (AF), largely because of a lack of clear alternatives. As such, the development of novel oral anticoagulants has been keenly awaited. Many potential alternatives have been developed all aimed at targeting a single step in the coagulation cascade so that a predictable anticoagulant response could be delivered. However, the first agent to be studied against warfarin in atrial fibrillation was dabigatran in the Randomized Evaluation of Long-term anticoagulant therapy (RE-LY) study. It was presented with much fanfare in 2009, as it became clear that this reversible thrombin inhibitor had indeed emerged as a viable alternative anticoagulant to warfarin.

The study design was such that dabigatran was investigated at two doses (110 mg bid and 150 mg bid) in a prospective, randomized, open-label trial against warfarin with a target international normalized ratio (INR) of 2.0-3.0. Over 18,000 patients with nonvalvular atrial fibrillation and at least 1 other stroke risk factor were studied over the course of 2 years. The higher dose was associated with a significant reduction in the primary end point of stroke or systemic embolism (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.52 to 0.81), with no difference in major bleeding rates compared with warfarin (dabigatran 3.32% vs warfarin 3.57%, P=0.31). In addition, there was a lower risk of intracranial hemorrhage (P<0.001), which despite the problems in reversing dabigatran, was no more likely to be fatal. There was also an observed trend to a reduction in total mortality (3.64% vs 4.13%, P=0.051). The lower dose was noninferior to warfarin in terms of stroke and systemic embolism (HR, 0.90; CI, 0.74 to 1.10), and resulted in a significant reduction in major bleeding rates (dabigatran 2.87% vs warfarin 3.57%, P=0.003).

Clearly, the results of this study were excellent and the excitement surrounding this new drug was largely merited. The higher dose would appear to offer improved stroke prevention (presumably because patients spend more time with a therapeutic INR), with no price to pay in terms of bleeding risk. This would therefore seem to be the more attractive option for the vast majority of patients. By contrast, the lower dose would appear more suitable for those at increased bleeding risk in whom stroke prevention was as good as warfarin, but bleeding was reduced. Either way you look at it warfarin seemed to come second best. However, there were a few notes of caution. Dabigatran was not particularly well tolerated in the study, and its discontinuation rates were actually higher than for warfarin. This was certainly unexpected and seems to have been the result largely of dyspepsia and other gastrointestinal symptoms. Furthermore, there was an observed trend to an increased myocardial infarction rate, which, while a preliminary finding, will need to be assessed in greater detail as part of future studies and registries.

Dabigatran has, however, been widely adopted in national and international guidelines around the world and looks set to play an increasing role in the future treatment of patients with atrial fibrillation. Its predictable therapeutic response ensures that patients will receive consistent and effective anticoagulation, obviating the need for routine monitoring. This is likely to offset at least in part the increased costs associated with prescribing this drug compared with warfarin, which of course in itself is cheap as chips.

Libyan leader Muammar al-Gaddafi celebrates the 40th anniversary of the coup d’état which brought him to power; scientists in Papua New Guinea announce the discovery of over forty new species, including a giant rat weighing approximately 1.5 kg; and Pulitzer Prize American author John Updike dies, aged 77.
Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation

G. Y. Lip, R. Nieuwlaat, R. Pisters, D. A. Lane, H. J. Crijns

_Chest_. 2010;137:263-272

Given the difficulties in weighing up the potential benefits and risks associated with warfarin therapy, doctors around the world looked to scoring systems for help. Many risk factors for stroke have been identified over the years and these have been incorporated into various scoring systems. However, the latest incarnation and the one currently recommended by many of the guidelines was introduced in this seminal paper.

The CHA2DS2-VASc score is simpler than it sounds particularly as it is based upon the widely accepted and commonly used CHADS2 score. Each letter of the acronym stands for a risk factor (sometimes in a somewhat contrived manner!) and a point is awarded for each one apart from age >75 and previous stroke which are deemed of particular importance and given 2 points (C = congestive cardiac failure, H = hypertension, A = age >75, D = diabetes mellitus, S = previous stroke/transient ischemic attack (TIA), V = vascular disease [prior myocardial infarction, aortic plaque, peripheral arterial disease], A = age (again!) 65-75, Sc = Sex category [ie, females]). A score of 0 is considered low risk (aspirin recommended), those with a score of 1 intermediate-risk (aspirin or warfarin recommended), and subjects with a score of ≥2 high-risk (warfarin recommended).

In this paper, the investigators from Birmingham compared their new scoring system with some of the conventional systems including Framingham risk scores and CHADS2. The study population was derived from the Euro Heart Survey on AF, which included 1084 patients with nonvalvular atrial fibrillation who were not on warfarin, taken from 184 hospitals across 35 countries. Patients were followed up for 1 year and the incidence of peripheral embolism (cerebro-vascular accident, TIA, peripheral embolism, pulmonary embolism) was examined. A major weakness of this study was that complete follow-up data were not available in one third of the patients enrolled.

Somewhat disappointingly, none of the risk scoring algorithms performed particularly well. The Framingham risk and the CHA2DS2-VASc scores did best with C-statistics of 0.638 and 0.606, respectively, which while only marginally better than tossing a coin, might have been improved had the follow-up period been longer! The C statistic for the CHADS2 score was 0.586 and interestingly classified >60% of patients as intermediate risk. In this group either aspirin or warfarin is recommended at the doctor’s discretion, so in practice this scoring system does not actually move the decision process forward in the majority of patients. The CHA2DS2-VASc score was designed in part to refine risk stratification in this intermediate group by incorporating several additional risk factors that they hoped would prove discretionary. Indeed, this approach appeared to be effective with far fewer classified in this grey intermediate area (only 15%), the majority of whom were shifted into the high-risk group. This represents a clear advantage of the CHA2DS2-VASc score and fits with the current trend of prescribing warfarin to the majority of patients. The second advantage of the CHA2DS2-VASc scores was that while fewer patients were deemed low-risk (9.2% vs 20% with the CHADS2 score) they appeared to be exactly that, experiencing no thromboembolic events during follow-up.

In summary, while imperfect as a risk prediction tool, the CHA2DS2-VASc offers advantages over other risk assessment tool (including CHADS2) that probably outweigh the slightly more complex method of scoring (counting up to 10 rather than 9). In particular with the advent of safer anticoagulant options the ability to identify truly low-risk patients who do not require blood thinning is likely to be of increasing importance.
Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score

G. Y. Lip, L. Frison, J. L. Halperin, D. A. Lane

*J Am Coll Cardiol.* 2011;57:173-180

With scoring systems established to help in the assessment of stroke risk there was now a need for similar strategies to help stratify a patient’s risk of bleeding. Just a year following their paper describing the CHA2DS2-VASc score (for meaning of letters see preceding summary), Lip and colleagues again came up with the goods. They published the following study, which sought both to examine the risk factors associated with bleeding among patients on warfarin and to compare several different risk scores for the prediction of such events. This included their own novel scoring system the HAS-BLED score, which they had recently proposed. Similar to CHA2DS2-VASc, each letter of the acronym stands for a specific risk factor and a point is awarded with the presence of each one (H = Hypertension; A = abnormal renal/liver function; S = stroke; B = bleeding history or predisposition; L = labile international normalized ratio, INR [>60% without the therapeutic range]; E = Elderly [age > 75]; D = drugs [antiplatelet or nonsteroidal]/alcohol excess). A score of 0 indicates patients at low-risk, 1 identifies those at intermediate-risk, and subjects with a score of 2 or more are considered high-risk. In contrast to previous systems, it was designed to be simple to use and specific to the risk of bleeding associated with anticoagulation prescribed for atrial fibrillation (AF).

The patients studied were derived from the SPORTIF (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation) III and V clinical trials that sought to establish the noninferiority of warfarin versus ximelagatran (a novel anticoagulant) in patients with nonvalvular AF. These studies showed that ximelagatran was noninferior to warfarin in reducing the risk of thromboembolism. However, ultimately, the drug was withdrawn due to concerns regarding liver toxicity.

A total of 7329 patients were studied (21% were new to anticoagulation), providing more than 11,000 patient-years of anticoagulant exposure. Major bleeding events occurred in 217 patients. On multivariate analysis, the independent predictors of a major bleed were concurrent aspirin use, renal impairment, age>75, diabetes, and LV dysfunction. The HAS-BLED risk score emerged as the best predictor of events, although once more it was not particularly powerful (C statistic of 0.659 among those on warfarin therapy, 0.654 across the entire cohort). A fifth of the cohort was classified as low-risk by HAS-BLED scoring and these patients had a very low bleeding event rate of <1% per year. The risk of actual bleeding events steadily increased on moving from low- to intermediate- and from intermediate- to high-risk scores.

Therefore, similar to the CHA2DS2-VASc score, the HAS-BLED provides a quick and easy to use assessment of bleeding risk that outperforms other more complex scoring systems. It is therefore a useful tool in determining the suitability of anticoagulation in a given patient, although it should be remembered that its predictive accuracy is not strong. The results of this study also suggest that other factors such as left ventricular dysfunction and diabetes should be considered when considering a patient’s bleeding risk, although their inclusion would suddenly make the components of the CHA2DS2-VASc and HAS-BLED scores remarkably similar!
Two years after the RE-LY trial (Randomized Evaluation of Long-term anticoagulation therapy), two further anticoagulants, rivaroxaban and apixaban, emerged as potential pretenders to warfarin’s throne. Both drugs act as oral and reversible factor X inhibitors, but have different pharmacokinetics, leading to different dosing regimens. Rivaroxaban reaches its peak plasma concentration 2 to 4 hours after oral administration, has a half-life of 5 to 13 hours, and is given as a once-daily preparation. It was studied as part of the ROCKET AF (Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for the prevention of stroke and Embolism Trial in Atrial Fibrillation) study: a double-blind randomized trial, which compared rivaroxaban (20 mg od) against warfarin in 14264 patients with nonvalvular atrial fibrillation (AF). This involved a different patient population to the RE-LY and ARISTOTLE (Apixaban for Reduction InSTroke and Other Thromboembolic Events in atrial fibrillation) trials in that it sought to recruit patients at increased thromboembolic risk. Indeed the average CHADS2 (Congestive heart failure/LV dysfunction, Hypertension, Age ≥75 y, Diabetes mellitus, Stroke/TIA/thromboembolism) score of participants in the study was 3.5, compared with 2.1 in both of the aforementioned trials.

Rivaroxaban was shown to be noninferior to warfarin in terms of the primary end point of stroke and systemic embolism (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.74 to 1.03) with no difference in the rate of major bleeding. Interestingly, while intracranial hemorrhage (0.5% per year vs 0.7% per year; P=0.02) and the rate of fatal bleeding (0.2% per year vs. 0.5% per year, P=0.003) were reduced with rivaroxaban, gastrointestinal bleeding and the need for transfusion were increased. The above intention to treat (ITT) analysis included all periods when patients were off study drug (for example, for procedures or at end of study, which accounted for ≈20% of the ITT duration). When an on-treatment analysis of the data was performed, this in fact indicated superiority of rivaroxaban over warfarin while on blinded treatment.

According to the primary end point, rivaroxaban can be considered to be noninferior to warfarin both in terms of stroke prevention and bleeding risks. However, unlike dabigatran a clear benefit was not observed over and above warfarin in terms of bleeding risk or stroke prevention, making it perhaps a less attractive agent. However, on the positive side, rivaroxaban may be easier to reverse than dabigatran via the administration of prothrombin complex concentrate, and the once-daily dosing regimen does hold considerable advantages over the twice-daily regimens of both apixaban and dabigatran, which are more likely to result in subtherapeutic anticoagulation if doses are missed. In addition, a reduced dose of rivaroxaban (15 mg once daily) was studied in ROCKET AF among patients with impaired renal function (creatinine clearance 30-59 mL/min). This demonstrated results consistent with the main study, and so there is stronger evidence for the use of this drug in patients with renal disease than there is with dabigatran, which should be used with caution. Indeed, on the basis of this trial rivaroxaban has also been approved alongside dabigatran as a novel anticoagulant in atrial fibrillation.

The African Union recognizes the National Transitional Council of Libya as the country’s legitimate leadership;
UBS chief executive Oswald Grübel resigns in the wake of a rogue trading scandal which leads to bank losses of 2.3 billion US dollars; and
Burma’s President Thein Sein suspends the controversial Myitsone Dam project following national and international criticism of its social and environment impacts.
Apixaban versus warfarin in patients with atrial fibrillation


Somewhat akin to London buses, 2011 also saw the emergence of apixaban. This was now the third novel anticoagulant to be tested head to head with warfarin in 2 years, a rush of clinical trials that certainly kept the editors of the New England Journal of Medicine on their toes. Like rivaroxaban, apixaban is also an oral reversible inhibitor of factor Xa with a rapid onset of action and a half-life of 12 hours. The recommended dose is 5 mg twice daily, although this should be reduced to 2.5 mg twice daily, in the presence of two of the following factors: age >80, creatinine >133 µmol/L, and body weight <60kg. Maximum plasma concentrations are obtained 4 hours after oral administration and it has a plasma half-life of 8 to 15 hours. Unlike dabigatran and rivaroxaban, this drug had also been the subject of a previous study AVERROES (Apixaban VERsus acetylsalicylic acid to pRevent stroKES) in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment, which had demonstrated that apixaban offered superior prevention of stroke to aspirin without an increase in bleeding risk.

This laid the foundation for ARISTOTLE (Apixaban for Reduction in STroke and Other Thromboembolic Events in atrial fibrillation) discussed here. Apixaban therapy was this time compared to warfarin in a randomized double-blind trial involving 18 201 patients with atrial fibrillation and at least 1 stroke risk factor. In many ways, the results were even better than those observed for the other novel anticoagulants. Not only did apixaban result in a 21% reduction in the primary end point of all-cause stroke or systemic embolism, but there was also a 31% risk reduction in the risk of major bleeding. Furthermore, this was the only drug in which these differences translated into a significant reduction in total mortality (3.52% vs 3.94%, \( P=0.047 \)). Thus, apixaban appears to hold considerable advantages over warfarin (and perhaps the other novel anticoagulants) on all fronts, with the added bonus that is was also well tolerated with lower discontinuation rates than those observed for warfarin.

However, it should be noted that somewhat unusually there was no significant reduction in the incidence of ischemic stroke with apixaban when this was examined in isolation (although neither was it increased compared with warfarin). Furthermore, despite these seemingly excellent results, this drug has still not yet been approved in either America or Europe. Indeed, rather intriguingly, the Food and Drug Administration recently requested more information regarding the integrity of some of the study data. The exact details of this delay are unclear, but it seems highly likely that apixaban will receive approval alongside dabigatran and rivaroxaban in the not too distant future. The challenge will then be to tease out the exact niche that each of these novel agents will have in the management of patients with atrial fibrillation. The results of AVERROES suggest that the role of aspirin may well be over, however it is possible that warfarin may still be recommended, particularly in patients who are well established on treatment and require little in the way of monitoring.

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Australian tennis player Samantha Stosur defeats Serena Williams 6-2, 6-3 to win the 2011 Women’s Singles title at the US Open;
UNICEF says child mortality below 5 years has fallen from 12 million in 1990 to 7.6 million in 2010; and the German Bundestag approves the European Financial Stability Facility to help address the European sovereign debt crisis
Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study

L. Friberg, M. Rosenqvist, G. Y. Lip

Circulation. 2012;125:2298-2307

As a result of the two studies by Lip et al detailed above (Chest. 2010;137:263-272, J Am Coll Cardiol. 2011;57:173-180, cardiologists were now armed with simple scoring systems associated with easy to remember acronyms for the assessment of both stroke and bleeding risk. While this is undoubtedly useful in clinical practice a quick screen of the components of the CHA2DS2-VASC* and HAS-BLED† scores quickly shows that half of the factors in the bleeding score also predict subsequent thromboembolic events. Indeed the CHADS2‡ score has been shown to be a useful predictor of not only thromboembolic events, but also of bleeding. The implication therefore is that patients with the highest risk of bleeding on warfarin will conversely also often have the most to gain in terms of stroke prevention. What should we therefore do in such patients?

In an attempt to address this issue and to determine the net clinical benefit of warfarin in terms of ischemic stroke and bleeding risk, Dr Lip (him again!) and colleagues in Sweden conducted the following study. 170 292 patients with atrial fibrillation were identified from the Swedish Hospital Discharge Register and studied for an average of 1.5 years. CHADS2, CHA2DS2-VASC, and HAS-BLED scores were calculated for all patients and patients were divided into different groups depending on their stroke and bleeding risks. A comparison of events among patients on and not on warfarin in these groups was then used to derive the primary end point of net benefit. This was defined as the number of avoided ischemic strokes with anticoagulation minus the number of excess intracranial bleeds with a weight of 1.5. While the weighting was somewhat arbitrary, this was designed to account for the generally increased morbidity associated with bleeds.

The first observation was that the scoring systems seemed to work: ischemic stroke rates rose with increasing CHA2DS2-VASC scores as did bleeding events with HAS-BLED. Also as expected, the overlap in components ensured that the two scores tended to mirror each other. Interestingly, when patients were categorized according to bleeding and stroke risk, in almost all groups the number of strokes exceeded the number bleeds so that there was a net clinical benefit in favor of warfarin (even accounting for the weighting). This was true even among those with the highest bleeding and stroke scores who in fact appeared to derive the greatest net benefit from warfarin, experiencing 12 fewer events per 100 years than those in whom warfarin was not given. The one exception to this rule were those patients with a CHA2DS2-VASC score of 0 (particularly those with an elevated bleeding risk) who did not appear to gain benefit from anticoagulation, presumably due to their low baseline risk of stroke. Use of the CHADS2 score yielded broadly similar results to the CHA2DS2-VASC score, except that as before it was less able to discriminate patients those low-risk subjects who did not derive a benefit from anticoagulation.

While clearly not small, this study was neither blinded nor randomized and it is likely that the characteristics of patients who were and were not prescribed warfarin will be very different. With this reservation in mind the results do indicate that anticoagulation appears to be of net benefit in almost all patient subgroups. The implication therefore is that we should be aggressive in our use of warfarin perhaps only reserving it in those with a very low risk of stroke or those with a truly unacceptable risk of bleeding.

*CHA2DS2-VASC: C = congestive cardiac failure; H = hypertension; A = age > 75; D = diabetes mellitus; S = previous stroke/transient ischemic attack (TIA); V = vascular disease (prior myocardial infarction, aortic plaque, peripheral arterial disease); A = age (again!) 65-75, Sc = Sex category (ie, females).
†HAS-BLED, H = Hypertension, A = abnormal renal/liver function, S = stroke, B = bleeding history or predisposition, L = labile international normalized ratio, INR (>60% without the therapeutic range), E = Elderly (age > 75), D = drugs (antiplatelet or nonsteroidal/ alcohol excess.
‡CHADS2, C = congestive cardiac failure, H = hypertension, A = age > 75; D = diabetes mellitus; S = previous stroke/transient ischemic attack (TIA)

2012

Adam Yauch, founding member of the Beastie Boys, dies aged 47 after a 3-year battle with salivary gland cancer; and François Hollande is elected the 24th President of France
# Atrial Fibrillation: Current Management

**Bibliography of One Hundred Key Papers**

selected by Keith A. A. Fox, PhD  
Center for Cardiovascular Science - Edinburgh - UK  
(e-mail: k.a.a.fox@ed.ac.uk)

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