Atrial fibrillation (AF) is becoming a major health care burden as elderly populations increase. The increased risk of stroke and thromboembolisms in patients with AF is well documented and anticoagulation with adjusted-dose warfarin is highly effective in reducing stroke risk, being superior to antiplatelet agents. Despite recognition of the epidemiological problem and the sound evidence base for thromboprophylaxis, as well as major guidelines recommending treatment, anticoagulation use is still suboptimal, given the dis-utility and limitations associated with warfarin.

Recent developments in thromboprophylaxis for AF include efforts for better risk stratification for predictions of thromboembolic risk. Constant efforts are underway to develop newer, less cumbersome, alternatives to warfarin with similar (or better) efficacy. This review article provides an overview of the recent progress made, the potential challenges involved and the future of these therapeutic approaches.


Key words; Atrial Fibrillation, CHADS2, CHA2DS2-VASC, Direct Thrombin Inhibitors, Factor Xa inhibitors, Newer antithrombotic agents, Oral antithrombotic therapy, Thromboembolism, Stroke, Warfarin

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence that increases with age. The risk of stroke and thromboembolisms is increased by 5-fold in people with AF.1

The risk of stroke in patients with non-valvular AF is not homogeneous and varies widely depending on age, occurrence of other risk factors such as hypertension, diabetes, congestive heart failure, and the presence of previous cerebrovascular accidents (CVA).2 Further, stroke severity is worse in patients with AF with an increased mortality and disability, perhaps related to larger infarcts and the increased size of the cardiogenic thrombus.3

In the Framingham Heart study, the attributable risk of stroke in AF patients rose from 1.5% at 50-59 years of age to 23.5% at 80-89 years.4 Ethnic and geographical differences in the clinical epidemiology of AF have been reported.5 For example, studies from China and Japan have shown a generally higher risk of stroke associated with AF. One epidemiological survey from China suggested the prevalence of AF to be 0.77%, with the incidence of ischemic stroke estimated to be high as 12.1% among patients with nonvalvular AF. A cross-sectional survey reported similar results (0.74% in males and 0.72% in females aged ≥35 years). Epidemiological studies in Japan have shown that the annual rate of ischemic stroke in case of nonvalvular AF to be 2.8 to 4.5%. More recently, the Japan Thrombosis Registry for Atrial Fibrillation, Coronary or Cerebrovascular Events (J-TRACE) reported that women with AF to be at higher risk for thromboembolisms than men.10

Evidence for antithrombotic therapy in AF

There is a considerable evidence base for antithrombotic therapy in AF patients for the prevention of stroke and thromboembolisms.11 A meta analysis by Hart et al. of 29 trials suggested that, compared with a placebo, the adjusted-dose of a Vitamin K antagonist (VKA, e.g. warfarin) reduced stroke risk by 64% (95% CI, 49% to 74%), with an absolute reduction of 2.7% (NNT to prevent 1 stroke in 1 year = 37) in primary prevention and 8.4% (NNT 12) for sec-
ondary prevention.

Aspirin caused a non-significant 19% (95% CI, -1 to 35%) reduction in the incidence of stroke with an absolute reduction of 0.8% per year (NNT-124) for primary prevention and 2.5% per year (NNT-40) for secondary prevention. Randomized data from all forms of antiplatelet therapy shows a 22% (6% to 35%) reduction in stroke risk compared with placebo. Warfarin was associated with a 39% (95% CI, 0.22 to 0.50) reduction compared with antiplatelet therapy.

**Suboptimal use of warfarin**

The use of VKAs is limited by a narrow window of therapeutic benefit, the need for regular monitoring of INRs, concerns about interactions with other drugs, increased risk of hemorrhaging including risk of major bleeding, inadequate compliance with INR monitoring and the desire to avoid VKA therapy.

Many studies have shown a suboptimal rate of anticoagulation in AF patients. In those patients with no contraindications regarding warfarin therapy, studies report huge variability in practice, with 15% to 79% of patients actually receiving warfarin therapy.

Bungard et al. categorized the factors leading to suboptimal warfarin use as: (i) patient-related, such as age, perceived risk of hemorrhaging, fear of frequent falls, non-compliance and unwillingness to undergo repeated testing; (ii) physician-related, such as perception of the risk benefit ratio for embolisms and hemorrhage, awareness and adoption of guidelines, fear of patient non-compliance, clinical uncertainty over indications and physicians’ experiences with warfarin; and (iii) health care system-related, such as inconvenience in monitoring and the availability of expertise in readily accessible areas.

Furthermore, a survey of 214 physicians showed important variations in thromboprophylaxis therapy and poor estimations of thromboembolic (and bleeding) risk.

**Optimal INR**

The optimal INR range providing effective thromboembolic protection with minimum risk of bleeding has been debated over the years. Hylek et al. studied 596 cases of ischemic stroke in a cohort of 13,559 patients with non-valvular AF, and found that an INR of <2.0 at admission independently increased the odds of severe stroke (odds ratio, 1.9; 95% CI, 1.1 to 3.4) and mortality (hazard ratio, 3.4; 95% CI, 1.1 to 10.1), when compared to an INR of 2.0 or greater. Mortality and the risk of hospitalization or death due to diseases of vessels of brain follows a U-shaped curve with lowest levels seen between INR 2.2-2.4.

**Net clinical benefit**

Singer et al., in an observational study, assessed the overall adjusted net clinical benefit with warfarin therapy as 0.68 (CI, 0.34 to 0.87) adverse events prevented per 100 patient years. The study also found that the adjusted net clinical benefit was greatest for patients with a history of ischemic stroke (2.48% per year, CI, 0.75% to 4.22%) and those aged 85 years or older (2.34% CI, 1.29% to 3.30%). These findings together with other recent studies, such as the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial, stress the importance of anticoagulation in the elderly.

**Should a lower therapeutic INR range be considered for some subgroups of AF patients?**

Various studies have reported racial background to be associated with warfarin dosage requirements, particularly among Iranians and Asians.

In a secondary prevention trial, Yamaguchi et al. studied 115 patients with NVAF who were less than 80 years old and had had a stroke or transient ischemic attack. The trial was stopped due to a significantly greater rate of major hemorrhagic complications (6.6% per year) in the conventional intensity group (INR 2.2-3.5) than low intensity anticoagulation group (INR 1.5-2.1) (0% per year), although the annual ischemic stroke rate was low in both groups (1.1% in the conventional group and 1.7% in the low intensity group). Nonetheless, the number of patients in this study was too small for a definite risk/benefit assessment. On the basis of this study, and other evidence, the Japanese AF guidelines recommend a target INR of 1.6-2.6 in patients with non-valvular AF aged ≥70 years (Fig. 1).

In another retrospective cohort study, 491 Chinese were observed for bleeding and thromboembolic events, and the INR-specific incidence of bleeding and thromboembolism was calculated. The authors showed that the distribution had a U-shaped curve with the lowest incidence of thromboembolism and bleeding between an INR of 1.8 and 2.4.

Various arguments have been put forward to explain a possible different target INR range, including polymorphisms in CYP2C9, use of herbal medicines among Chinese which have been identified to have antiplatelet/antithrombotic effects, as well as a possible increased incidence of intracranial hemorrhage reported in Japanese.
More recently, a prospective multicentred randomized study of 704 Chinese patients with NVAF comparing Warfarin (INR 2.0 to 3.0) with aspirin (150 to 160 mg /day), showed reduced primary endpoints of death and ischemic stroke in the warfarin-treated group compared to the aspirin-treated group (2.7% vs 6.0% \( p=0.03 \); a relative reduction of 56%) \(^{(38)}\). The thromboembolic was significantly higher rate in the aspirin-treated patients (10.6% vs 5.4%, \( p=0.01 \)). Warfarin was associated with an increased rate of bleeding compared to aspirin (6.9% vs 2.4%, \( p<0.05 \)), with a major bleeding rate of 1.5%. All major bleeding events occurred with an INR of >3.0. Out of the 19 thromboembolic events, 15 occurred with an INR of less than 2.0, and the independent risk factors for major bleeding during warfarin treatment were age >75, systolic blood pressure ≥160 mmHg, an elevated serum creatinine level and an INR of >3.0. The combined end point was statistically lower for the adjusted dose of warfarin (8.4% vs. 13.0%, \( p=0.047 \)). An INR

![Fig. 1. Anti thrombotic therapy in patients with atrial fibrillation](image-url)

Adapted from Japanese guidelines \((33)\). Solid arrows suggest guideline recommendation (Class I or IIa). Dotted arrows suggest options to be considered (Class IIb or III). \(^{a}\)Moderate risk factors are age≥75 years, hypertension, heart failure, left ventricular ejection fraction ≤35, diabetes mellitus. \(^{b}\)Other risk factors are age 65 to 74 years, female, coronary artery disease, thyrotoxicosis, cardiomyopathy.
of 2.0 to 3.0 was associated with the lowest combined rate of bleeding and thromboembolisms.

Another subgroup subjected to less intense anticoagulation treatment, such as an INR of 1.5-2.0, is the elderly. Pengo et al.\(^\text{39}\) compared low intensity INR (1.8, range 1.5-2.0) with standard intensity INR (2.5, 2.0-3.0) for primary prevention in AF patients aged ≥75 and studied as composite endpoints, thromboembolism and major hemorrhage. There were fewer reported events in the lower intensity group than standard intensity group (3.5 vs. 5.0 per 100 patient years respectively, HR=0.7, 95% CI 0.4 to 0.11, \(p=0.1\)). The difference was mainly due to fewer major bleeding events in the low intensity category (1.9 vs 3.0 per 100 patient years: HR 0.6, 95% CI 0.3-1.2, \(p=0.1\)). Nonetheless, the study was not powered for the efficacy outcomes (that is, reduction of stroke and thromboembolism), the patients had a CHADS\(_2\) score of 2.0 and 2.1 in the low intensity INR and standard intensity INR, and the patients had prior warfarin exposure. These factors may have influenced the outcome producing fewer ischemic events.

The BAFTA\(^\text{29}\) study and the Warfarin versus Aspirin for Stroke Prevention in Octogenarians (WASP-O)\(^\text{40}\) study demonstrated superiority of warfarin over aspirin with a similar or even higher rate of adverse events in the aspirin-treated group. In the BAFTA study\(^\text{29}\), of the 973 patients aged 75 years or over, the stroke rate was 5.0% in the aspirin group compared with 2.7% in the warfarin group, accounting for a 46% relative risk reduction (\(p=0.002\)). More importantly, major extra cranial haemorrhage rates were low in the warfarin group (1.4% per year) and not significantly different from that seen in the aspirin group (1.6% per year). The small WASPO study\(^\text{40}\) involved elderly patients aged 80 to 90 years, and showed significantly more adverse events with aspirin 300mg (33%, compared to warfarin (INR 2.0-3.0), 6%; \(p=0.002\)).

**Risk stratification for stroke**

The goal of stroke prediction models is to help clinicians and patients select the most appropriate antithrombotic therapy (ATT) for stroke prevention. Based on stroke risk factors identified in systematic reviews\(^\text{41, 42}\), numerous schemes have been devised for predicting stroke risk.

The most popular of these is the CHADS\(_2\) score which is an amalgamation of the risk factors used in Atrial Fibrillation Investigators and Stroke Prevention in Atrial Fibrillation Investigators stroke risk schema\(^\text{43}\) (Table 1). In the original validation, this schema classifies patients into low, intermediate and high risk for thromboembolism, based on a CHADS\(_2\) score of 0, 1-2 and ≥3 respectively. The CHADS\(_2\) score is simple and has been well validated, and is the basis of other stroke risk schema such as the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines\(^\text{44}\) and the ACCP8 guidelines\(^\text{45}\).

Many limitations of the CHADS\(_2\) score have also been debated\(^\text{46}\). CHADS\(_2\) has not undergone an impact analysis and may not be applicable in the era of new oral anticoagulant agents with lower risk of bleeding. In most validation studies, the CHADS\(_2\) risk stratification classifies a large percentage of patients into the intermediate risk group\(^\text{46}\). This is less useful in clinical practice as current treatment guidelines recommend either warfarin or aspirin for moderate risk.

The Japanese AF guidelines issued by the Joint Working Group of Guidelines for the Diagnosis and Treatment of Cardiovascular Diseases\(^\text{33}\) (Fig. 1) suggest anticoagulation therapy based on an evaluation of the risk of cerebral infarction and bleeding in high risk patients and patients with ≥2 moderate risk factors (class I indication). High risk factors include a history of cerebral infarction, TIA or systemic embolism, mitral stenosis, and a mechanical heart valve. Moderate risk factors are age ≥75 years, hypertension, heart failure, left ventricular dysfunction and diabetes mellitus. The guidelines also recommend a target INR of 1.6 to 2.6 for people ≥70 years of age.

In the UK, the NICE guidelines have recommended an algorithm-based approach, being more inclusive of stroke risk factors identified by a systematic review\(^\text{47}\). These include a history of stroke, TIA or thromboembolic events, increasing age, hypertension, clinical evidence of valve disease, heart failure or impaired left ventricular function on echocardiography, diabetes mellitus and vascular disease. Using the NICE guideline, ‘high risk’ means those who are truly ‘high risk’, ie with stroke/TIA or systolic heart failure, or age >75 plus one ‘established’ clinical risk factor. In contrast, ‘low risk’ refers to those who are really ‘low risk’, i.e. age <65 with no risk factors. The ‘moderate risk’ category essentially encompasses those with one risk factor, age ≥75 only, or age 65-74 [one ‘less validated risk factor’] plus one ‘more established’ risk factor (eg hypertension, diabetes, or vascular disease).

Most guidelines recommend oral anticoagulation for ‘high risk’ patients, aspirin for ‘low risk’ patients, and oral anticoagulation or aspirin for ‘moderate risk’ patients. Stroke risk is a continuous variable and artificial classifications into high, moderate and low risk strata perhaps misclassifies many patients with AF, al-
though these categorizations largely evolved to enable the ‘high risk’ strata to be best identified so they could be targeted for warfarin, given the dis-utility associated with warfarin. However, many of the published stroke risk stratification schema only have modest predictive value for the high risk category\(^{58,49}\) and some have argued for a paradigm shift so as to better identify truly low risk AF patients\(^{50}\).

Given the availability of new oral anticoagulant drugs that overcome the limitations and disadvantages of warfarin, this artificial categorization into high/moderate/low risk strata should perhaps be deemphasized and a more risk factor-based approach promoted. This would depend on a comprehensive stroke risk scoring system for non-valvular AF patients that is more inclusive (rather than exclusive) of risk factors for stroke and thromboembolism.

The new 2010 ESC guidelines\(^{31}\) (see Fig. 2) seem to address the recognized caveats in the common risk stratification schemes by suggesting an unique risk factor-based approach for more detailed stroke risk assessment, and emphasize the importance of the cumulative effect of risk factors. The CHADS\(^2\) score is recommended as an initial simple risk assessment to identify high-risk patients who need antiocoagulation. In the patient with a CHADS\(^2\) score of 0-1, or where a more detailed comprehensive risk assessment is being called for, the CHA\(_2\)DS\(_2\)-VASc risk scoring system (see below). A discussion of the pros and cons of oral anticoagulation therapy, evaluation of bleeding risk, ability to sustain adjusted dose chronic anticoagulation, and patient preferences is also needed.

Additional risk factors shown to influence thromboembolisms are female gender, age 65-74 years, LV dysfunction, vWF, and vascular disease. The CHA\(_2\)DS\(_2\)-VASc score includes age 65-74 years, vascular disease (prior myocardial infarction, peripheral vascular disease or aortic plaque), and female gender\(^{52}\) [see Table 2]. In the original validation study, it showed an improvement in the stratification of the intermediate risk group, with only 15.1% of patients classified in this category compared with 61.9% using CHADS\(_2\). Also the low risk group in this category was ‘truly low risk’ with no thromboembolic events recorded, whereas 1.4% of events occurred in the low risk group in CHADS\(_2\). Also the c-statistic (a measure of how good a schema is for predicting high-risk patients at risk of stroke events) of this stratification was comparable with CHADS\(_2\) scoring and better than some other risk stratification schema\(^{58}\).

### Bleeding risk assessment

The risk factors for bleeding in conventional anticoagulant therapy are identified commonly as cerebrovascular disease, advanced age, history of myocardial infarction or ischemic heart disease, uncontrolled hypertension, anaemia, renal dysfunction, history of bleeding, intensity of anticoagulation, concomitant use of other antithrombotic agents, etc. It is notable that as stroke risk increases bleeding risk also increases. For example, Poli et al.\(^{53}\) studied 783 patients with AF on oral anticoagulation, and observed that major bleeding rates were higher in patients over 80 years of age (1.9%) than those <80 years of age (0.9%) \((p = 0.0004)\). Similarly, Hylek et al. studied patients on warfarin and showed the incidence of major hemorrhage to be 13.1 per hundred patient years in those >80 years old and 4.0 per hundred patient years in those <80 years \((p = 0.009)\).

Various models for the prediction of bleeding have been proposed. One such model uses 8 variables in the scoring of risk: age ≥70, gender, remote bleeding, recent bleeding, alcohol abuse, diabetes, anaemia and antiplatelet use. Bleeding rates are grouped as low (0.9%), moderate (2.0%) and high (5.4%)\(^{55}\).

A new scoring system based on the EuroHeart survey of an AF patient cohort has been proposed with the acronym HAS-BLED\(^{56}\) (uncontrolled Hypertension, Abnormal renal/liver function, Stroke,
Bleeding history or predisposition, Labile INR, Elderly >65 years, Drugs/alcohol concomitantly). One point is given for each risk factor with a maximum score of 9. A score of 3 or more suggests high risk of bleeding, and the predictive accuracy for one year bleeding risk was consistent in different populations (c statistic- 0.72), making this a potential practical tool in clinical decision making, as recommended in recent guidelines \(^{51}\).

**Combined OAC and antiplatelet therapy**

The increasing burden of CAD in the elderly and the relative increase in coronary intervention in both emergency and elective approaches pose a need for a consensus on antithrombotic therapy in patients undergoing percutaneous angioplasty with nonvalvular AF and high thromboembolic risk. Therapy with warfarin and dual antiplatelet therapy (DT) increases the risk of total bleeding events by 5 fold\(^{57-62}\), but withholding warfarin increases stroke and thromboembolic complications\(^{63}\). In this group of patients with AF or atrial flutter undergoing PCI, there is wide variability in practice.

The largest dataset comes from Gao et al.\(^{64}\), who studied antithrombotic regimes in AF patients undergoing drug-eluting stent implantation - they showed that the most common treatment was DT (57.1%)
followed by triple therapy (TT) (22.8%) and antiplatelet monotherapy plus warfarin. Their analysis showed that overall major adverse cardiac and cerebral events were significantly lower in the triple therapy group (8.8% vs 20.1% vs 14.9% p < 0.01) compared to DT or antiplatelet monotherapy plus warfarin. This was largely driven by a reduction in the ischemic stroke rate with the administration of warfarin (0.7 vs 0.8 vs 3.6% p = 0.08 in TT vs DT vs antiplatelet monotherapy with warfarin). A meta-analysis of studies comparing combinations of oral anticoagulants and aspirin with dual antiplatelet therapy showed the composite endpoint of death, myocardial infarction and need for revascularisation to be significantly lower in antiplatelet therapy (RR 0.41; 95% CI 0.25-0.69).

The ESC Working Group on Thrombosis recently published recommendations for antithrombotic management in patients requiring VKA for AF and presenting with ACS and/or undergoing PCI. The recommendations are summarised in Table 3. Current evidence is very limited for this patient population and many of the recommendations are made largely based on a limited number of small single centre trials or observational data from cohorts.

Estimations of bleeding risk are also crucial for preserving the delicate balance between prevention of thromboembolism, recurrent cardiac ischemia or stent thrombosis and bleeding risk. In the ACS setting, some accepted predictors of major bleeding include advanced age, female gender, history of bleeding, renal impairment and use of glycoprotein inhibitors. The recommendations call for triple therapy for a period of time in all patients with a target INR of 2.0-2.5, but the duration will depend on the bleeding risk, type of stent, and PCI setting.

### New oral anticoagulants.

Use of Warfarin increased steadily after a convincing demonstration of stroke prevention in AF. However, it has reached a plateau with only approximately 30% to 60% of eligible patients receiving the therapy. There has been a search for new oral anticoagulants with ideal characteristics, namely rapid onset of action, predictable pharmacokinetics, predictable anticoagulant response, rapid offset of action, availability of safe antidote, no off-target effects, reasonable cost, etc.

A number of oral anticoagulants have undergone phase II and phase III trials (see Table). The newer anticoagulants are broadly classified based on their mechanism of action as oral direct thrombin inhibitors and oral Factor Xa inhibitors.

### Oral Direct Thrombin Inhibitors.

Direct thrombin inhibitors (DTIs) are a new class of anticoagulants that bind directly to thrombin and block its interaction with their substrates. They bind to one or two of the three domains: catalytic site or active site, exosite 1- fibrin binding domain and exosite 2- heparin binding domain. Heparin and LMWH can bind only with free thrombin, but DTIs can bind both free and fibrin-bound thrombin improving the effectiveness. Also, a lack of binding with plasma proteins produces a more predictable response than unfractionated heparin. By reducing thrombin-mediated activation of platelets, DTIs also have antiplatelet effects. Among the available

<table>
<thead>
<tr>
<th>CHA2DS2-VASc acronym</th>
<th>Score</th>
<th>CHA2DS2-VASc score</th>
<th>Stroke rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
<td>1.3%</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>2</td>
<td>2</td>
<td>2.2%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>3</td>
<td>3.2%</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
<td>4</td>
<td>4.0%</td>
</tr>
<tr>
<td>Vascular diseases</td>
<td>1</td>
<td>5</td>
<td>6.7%</td>
</tr>
<tr>
<td>(prior MI, PAD, aortic plaque)</td>
<td></td>
<td>6</td>
<td>9.8%</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
<td>7</td>
<td>9.6%</td>
</tr>
<tr>
<td>Sex category (female gender)</td>
<td>1</td>
<td>8</td>
<td>6.7%</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
<td>9</td>
<td>15.2%</td>
</tr>
</tbody>
</table>
DTIs, ximelagatran, dabigatran and AZD0837 have been studied in AF patients. Ximelagatran has since been withdrawn due to liver toxicity issues, but dabigatran is at an advanced stage of development for stroke prevention in AF.

**Dabigatran Eteixilate**

This is the prodrug of Dabigatran, a non-peptide small molecule that specifically and reversibly binds thrombin. Bioavailability is low (6.8%) and intestinal absorption is pH sensitive, thus decreasing its absorption in the presence of proton pump inhibitors. The peak plasma concentration is reached 2-3 hrs after the oral dosing. The half life is 12-17 hours with predominantly renal excretion (80%). It is safe in hepatic impairment as it is independent of cytochrome P450 enzyme. Dabigatran etexilate was approved by the European Medicines Agency (EMEA) in April 2008, in Canada in June 2008 and in Australia in November 2008, following successful phase III clinical trials in patients undergoing total hip and knee replacements.

Dabigatran etexilate has been studied in AF patients with promising results in the landmark Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. The trial compared two blinded doses of Dabigatran etexilate (110 mg and 150 mg twice daily) against controlled open label warfarin for secondary prevention of stroke and systemic embolism. This was a noninferiority trial involving 18,113 patients, in which the participants had AF and at least one risk factor for stroke (mean CHADS2

<table>
<thead>
<tr>
<th>Hemorrhagic risk</th>
<th>Clinical setting</th>
<th>Stent implanted</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low or intermediate</td>
<td>Elective</td>
<td>Bare metal</td>
<td>1 month: triple therapy of warfarin (INR2.0-2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day + gastric protection.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Up to 12th month: combination of warfarin (INR2.0-2.5) + clopidogrel 75 mg/day (or aspirin ≤100 mg/day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Life long: warfarin (2.0-3.0) alone</td>
</tr>
<tr>
<td></td>
<td>Elective</td>
<td>Drug eluting</td>
<td>3 (olimus group) to 6 (paclitaxel) months: triple therapy of warfarin (INR2.0-2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day.</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Up to 12th month: combination of warfarin (INR2.0-2.5) + clopidogrel 75 mg/day (or aspirin ≤100 mg/day)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Life long: warfarin (2.0-3.0) alone</td>
</tr>
<tr>
<td></td>
<td>ACS</td>
<td>Bare metal/drug eluting</td>
<td>6 months: triple therapy of warfarin (INR2.0-2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day</td>
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<td></td>
<td></td>
<td></td>
<td>Up to 12th month: combination of warfarin (INR2.0-2.5) + clopidogrel 75 mg/day (or aspirin ≤100 mg/day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Life long: warfarin (2.0-3.0) alone</td>
</tr>
<tr>
<td>High (HAS-BLED Score ≥3)</td>
<td>Elective</td>
<td>Bare metal</td>
<td>2 to 4 weeks: triple therapy of warfarin (INR2.0-2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Life long: warfarin (2.0-3.0) alone</td>
</tr>
<tr>
<td></td>
<td>ACS</td>
<td>Bare metal</td>
<td>4 weeks: triple therapy of warfarin (INR2.0-2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Up to 12th month: combination of warfarin (INR2.0-2.5) + clopidogrel 75 mg/day (or aspirin ≤100 mg/day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Life long: warfarin (2.0-3.0) alone</td>
</tr>
</tbody>
</table>

a- combination of warfarin (INR 2.0-3.0) + Aspirin ≤100 mg/day may be recommended.

b- drug eluting stents should be avoided.

Table 3. Recommendations for antithrombotic therapy in atrial fibrillation patients treated with vitamin K antagonists undergoing percutaneous coronary intervention. Reproduced from Lip et al.57
score was 2.1), followed up for 2 years.

The primary outcome of stroke and systemic embolism occurred in 1.69% of patients per year in the Warfarin group compared to 1.53% patients per year in the 110 mg BID dabigatran group (p<0.001 for non-inferiority) and 1.22% per year in 150 mg BID dabigatran group (p<0.001 for superiority). The rate of major bleeding was 3.36% per year in the Warfarin group compared with 2.71% in the 110 mg dabigatran group (p=0.003) and 3.11% per year in the 150 mg dabigatran group (p=0.31). The rate of hemorrhagic stroke was higher in the warfarin group at 0.38% per year, as compared with 0.12% per year in the 110 mg dabigatran group (p<0.01) and 0.10% per year in the 150 mg dabigatran group (p<0.001). Dyspepsia occurred in 5.8% of patients in the Warfarin group compared with 11.8 and 11.3% of patients in the 110 mg and 150 mg dabigatran groups respectively. However, the rate of discontinuation was higher in the dabigatran group, 14.5%, 15.55% and 10.2% in the 110 mg dabigatran, 150 mg dabigatran and warfarin groups respectively at 1 year and 20.7%, 21.2% and 16.6% at 2 years. Thus, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism similar to those associated with warfarin, as well as lower rates of major hemorrhage. The dose of 150 mg, compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.

A subgroup analysis showed, in patients ≥75 years, rates of major bleeding were similar or higher (4.17%, 4.81% and 4.09% in the dabigatran 110 mg, dabigatran 150 mg and warfarin groups respectively). In 3623 patients with prior TIA or stroke, analysis showed a significant reduction of hemorrhagic stroke with both doses of dabigatran (2 (0.08% per year, RR 0.11 95 % CI 0.03-0.47 p =0.003) for 110 mg BID and 5 for 150 mg BID (0.20/year RR0.27 95 % CI 0.10- 0.72 p =0.009) vs. 18 (0.77% per year) for warfarin). Also low stroke rates (0.03% for 110 mg BID, 0.02% for 150 mg BID and 0.03% for warfarin p =0.99 and p =0.42 respectively for 110 mg BID and 150 mg BID) were obtained for the subgroup of 1,257 patients undergoing cardioversions.

**Oral Factor Xa inhibitors.**

Several factor Xa inhibitors are currently under development in phase II and phase III trials for stroke prevention in AF. The parental forms are indirect Factor Xa inhibitors, of which only Idraparinuax (and its biotinylated form) has been studied in AF.

The AMADEUS trial was an open label noninferiority trial, which compared the safety of idraparinua-x 2.5 mg, subcutaneous weekly with adjusted dose warfarin. The trial was stopped after 10 months due to an excess of clinically relevant bleeding with Idraparinua (11.3 % versus 9.7 % per patient year; p <0.0001). Biotinylated Irdaparinux is an indirect Factor Xa inhibitor, with a biotin molecule attached to idraparinux, allowing rapid reversal with an injection of avidin. This drug is being investigated in the phase III once weekly injection of Biotynilated Idraparinuax Versus Oral Adjusted-dose Warfarin to Prevent Stroke and Systemic Thromboembolic Events in Patients With Atrial Fibrillation (BOREALIS-AF) trial as a double blind double dummy non inferiority study in patients with AF and CHADS2 score ≥ 2. It is administered subcutaneously at 3 mg weekly for 7 weeks and then 2 mg or 1.5 mg weekly. The trial has recently been terminated early (www.clinicaltrials.gov identifier: NCT00580216). Other factor Xa inhibi-tors which have created lot of interest in recent years are the oral direct factor Xa inhibitors.

**Rivaroxaban**

Rivaroxaban is an oral direct factor Xa inhibitor with competitive and reversible binding. It has a very high oral bioavailability (60-80%), its intestinal absorption is not affected by pH, and it reaches a peak plasma concentration in approximately 3 hours. The half life is 5-9 hrs. One third of the drug is excreted by the kidneys and two thirds is metabolize in liver with cytochrome-P450. Rivaroxaban binds to both free factor Xa and factor Xa bound to prothrombinase complex. Rivaroxaban was approved by EMEA in October 2208, Canada in September 2008 and Australia in November 2008 following phase III clinical trials in 10000 Patients undergoing Total knee or hip replacement.

In AF, Rivaroxaban is undergoing phase III clinical trials in prevention of thromboembolic events in NVAF. The ROCKET –AF trial investigated rivaroxaban at 20 mg per day compared to adjusted dose warfarin for prevention of thromboembolism in AF (www.clinicaltrials.gov identifier: NCT00403767) and preliminary results showed that rivaroxaban met
its primary efficacy endpoint (stroke and systemic embolism versus dose-adjusted warfarin). The rates of the composite of major and non major clinically relevant bleeding were comparable.

**Apixaban**

This is an oral direct Factor Xa inhibitor with reversible binding with oral bioavailability of 50%. It reaches a peak plasma concentration in 3 hours and has a half life of 9-14 hours. The drug is metabolized in the liver cytochrome P450, but one third is excreted by kidneys. In phase III clinical trials in patients with orthopaedic surgery, Apixaban with Enoxaparin for Thromboprophylaxis after knee replacement (ADVANCE -I) did not show apixaban to be inferior to heparin due to a low event rate in the enoxaparin treatment group, but another trial (ADVANCE-2) showed the superiority of apixaban 2.5 mg BID over 40 mg QD dose of enoxaparin. Lower bleeding rates were reported in the apixaban group (3.5%) than enoxaparin group (4.8%).

Apixaban is under investigation in AF patients in the ARISTOTLE trial (www.clinicaltrials.gov identifier: NCT00412984), where a 5 mg BID dose of apixaban is compared with dose adjusted warfarin. Aspirin versus Acetylsalicylic acid to prevent Strokes (AVERROES) is a phase III trial of apixaban in 5600 patients who are not eligible for oral anticoagulation with warfarin and hence this compares 5 mg BID apixaban with aspirin (www.clinicaltrials.gov identifier: NCT00496769). The AVERROES trial was stopped early because of benefit and was presented at the ESC meeting in Stockholm, on 31 August 2010. This showed the primary outcome of stroke and systemic embolism to be significantly lower with apixaban (4.0% with aspirin compared to 1.7% per year with apixaban HR 0.43 95% CI 0.30-0.62, p = 0.000004), accounting for a 57% reduction of stroke and systemic embolism. The rate of major haemorrhage 1.2% with aspirin and 1.5% with apixaban (HR 1.26, 95% CI 0.79-2.00, p = 0.33), did not differ significantly. The rate of hemorrhagic stroke was equal in both groups (0.2% per year HR 1.15,95% CI 0.42-3.17. p = 0.79).

**Endoxaban (DU-176b)**

This is an oral direct factor Xa inhibitor engineered from a parental direct factor Xa inhibitor (DZ-9065a) by replacing an amide moiety with less basic moieties. A phase II trial in 1,146 patients with AF was conducted with 30 and 60 mg QD or BID compared with dose adjusted warfarin, whereby the 60 mg BID dose arm in this study was terminated due to increased bleeding, while the 30 mg and 60 mg QD was found to be safe and well tolerated compared to warfarin.

A large phase III double-blind, randomized clinical trial (ENGAGE AF-TIMI 48) is currently underway in 16,500 patients with AF, where DU-176b is given in 30 mg and 60 mg QD doses compared with dose adjusted warfarin in a double-dummy manner. (www.clinicaltrials.gov identifier: NCT00781391).

**Betrixaban**

This is a direct oral factor Xa inhibitor with a reversible mechanism of action, with an oral bioavailability of 47% and almost exclusive biliary elimination. Phase II clinical trials in orthopaedic surgery patients (EXPERT trial) paved the way for a phase II randomised dose finding study in 500 patients with AF (Explore Xa) (www.clinicaltrials.gov identifier: NCT00742859). Betrixaban was administered in doses of 40 mg, 60 mg, and 80 mg QD and compared with open label warfarin. The primary end points of major and clinically relevant non major bleeding were less with 40 mg QD dose of betrixaban compared to warfarin (0.8% versus 5.5% p = 0.035). These results were reported in 2010 American College of cardiology Scientific sessions-Late Breaking Clinical Trials in Atlanta, March14-16, 2010.

**YM150**

YM150 is a oral factor Xa inhibitor being investigated in phase II clinical trials in NonValvular AF in different dosing regimes in 2 separate studies, one involving 448 patients compared with warfarin (www.clinicaltrials.gov identifier: NCT00448214) and OPAL-2 study (www.clinicaltrials.gov identifier: NCT00938730). A recent phase II trial was reported in the European Society of Cardiology 2010, in a predominantly Asian population to assess the safety of different dosing regime showed that, in doses of 30mg, 60mg, 120mg, 240mg, whereby the clinically relevant non major bleeding rates were 2.2%, 2.2%, 3.2% and 16.2% respectively, compared to warfarin (2.1%).

**Other novel anticoagulants under development.**

ATI-5293 - Tecarfarin is a selective oral Vitamin K epoxide reductase enzyme inhibitor. In contrast to warfarin, however, it is metabolised by carboxyl esterase and not by cytochrome P450, hence avoiding a number of potential drug interactions and genetic interactions with the CYP systems and improving the ability to maintain INR in the therapeutic range. It is currently under phase II evaluation in 600 people.
with atrial fibrillation, atrial flutter, prosthetic heart valves, VTE, myocardial infarction and cardiomyopathy (www.clinicaltrials.gov identifier: NCT00691470).

**Challenges with new antithrombotic therapies**

The newer anticoagulants are being developed to eliminate the difficulties faced in warfarin therapy, like slow onset and offset of action, variability in predictability and dose response, food and drug interaction, etc. but carry with them a new set of challenges.

**Monitoring**

Currently there are no standardized monitoring tests for new agents. Ecarin clotting time (ECT) directly assesses the activity of thrombin in plasma and has shown a linear dose-response to therapeutic concentrations of dabigatran. Neoplatin-induced prothrombin time shows a dose-dependent correlation to rivaroxaban plasma levels, but neither of these have been established in major clinical trials.

Dabigatran acts on the thrombin-mediated conversion of fibrinogen to fibrin and has an effect on all routine coagulation assays. Various assays behave differently to increasing dabigatran concentrations. The maximal effect of dabigatran on clotting parameters occurs at the same time as maximal plasma concentrations. Hence it is important to know the time of administration relative to time of sampling. The APTT concentration response curve is curvilinear and flattens out at higher concentrations, and hence not suitable for precise quantification but can help determine excess anticoagulant activity.

Dabigatran has very little effect on PT in normally clinically relevant plasma concentrations and is hence unsuitable for measuring anticoagulant activity. Thrombin clotting time (TT) is a direct measure of the activity of DTIs, particularly sensitive for effects of dabigatran and has a linear dose-response curve, but maximum measurement times in coagulometers are reached with 600 ng/mL of dabigatran. As it is highly sensitive, TT can be used for the identification of any dabigatran in blood but it not useful in emergency monitoring. Activated clotting time (ACT) is based on the aPTT principle and hence, follows the flat dose response curve limiting its utility.

The hemoclot thrombin inhibitor assay is a diluted TT assay which allows quantification of DTI activity in plasma. This assay shows a linear relationship between the dabigatran concentration with no matrix effect. Ecarin clotting time (ECT) is a specific assay for thrombin generation, whereby ecarin (a snake venom) specifically converts prothrombin into zyzo thrombin, an unstable thrombin precursor which DTIs are able to inhibit. Studies have shown a close linear relationship between ECT prolongation and plasma DTI concentration. A ECT ratio of 2-4 has been observed with dabigatran 150 mg BID. With the development of commercial kits this may become a practical option.

Samama et al. has reported on the monitoring of rivaroxaban and other factor Xa inhibitors using various coagulation assays. Prothrombin Time (PT), diluted PT and aPTT were prolonged by rivaroxaban in dose-dependent manner but the results vary based on the reagents used in the assay. Modifications of PT with specific calibrators may allow the PT measurements to be expressed in plasma concentrations of rivaroxaban in μg/mL.

Other tests such as the dilute Russell’s viper venom time, one-step prothrombinase-induced clotting time, Heptest and factor Xa chromogenic assays have been studied for measuring pharmacodynamics but these tests are not specific and not commercially available. A paradoxical response noted in Heptest and prothrombinase induced clotting time producing dose-dependent clotting time prolongation at higher concentrations but a reduction of clotting times at lower concentrations. The chromogenic anti-factor Xa assay has also shown a dose-dependent relationship between antifactor Xa levels and rivaroxaban concentrations. In comparison with rivaroxaban, frondaparinux does not prolong PT as it acts on the free factor Xa only. Different tests or calibrators are needed for each compound to measure direct and indirect factor Xa inhibitors.

**Reversal of anticoagulation**

The shorter half life of most of the newer anticoagulants helps in planning for elective surgical treatments, by discontinuing the medication according to renal function. Dabigatran discontinuation should take into account creatinine clearance and risk of bleeding in surgery. If a rapid reversal of anticoagulation is required, there are no specific reversal agents available. There are no published data regarding use of reversal agents, but some pre-clinical and anecdotal case reports suggest use of some reversal agents.

In cases of potential overdose, activated charcoal given within 1-2 hours of ingestion has been shown to absorb dabigatran (as it is a lipophilic molecule) in vitro studies but studies in vivo are lacking. Also, the removal of dabigatran from plasma via hemoperfusion over a charcoal filter is under evaluation. In cases of bleeding, management is tailored based on severity and location. Adequate diuresis must be maintained as
it is renally excreted with supportive strategy including the transfusion of blood products. In the bleeding is life threatening, a recombinant activated factor VII can be used.

Recombinant activated factor VII is a potent procoagulant and general hemostatic agent that can initiate haemostasis at sites of bleeding by activating thrombin on the surface of platelets in the absence of tissue factor. This had been proposed as a potential “off label” indication for the reversal of life-threatening haemorrhage but not firmly established. Prothrombin complex concentrates, both un-activated and activated, have been suggested to reverse the effect of direct factor Xa inhibitors but sufficient clinical data are lacking. Dabigatran is dialysable due to relatively low protein binding. This is supported by an open label study in dialysis patients with end-stage renal failure, showing the mean proportion of drug removed by dialysis to be 62% at 2 hours and 68% at 4 hours.

A potential antidote for factor Xa inhibitors is in preclinical development, namely, a plasma-derived factor Xa whose active site has been chemically modified to render it inactive and causing competitive inhibition. Newer DNA and RNA aptamers blocking coagulation factors can be inhibited by specific DNA and RNA-based antidotes.

Biotin/avidin systems have been found to be useful, specifically as an antidote for biotinylated iraparin, utilizing the strong affinity of avidin for biotin.

Methodological challenges

Tailoring the risk stratification of specific patients receiving newer anticoagulant treatments may be needed to get the net clinical benefit. Most trials select good responders and previously warfarin experienced patients, excluding the patients with higher bleeding risks, creating an artificial group compared with the real life circumstances.

Alternative treatment strategies

Several surgical, echocardiography and autopsy studies show that 90% of all cardiogenic thrombi in non valvular AF originate from the left atrial appendage. The risk of embolic stroke is high when left atrial appendage flow velocity is below 20 cm/s (13.1% per year) and in patients with spontaneous echocardiographic contrast (SEC) (18.2% a year).

Of 772 participants of the Stroke Prevention in Atrial Fibrillation (SPAF-III) study, 55% had SEC of which 13% were dense. Dense SEC was strongly associated with clinical predictors of stroke. Surgical excision/exclusion of left atrial appendage is performed with other cardiac surgeries in patients with high risk of left atrial thrombus. Thoracoscopic snaring of the appendage is also possible but more recent interest is in occlusion of the appendage by devices like Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) and WATCHMAN devices.

The PLAATO feasibility study in North America enrolled 64 patients who were contraindicated for warfarin treatment. The mean CHADS2 score of the patients was 2.9. The annual stroke rate was 3.8% (anticipated stroke rate was 6.6%) corresponding to 50% estimated stroke reduction. But this was a non-randomized study with a small number of patients. The European PLAATO study enrolled 180 patients with similar characteristics to the American counterparts. The primary end point of LAA closure was assessed by trans-oesophageal echocardiography at 2 months. LAA occlusion was successful in 90% of cases (95% CI, 83.1 to 92.9%). The stroke rate was 2.3% per year, compared with the expected rate of 6.6%. The PLAATO study was discontinued in 2006.

More recently, the WATCHMAN left atrial appendage Protection system for embolic protection in atrial fibrillation (PROTECT-AF) study was carried out in 59 worldwide centres, which randomized patients with CHADS2 ≥1 to device and warfarin therapy and enrolled 800 patients over a 3-year period. The mean age was 72 years and a majority of the patients had a CHADS2 score of 1 or 2. WATCHMAN device met the non-inferiority criteria at the end of three years. However there was a significant increase in peri-cardial effusion (5.5%) in the device group requiring subcutaneous and surgical drainage. LAA occlusion may prevent thromboembolism from LAA, yet may not completely protect AF patients from stroke as the device does not treat underlying risks of thromboembolism in these patients.

Controversy exists about the risks and benefits of LAA occlusion for prevention of thromboembolism. Thromboembolism in AF is not proved to be exclusive from the LAA, and other sites such as the atria, ventricular surfaces and aorta might be important sources of thrombi. Also, the hypercoagulable state reported in AF patients cannot be counteracted by LAA occlusion. There is also potential for adverse hemodynamic and physiological changes after LAA occlusion. Indeed, incomplete closure of LAA causing stagnant blood flow promoting thrombosis is a possibility. Finally, the potential post-interventional requirement of aspirin, clopidogrel and oral anticoagulation may also be problematic for patients with a true contraindication to anticoagulation therapy.
Conclusions

Increasing recognition of the risk of thromboembolism, refinement of the risk stratification of thromboembolism in AF (such as the CHA2DSVASC score) and using a risk factor-based approach have increased the need for oral anticoagulation for patients with AF. There is also considerable improvement in monitoring and better predictions of bleeding risk.

Despite this, the use of oral anticoagulation is a major problem and the newer anticoagulants are promising to widen the choice of anticoagulants and probably acceptability. The new oral anticoagulants bring in a new set of therapeutic challenges such as the lack of ability of dose adjustment via haematological monitoring, drug interactions, the need for compliance and the need for reversal agents in cases of major bleeding when they become widely used, in the ’real world’.

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