Anticoagulation in atrial fibrillation: the present and the future

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Summary

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia and associated with significant mortality and morbidity. It is a powerful predictor of future embolic stroke, such that anticoagulation is recommended in the majority of patients. For many years this has predominantly been in the form of vitamin K antagonists. However, there are well-documented difficulties with their administration that result in poor compliance and high discontinuation rates. Over recent years several oral alternative anticoagulant agents have become available with the potential to overcome many of these pitfalls. In this review, we discuss current recommendations for anticoagulant therapy in AF and how these may change in the future with the introduction of novel therapeutic options.

Introduction

Atrial fibrillation (AF) is the most common cardiac dysrhythmia, affecting over six million people in the European Union.[1] Its prevalence increases with age, affecting 0.2% of the population aged 20–55, but 9% of patients over the age of 80.[2] AF is associated with significant morbidity and mortality[3] and is a strong independent risk predictor for embolic stroke. As a consequence, the default antithrombotic treatment for patients with AF is with vitamin K antagonists (mainly warfarin). Nevertheless, a substantial proportion of patients remain untreated with warfarin or discontinue warfarin anticoagulation. Several alternative oral anticoagulants have recently become available with the potential for improved compliance and reduced bleeding and stroke complications. The aim of this review is to discuss the current status of anticoagulation in AF and to examine the novel agents with the potential to change practice.

Stroke risk in AF

The most common thromboembolic complication observed in AF patients is ischaemic stroke. Patients with AF experience up to a five-fold increase in the risk of stroke with an annual incidence of 4.5% in patients left untreated.[4] Furthermore, strokes in the context of AF are more likely to be severe and are often fatal. The risk of thromboembolic complications in non-valvular AF can be predicted using the $CHADS_2$ scoring system, which is based upon the presence of heart failure, hypertension, age ≥75 years, diabetes mellitus and prior stroke or transient ischaemic attack. Those with a $CHADS_2$ score of 0 have an annual risk of 2%, which rises to 18% in those with a score of 6.[5] Recently, the CHA_2DS_2-VASc scoring system has been introduced which also incorporates gender and peripheral vascular disease.[6] The CHA_2DS_2-VASc score has been shown to refine the risk prediction offered by $CHADS_2$ scoring and to improve the identification

of those at very low risk for stroke (who do not need anticoagulation). It has been incorporated in the most recent European Society of Cardiology (ESC) guidelines.[1] These guidelines suggest using oral anticoagulation in AF if the $CHADS_2$ score is ≥2 or in those with a CHA_2DS_2-VASc score of ≥1.

Warfarin therapy

Warfarin is an oral vitamin K antagonist. It exerts its anticoagulant effect by inhibiting the production of several different coagulation factors and has served as the mainstay for thromboembolic prophylaxis in AF.

In patients with non-valvular AF and no history of stroke or transient ischaemic attack, a systematic review and meta-analysis of five randomized trials showed that warfarin significantly reduced the risk of stroke without a significant increase in bleeding rates, albeit in the presence of wide confidence intervals (CIs).[7] A further meta-analysis demonstrated that while aspirin and warfarin were both more effective than no therapy (relative risk reductions of 20% and 60%, respectively) warfarin provided superior stroke protection (relative risk reduction warfarin versus aspirin of 38%; 95% CI, 18–52%).[8] It should also be noted that despite their lower efficacy in stroke prevention, antiplatelet agents have been associated with similar bleeding rates to warfarin.[9]

Limitations of warfarin therapy

Bleeding is the main hazard associated with warfarin use. Therefore, when deciding whether anticoagulation is appropriate for a patient, careful assessment of both their stroke and bleeding risks is required. In order to help facilitate this process scoring systems have been developed to quantify the risk of bleeding. For example the, HAS-BLED[10] score assigns one point for each of the following factors: hypertension, abnormal renal function, abnormal liver function, stroke, bleeding, labile international normalized ratio (INR), age >65 years and drugs or alcohol use. It is clear that many of the same risk factors predict both bleeding and stroke risk, but a recent analysis demonstrates clear evidence of net clinical benefit in favour of anticoagulation in those with higher stroke risk and HAS-BLED scores (Figure 1).[11] The risk of major bleeding varies from 1% in patients with a score of 0 to 9% in patients with a score of ≥5. This score can then be weighed against the $CHADS_2$ score in order to help decide upon anticoagulation (Figure 2),[11] although in practice other factors must also be considered including the risk of falls, drug compliance and patient preference.

Despite the clear recommendations in the guidelines, warfarin is significantly under-prescribed in clinical practice, particularly in those at highest risk of stroke.[12] Furthermore, over a quarter of patients will discontinue the drug after one year,[13] indicating that there are real problems with the instigation and maintenance of anticoagulation using vitamin K antagonists. Warfarin remains a difficult drug to administer and monitor in the general community, and this issue may lead to patient dissatisfaction and complications. Over-anticoagulation significantly increases the risk of intracranial haemorrhage and other forms of bleeding, while recent studies have shown that on average patients spend a third of their time with sub-therapeutic INRs, during which they remain exposed to the risk of thromboembolism.[13]

Despite these disadvantages, warfarin has for many years remained the treatment of choice in AF, largely because of a lack of clear alternatives. The development of novel oral anticoagulants has therefore been keenly awaited and the results of recent trials investigating the efficacy of these agents have generated considerable excitement among both clinicians and patients alike.

Novel anticoagulant strategies

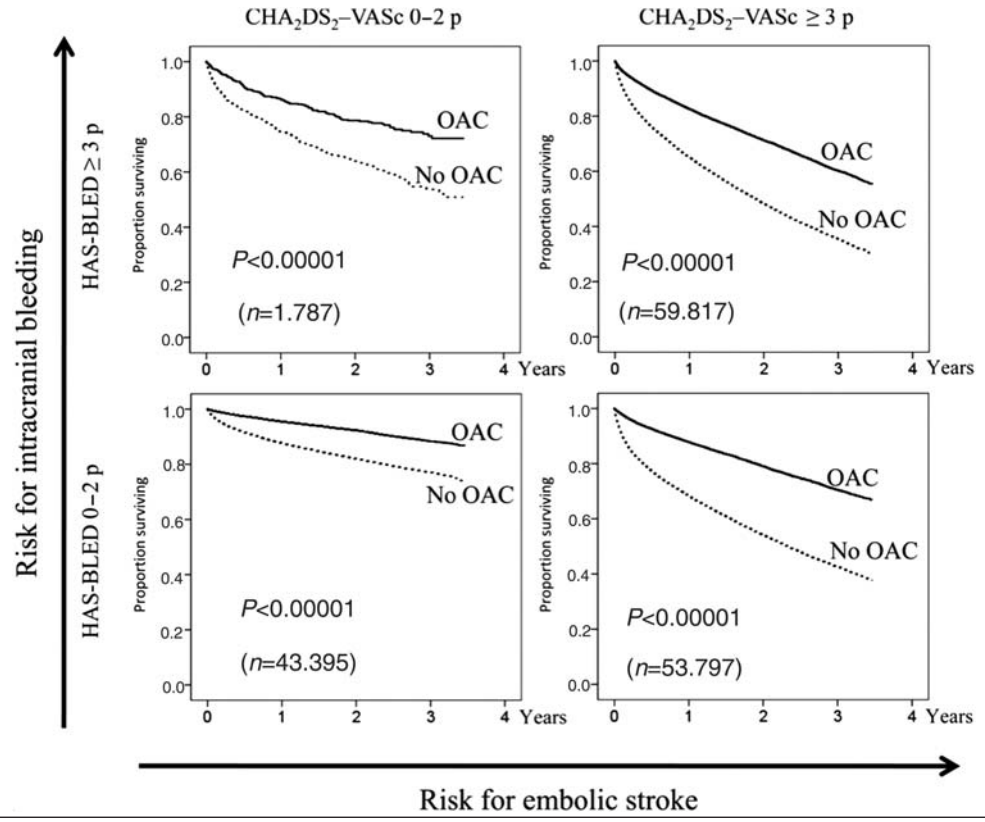
To date three novel oral anticoagulants have been investigated in large randomized controlled trials of patients with AF. Unlike warfarin, these agents all target a single step in the coagulation cascade resulting in a predictable anticoagulant response (Figure 2). Routine anticoagulant monitoring is therefore not required, and patients can be prescribed a standard dose.

Apixaban

Apixaban is an oral reversible inhibitor of factor Xa with a rapid onset of action and a half-life of 12 hours (Figure 2). Maximum plasma

Figure 1

Balancing risk using the $CHADS_2$-VASc and HAS-BLED scores. All-cause mortality, ischaemic stroke and intracranial bleeds in relation to oral anticoagulant (OAC) treatment in patients with different combinations of stroke and bleeding risks on the CHA_2DS_2-VASc and HAS-BLED risk scores. Reprinted from Friberg L, Rosenqvist M, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. *Circulation* 2012;125:2298–307, with permission from the American Heart Association, Inc.

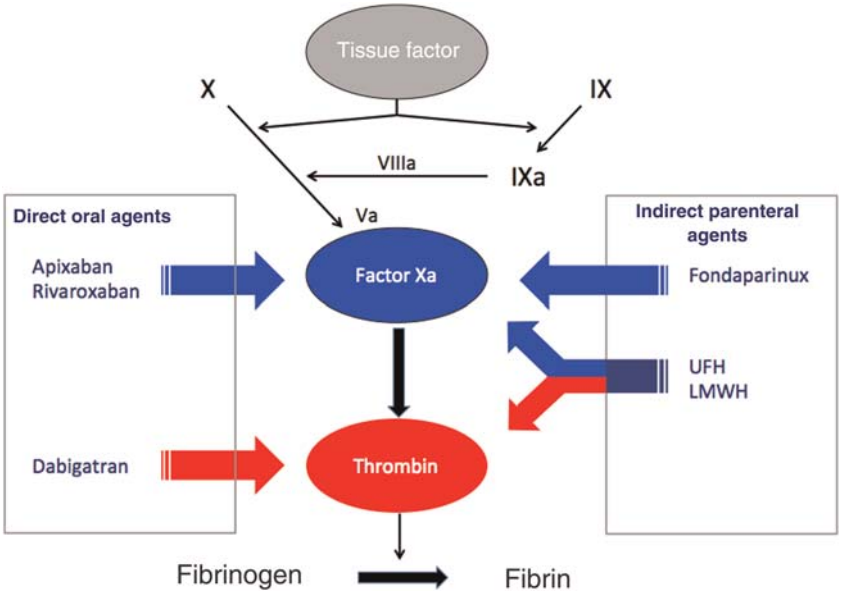


concentrations are obtained four hours after oral administration and it has a plasma half-life of 8–15 hours. The recommended dose is 5 mg twice daily, but this is reduced to 2.5 mg twice daily in patients with two of the following: age >80, creatinine >133 μmol/L and body weight <60 kg. It is partially excreted by the kidneys and should not be used in patients with a creatinine clearance <15 mL/min and used with caution between 15–30 mL/min.

There is no specific antidote or reversal agent for apixaban or indeed the other factor Xa inhibitor rivaroxaban. Furthermore, haemodialysis is unlikely to be useful due to the high protein binding of these drugs. However, there is evidence that administration of prothrombin complex concentrate can immediately and completely reverse the anticoagulant effect of rivaroxaban.[14]

Apixaban is not yet approved for clinical use. It was first tested against aspirin in the AVERROES (apixaban versus acetylsalicylic acid to prevent stroke in AF patients who have failed or are unsuitable for vitamin K antagonist treatment) trial in AF patients with at least one stroke risk factor and who were considered unsuitable or who were unwilling to take warfarin.[15] Apixaban reduced the primary endpoint of stroke or systemic embolic event by 64% (relative risk, 0.44; 95% CI, 0.33–0.64; $P < 0.001$) and did so without a significant increase in the bleeding rate.

Figure 2
Coagulation cascade with targets for current and novel anticoagulant agents. LMWH, low-molecular-weight heparin; UFH, unfractionated heparin



In the subsequent ARISTOTLE (apixaban for reduction of stroke and other thromboembolic events in atrial fibrillation) trial, AF patients with at least one risk factor were randomized to apixaban therapy or to warfarin.[16] A 21% reduction in the primary endpoint of stroke (infarct or haemorrhagic) or systemic embolism was observed and there was a 31% risk reduction in the risk of major bleeding with the use of apixaban. Total mortality was also significantly reduced (3.52% versus 3.94%; $P = 0.047$), as were the rates of intracranial bleeding (0.33% per year versus 0.80% per year; $P < 0.001$). There was no significant reduction in the incidence of ischaemic stroke. Apixaban was well tolerated with a lower discontinuation rate than warfarin.

Dabigatran

Dabigatran is a reversible thrombin inhibitor with a peak plasma concentration of two to three hours after administration (Figure 2). It has a bioavailability of 6.5% and is renally excreted (80%) and has a half-life of 11 hours. It is approved for use in AF in many countries across the world, most frequently at a dose of 150 mg twice daily, but this should be reduced in patients at high risk of bleeding to 110 mg twice daily, including all patients over 75. It should not be co-administered with dronedarone and the lower dose should be used with verapamil. There is currently no specific antidote or reversal agent available and because it is a thrombin inhibitor the administration of coagulation factors (including prothrombin complex concentrate) appears ineffective.[14] Due to the very high renal excretion, care must be taken in those with acute or chronic renal dysfunction, in which cases the lower dose should be used or the drug withheld. Close attention must therefore be paid to renal function in the context of intercurrent illnesses such as sepsis. Haemodialysis may be useful in over-dosage alongside activated charcoal to prevent absorption.

Dabigatran was first tested in AF in the RE-LY (randomized evaluation of long term anticoagulant therapy) trial.[17] Both dabigatran doses were investigated in a prospective, randomized, open-label trial against warfarin with a target INR of 2.0–3.0. Over 18,000 patients with non-valvular AF and at least one other stroke risk factor were studied with a median treatment duration of two years. The 150 mg twice daily dose was associated with a significant reduction in the primary

endpoint of stroke or systemic embolism (hazard ratio [HR], 0.65; 95% CI, 0.52–0.81; $P < 0.001$ for superiority), with no difference in major bleeding compared with warfarin (dabigatran 3.32 versus warfarin 3.57; $P = 0.31$). In addition, there was a lower risk of intracranial haemorrhage ($P < 0.001$) which, despite the problems in reversing dabigatran, was no more likely to be fatal.[18] There was also an observed trend to a reduction in total mortality (3.64% versus 4.13%; $P = 0.051$). The 110 mg twice daily dose was non-inferior to warfarin in terms of stroke and systemic embolism (HR, 0.90; 95% CI, 0.74–1.10; $P < 0.001$ for non-inferiority), and resulted in a significant reduction in major bleeding rates (dabigatran 2.87 versus warfarin 3.57%; $P = 0.003$). Overall results were better for dabigatran at centres with poor INR control.[19]

Dabigatran appears to be less well tolerated than apixaban. It is associated with side-effects in the form of dyspepsia and gastrointestinal bleeding and discontinuation rates in RE-LY were higher than for warfarin. There was also a trend to an increased incidence of myocardial infarction in RE-LY (warfarin 0.53% per year versus dabigatran 110 mg twice daily 0.72%; $P = 0.07$; dabigatran 150 mg twice daily 0.74%; $P = 0.048$) and in a pooled analysis of studies of dabigitran.[20]

Rivaroxaban

Like apixaban, rivaroxaban is a reversible, direct factor X inhibitor. It reaches its peak plasma concentration two to four hours after oral administration, has a half-life of 5–13 hours and is given as a once daily preparation. In part it is renally excreted (30% unchanged) and should be avoided in patients with a creatinine clearance of <15 mL/min and used with caution between 15–30 mL/min.

Rivaroxaban was tested in a double-blind randomized trial design against warfarin in the ROCKET-AF (rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation) trial.[21] This differed from ARISTOTLE and RE-LY in that it involved patients at higher risk of cerebrovascular events with a mean $CHADS_2$ score of 3.5 (compared with 2.1 in both other studies). Rivaroxaban was shown to be non-inferior to warfarin in terms of the primary endpoint of stroke and systemic embolism (HR with rivaroxaban, 0.88; 95% CI, 0.74–1.03; $P < 0.001$ for non-inferiority and $P = 0.117$ for superiority). The intention-to-treat analysis included all periods when patients were off study drug (for example, for procedures or at end of the study –20% of the intention-to-treat duration). An on-treatment analysis indicated superiority of rivaroxaban while on blinded, treatment.[21] Overall there was no difference in the rate of major bleeding, but intracranial hameorrhage (0.5% per year versus 0.7% per year; $P = 0.02$) and the rate of fatal bleeding (0.2% per year versus 0.5% per year; $P = 0.003$) were reduced with rivaroxaban, while gastrointestinal bleeding and the need for transfusion were increased. A reduced dose of rivaroxaban (15 mg once daily) was used in those with moderate renal dysfunction (CrCl 30–59 mL/min) and showed results consistent with the main study.[22] Similar to dabigatran, premature discontinuation was more common with rivaroxaban than warfarin.

Practical considerations

As with any novel therapeutic strategy, questions have arisen as to how these alternative anticoagulant agents will become incorporated into everyday clinical practice; these have largely focused on dabigatran given its wider availability. Perhaps the most significant concern revolves around the management of patients who present with bleeding. While different strategies have been discussed above, uncertainty persists as to the optimal management in many clinical scenarios, for example in patients who are bleeding and haemodynamically unstable and in whom dialysis may not be feasible. Focus in these patients should probably revolve around blood transfusion, instigating immediate measures to control the source of bleeding alongside oral administration of charcoal for gastric absorption of dabigatran and administration of prothrombin complex concentrate, although as discussed the efficacy of the latter is debated.

The signal to an increased myocardial infarction rate in patients on dabigatran in the RE-LY trial[17] may indicate that dabigatran is less effective

than warfarin in reducing cardiac events and also raises the question as to how these patients should be managed following myocardial infarction. Data are not currently available, but we would recommend a similar approach to those on warfarin (i.e. initially continuing anticoagulants alongside dual antiplatelet therapy and where percutaneous intervention is warranted preferentially selecting bare metal stents).

Interestingly discontinuation rates for dabigatran were higher than warfarin in the RE-LY study, which raises concerns with respect to drug compliance.[17] Furthermore, the twice daily dosing and short half-life of dabigatran and rivaroxaban ensure that missed doses are more likely to result in clinical consequences than in the case of warfarin. Patients will therefore require education as to the importance of strict drug compliance. On the positive side a shorter half-life is likely to prove advantageous with respect to elective surgery because it will allow patients to stop therapy much closer to their operation date, in general 24 hours before, although this may have to be extended in the context of renal dysfunction or neurosurgery. Indeed, a recent study has shown similar rates of perioperative bleeding with dabigatran versus warfarin even in the context of emergency operations.[23] Data have also emerged with respect to dabigatran use and the safety of cardioversion. In an analysis of over 1000 patients from the RE-LY trial, dabigatran was demonstrated to be as efficacious as warfarin, with similarly low stroke rates, but with clear advantages with respect to dosing and monitoring.[24]

Conclusions

AF is undertreated with vitamin K antagonists; however, novel oral anticoagulants with more predictable pharmacokinetics are now available. These do not require dose monitoring and include both direct thrombin and factor Xa inhibitors. Apixaban has been shown to be better than aspirin in those unable to take warfarin, while dabigatran, rivaroxaban and apixaban are at least non-inferior to warfarin. Indeed, 150 mg twice daily dabigitran and apixaban 5 mg twice daily have been shown to be superior in their ability to reduce cerebrovascular events and systemic embolism without increasing bleeding rates.

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