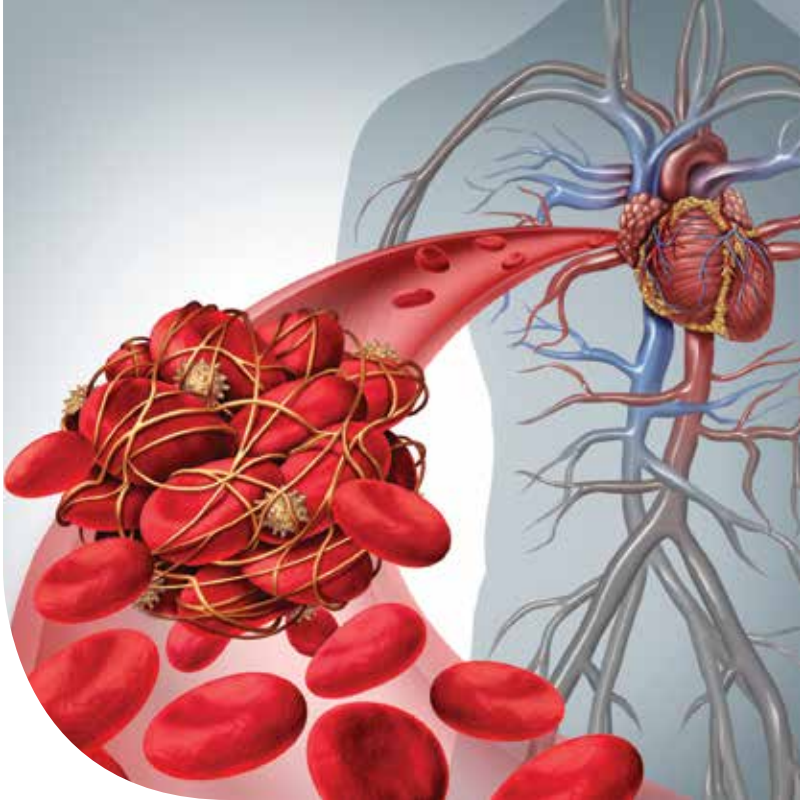
How should we be using nonvitamin K antagonist oral anticoagulants?



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In future, nonvitamin K antagonist oral anticoagulants should be the predominant therapy for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF). The recommended parameters for prescribing represent a shift towards considering which patients with NVAF do not require anticoagulation, rather than focusing on those who do.

Atrial fibrillation (AF) is the most common cardiac dysrhythmia, and its prevalence is predicted to increase significantly worldwide and in Australia over the next two decades.[1] The prevalence of AF increases with age, ranging from about 1% in people aged 55 to 59 years and more than 17% in people aged 85 years or more.[2] It is therefore the most common cause of stroke in the elderly. Detection of AF and appropriate initiation of anticoagulation is thus the most effective way to reduce the incidence of stroke in this group of patients.

Ischaemic cerebrovascular accidents, the most common cause of stroke in Australia, are a clinical manifestation of embolisation associated with AF in around 75% of cases.[3] The prevalence of a cardioembolic aetiology for stroke increases with age, with 35% or more of stroke in patients over 80 years of age attributed to this source, mostly due to AF.[4] Strokes associated with AF tend to be larger and are more likely to be fatal or disabling.[5] As a result, long-term oral anticoagulation is recommended for most patients with AF to reduce the risk of ischaemic cerebrovascular accident.

Who needs anticoagulation?

All patients with AF associated with valvular heart disease (prosthetic mechanical valves and moderate–severe mitral stenosis) should be considered for therapeutic anticoagulation with a vitamin K antagonist, because their stroke risk is prohibitively high without anticoagulation.[6,7] The indication for anticoagulation for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF) depends on their risk of stroke, which can be evaluated using the $CHADS_2$ score and the

Key points

- **Atrial fibrillation is a common cardiac arrhythmia, and the most common cause of stroke in the elderly.**
- **Current US and European guidelines recommend the use of nonvitamin K antagonist oral anticoagulants (NOACs) over warfarin or aspirin for patients with nonvalvular atrial fibrillation (NVAF) who require anticoagulation for stroke prevention.**
- **Risk scores such as the CHA_2DS_2-VASc and HAS-BLED scores have been developed to guide appropriate anticoagulation in patients with NVAF.**
- **NOACs have been rigorously studied in clinical trials and the real world and have been shown to be safer and/or more efficacious than warfarin.**
- **The inability to reverse anticoagulation with NOACs has been a concern in clinical practice, but reversal agents are now becoming available.**

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CHA_2DS_2-VASc score.[8] The advantage of the CHA_2DS_2-VASc score over the $CHADS_2$ score is that it is better at identifying patients who are truly low risk who would not benefit from anticoagulation, thereby avoiding inappropriate treatment.

Looking at current anticoagulation guidelines for NVAF, the 2014 US guidelines recommend use of vitamin K antagonists or nonvitamin K antagonist oral anticoagulants (NOACs) in both men and women if the CHA_2DS_2-VASc score is two or more. However, if the CHA_2DS_2-VASc score is one, anticoagulation with a vitamin K antagonist, a NOAC or aspirin can be considered, depending on the individual patient characteristics and preferences. In a patient with a CHA_2DS_2-VASc score of 0, neither anticoagulation nor aspirin is recommended.[6]

The most recent iteration of the European position statement on managing AF also uses the CHA_2DS_2-VASc score and makes different recommendations depending on sex.[7] It is recommended that men with a CHA_2DS_2-VASc score of two or more should be prescribed anticoagulation for stroke prevention, but if the CHA_2DS_2-VASc score is one anticoagulation should be considered depending on patient characteristics and preferences. For women, there has been a liberalisation of the recommendations for anticoagulation due to the recognition that female sex is a relatively weak risk factor for stroke. It is advised that if a woman has a CHA_2DS_2-VASc score of three or more anticoagulation is recommended, but if the score is two anticoagulation should be considered. If the CHA_2DS_2VASc score is 0 in men and women or is one in a woman, neither anticoagulation nor aspirin is necessary. These guidelines also state that NOACs are to be preferred over vitamin K antagonists for stroke prevention in NVAF, and that aspirin is not to be used for stroke prevention in NVAF, which we agree is appropriate.

The risk of bleeding must always be taken into account when considering anticoagulation, both when initiating treatment and in the longer term. Physicians often tend to do this intuitively, but the HAS-BLED score has been used in numerous countries to allow a more systematic and objective assessment of bleeding risk to be made.[9] This score was developed to evaluate the one-year risk of major bleeding in patients with AF, allowing for risk–benefit assessment in patients with AF. The HAS-BLED score should be used to identify potentially reversible bleeding risks, such as uncontrolled hypertension, abnormal hepatic and renal function and other medications that predispose to bleeding. Although the HAS-BLED score has been shown to be superior to other bleeding assessment tools, it has yet to be validated outside of Europe. In addition, a high HAS-BLED score should not be used as a reason to not anticoagulate patients with a CHA_2DS_2-VASc score that would warrant anticoagulation, as the net clinical benefit shown across numerous studies is still in favour of anticoagulation.[9-11]

Direct-acting anticoagulants

The development of novel anticoagulants in addition to warfarin has revolutionised the management of stroke prevention in patients with NVAF. Until recently, warfarin was the only proven anticoagulant to be effective in this regard, but several large clinical trials have demonstrated that NOACs have the potential to replace warfarin in most patients for this indication.[11] The current NOACs approved for use and available in Australia are the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban and apixaban. These agents have similarities and differences that are clinically significant and need to be considered when prescribing them.

All three NOACs are orally bioavailable. Interestingly, despite having similar half-lives, rivaroxaban was used in a once-daily dosing regimen in the ROCKET AF trial, whereas dabigatran and apixaban were tested in clinical trials in twice-daily dosing preparations.[12-14] They have a rapid onset of action, so full anticoagulation is achieved within one to two hours of dosing.[12-14] They also have a rapid offset of action compared with warfarin, so that within 24 hours of taking the last dose most of the anticoagulant effect has worn off. However, their excretion is affected to varying degrees by renal function. Dabigatran is highly dependent on renal excretion, with 80 to 85% excreted unchanged in the urine. Renal excretion of rivaroxaban and apixaban is 25% and 33%, respectively.[15] Thus, in the presence of renal dysfunction, a longer treatment discontinuation period is required to allow coagulation status to return to normal, which is important if a patient requires surgery.

Minimal food interactions occur with NOACs, although it is recommended that rivaroxaban be taken with meals to improve absorption and dabigatran be taken with meals to reduce the risk of dyspepsia. The bioavailability of dabigatran is low, but is increased by p-glycoprotein inhibitors, such as verapamil and amiodarone. Apart from this, there are few other clinically significant drug interactions with dabigatran. Rivaroxaban and apixaban have potential interactions with medications metabolised by the cytochrome P450 system, but most of these drugs, such as ritonavir, azoles and carbamazepine, are not routinely encountered in clinical cardiovascular practice.

None of the new agents require routine monitoring to evaluate the extent of anticoagulation, and the relationship between standard measures of anticoagulation (INR, activated partial thromboplastin time [APTT]) and drug levels is nonlinear and thus not helpful in determining the extent of anticoagulation.[16-19] These tests, however, can be used to assess medication adherence or to assess if the active drug is likely to be in the circulation. INR and APTT levels would be elevated if the drug is present; normal levels of these parameters would suggest very little if any active drug is present, making it safe to have surgery or invasive procedures.

Clinical trials

The RE-LY study was the first study of a NOAC to be published.[12] It evaluated dabigatran use in patients with NVAF who had one or more risk factors for stroke. An open-label PROBE design with the primary endpoints of stroke and systemic embolism was used to test the efficacy and safety of two doses of dabigatran against warfarin, with a target INR of two to three. Pleasingly, both the 110 mg twice daily and 150 mg twice daily doses of dabigatran reduced the incidence of intracranial haemorrhage when compared with warfarin. The higher dose was

shown to be superior to warfarin in reducing stroke and systemic embolism, and in particular there was a significant reduction in ischaemic stroke compared with warfarin. Patients taking this higher dose had comparable bleeding to patients taking warfarin, but post hoc analysis revealed gastrointestinal bleeding rates were higher in patients aged more than 75 years with dabigatran.[20] As a result, it is recommended that the lower 110 mg twice-daily dosing schedule be used in this age group of patients in Australia. The lower dose was shown to be noninferior to warfarin in reducing stroke and embolism in patients with NVAF and had lower rates of bleeding, although this advantage was attenuated in patients who were more than 75 years of age or those who had moderate degrees of renal impairment.[20]

The ROCKET AF study examined rivaroxaban versus warfarin in patients with two or more risk factors for stroke, and the average $CHADS_2$ score in this study was 3.5, compared with the mean score of 2.1 in both the major dabigatran and apixaban trials.[13] In the ROCKET AF trial, there was an even lower warfarin time in therapeutic range (TTR) of 55% in the warfarin-treated group, perhaps because of an increased number of patients with heart failure compared with the other studies, compounded by a different means of calculating the TTR. Most patients received the full 20 mg once daily dose but a dose reduction to 15 mg was prescribed to patients with impaired renal function and a creatinine clearance of less than 50 mL/min. Both doses showed similar efficacy to warfarin in reducing stroke and systemic embolism, and there were similar bleeding rates, although there was an excess in major and nonmajor clinical gastrointestinal bleeding in patients on rivaroxaban compared with warfarin. Despite this, both doses, as with dabigatran and apixaban, showed a significant reduction in intracranial haemorrhage and a trend towards a decrease in all-cause mortality. In prespecified statistical analysis and on-treatment safety analysis, rivaroxaban showed superiority to warfarin in terms of its primary endpoint, but this claim was not accepted by regulatory authorities in Australia or the USA, where the medication has been registered on the basis of noninferiority.

The ARISTOTLE study looked at a similar population of patients with NVAF as the RE-LY study.[14] This was a double-blind, double-dummy trial that randomly assigned patients to treatment with apixaban or dose-adjusted warfarin. Inclusion criteria for eligibility required patients to have one or more risk factors for stroke. As mentioned above, the average $CHADS_2$ scores in the RE-LY and ARISTOTLE trials were identical, at 2.1. In addition, the TTR for warfarin in the ARISTOTLE study was similar to that in the RE-LY trial, at 62% and 64%, respectively. Apixaban was given at 5 mg twice daily to 95% of participants, but a dose reduction to 2.5 mg twice daily was used in a small number of patients who had two criteria out of age more than 80 years, serum creatinine greater than 133 mg/dL or body weight greater than 65 kg. The main outcomes of the study showed that apixaban was superior to warfarin in reducing stroke and systemic embolism, driven primarily by a reduction in haemorrhagic stroke. Reduction in ischaemic stroke was similar for apixaban and warfarin. Major and clinically relevant nonmajor bleeding was significantly less with apixaban than with warfarin, and intracranial haemorrhage was also significantly reduced. Although there were strong trends for reduced total mortality with dabigatran and rivaroxaban compared with warfarin, apixaban was the only NOAC that showed a statistically significant difference in this regard ($p = 0.048$).

Bleeding

When any antithrombotic agent is used, whether it be aspirin alone, dual antiplatelet therapy or anticoagulation with warfarin or one of the newer agents, there is an increased risk of bleeding. Although bleeding in patients taking anticoagulants is usually minor, major haemorrhage can be life-threatening or fatal. It is difficult to compare the bleeding rates between the different NOACs because, although the primary endpoint for efficacy in all three trials was the same, different definitions for bleeding were used. Bleeding was extensively evaluated as a key safety outcome in all the clinical trials of the novel therapies, and bleeding rates were either comparable to or better than those seen with warfarin.[21] If bleeding did occur, however, outcomes were generally better for patients taking the novel agent compared with those taking warfarin, despite the lack of a reversal agent being available until recently.[22-23]

New reversal agents for oral anticoagulants

One of the concerns in clinical practice with the introduction of the NOACs is that there has been no reversal agent available for any of them in the event of overdose or catastrophic bleeding. Recently, idarucizumab, a specific reversal agent for dabigatran, became available. It is a monoclonal antibody specifically targeting free or thrombin-bound dabigatran. The RE-VERSE AD study, an update of which was recently published, showed idarucizumab to be efficacious.[24,25] In this study, idarucizumab was given to patients on dabigatran who were bleeding or in whom urgent surgery was required. Given in two 2.5 g boluses over several minutes, it reduces the plasma levels of dabigatran within minutes for a prolonged period of time. It is now available in Australia, is approved by the TGA and is used in many emergency departments and hospitals.

Andexanet-alfa is a reversal agent for factor Xa inhibitors that is undergoing phase III clinical trials. It has the potential to block the anticoagulant effects of rivaroxaban, apixaban, edoxaban and low-molecular-weight heparins. Preliminary data on the effect of andexanet-alfa infusion in patients who were bleeding while taking rivaroxaban and apixaban show it reduced levels of both circulating NOACs, but when the infusion stopped the levels started to rise again.[26] Bleeding was more manageable when andexanet-alfa was used in this context, but its use in patients who require urgent surgery while taking factor Xa inhibitors has not been evaluated. This agent has been approved for reversal in the USA by the FDA, but is still several years away from being approved and available in Australia.

Conclusion

The current European AF guidelines recommend that men who have a CHA_2DS_2-VASc score of two or more and women whose score is three or more should be anticoagulated to reduce stroke risk if they

have NVAF, and the European Society of Cardiology has strongly recommended the NOACs over warfarin for this indication. Depending on the agent used and dose chosen, all the NOACs were shown to be superior to or noninferior to warfarin in reducing stroke and systemic embolism in NVAF. With respect to bleeding, superiority or noninferiority compared with warfarin has also been shown, but it is difficult to compare bleeding rates between the studies because the definitions for bleeding were different. All the new agents at all doses significantly reduced intracranial bleeding compared with warfarin.

The NOACs are now available for stroke prevention in patients with NVAF and have triggered a paradigm shift in treatment philosophy in this area. Most governing bodies are now actively encouraging treating physicians to consider which patients with NVAF do not require anticoagulation, rather than focusing on those who do require it. All the new agents are more effective or similar to warfarin in terms of stroke reduction and bleeding, and our expectation is that they will in time replace warfarin for stroke prevention in patients with NVAF. Warfarin will still be needed for patients who have valvular AF and those who have NVAF with severe renal dysfunction (creatinine clearance, <25 to 30 mL/min), but in future the NOACs should be the predominant therapy for stroke prevention in patients with NVAF, given the impressive safety and efficacy results of the various clinical trials and the greater patient tolerability of these new agents compared with warfarin. **CT**

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