NOACs in cardiovascular disease

What is their role?

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The nonvitamin K antagonist oral anticoagulants (NOACs) dabigatran, rivaroxaban and apixaban overcome many of warfarin's limitations and are available for use for the prevention of stroke in atrial fibrillation and the prevention and treatment of venous thromboembolism.

Thrombosis is the event that leads to most deaths and ill health globally. In addition to its role in instigating myocardial infarction, stroke and pulmonary embolism, thrombosis is also a common cause of mortality and morbidity in patients with sepsis and malignancy. Accordingly, antithrombotic therapies have a major role in reducing the burden of thrombotic disease.

Antithrombotic drugs fall into the two broad categories of those that inhibit platelet function and those that reduce fibrin generation. Of those that reduce fibrin generation, vitamin K antagonists (VKAs) such as warfarin have been the only orally active drugs available until recently. Although warfarin is highly effective in the management of thromboembolism, its use is limited by a narrow therapeutic index, the need for frequent monitoring and multiple drug and food interactions. The non-VKA oral anticoagulants (NOACs) overcome many of these limitations and are available for use in several thrombotic conditions.

NOACs reduce fibrin formation by inhibiting thrombin directly (direct thrombin inhibitors) or the enzyme responsible for thrombin formation (factor Xa inhibitors). Dabigatran is the only direct thrombin inhibitor available in Australia. Two of the three factor Xa inhibitors with published phase 3 trial results, rivaroxaban and apixaban, are available in Australia; the other, edoxaban, has recently become available in the USA. Other factor Xa inhibitors (such as betrixaban) are in a late stage of development. NOACs have been studied for the prevention and treatment of venous thromboembolism (VTE), the prevention of stroke in patients with atrial fibrillation (AF) and the reduction of recurrent cardiac events following an acute coronary

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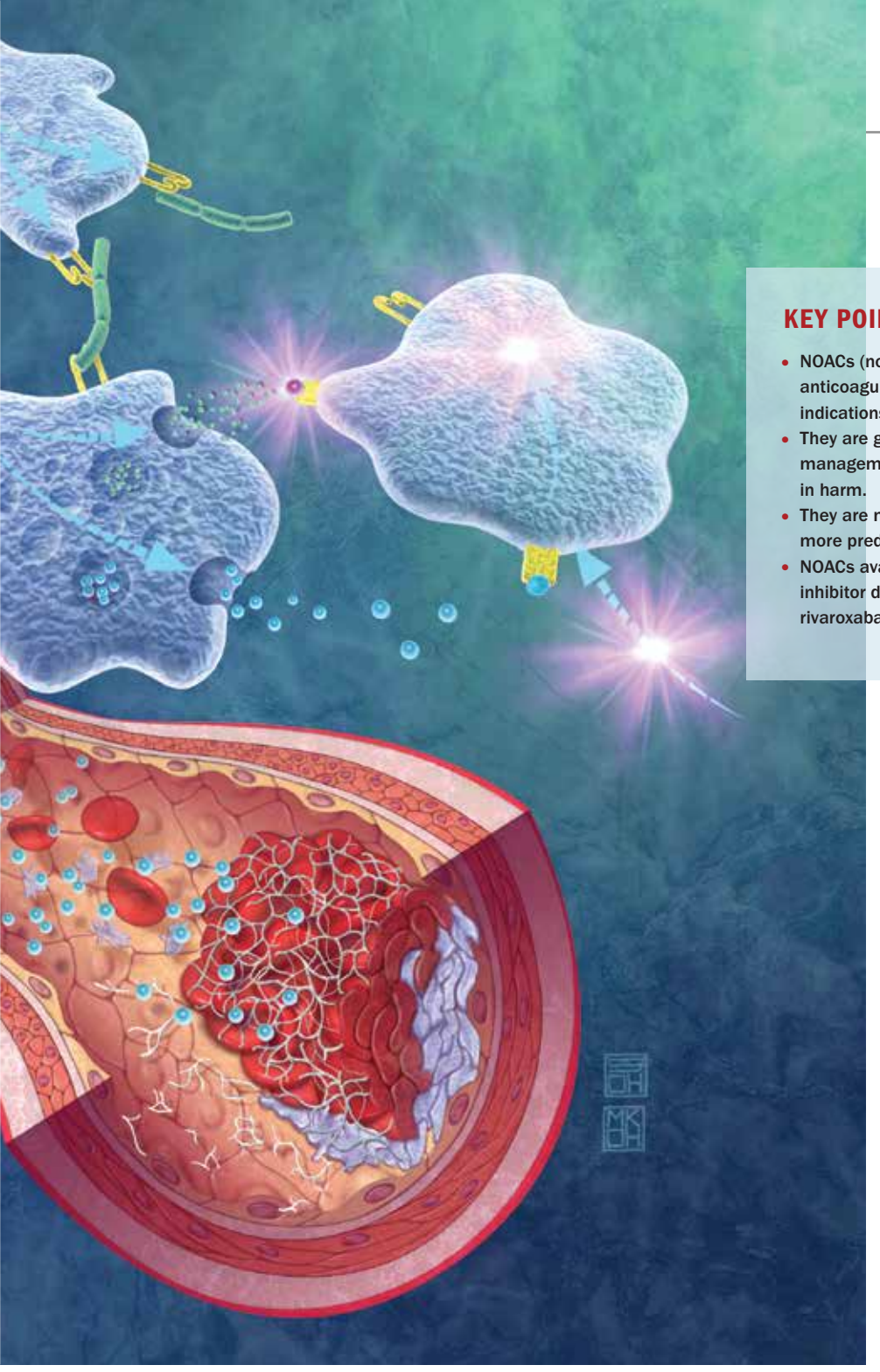

KEY POINTS

- NOACs (nonvitamin K antagonist oral anticoagulants) are available for a range of indications.
- They are generally as effective as warfarin in the management of thromboembolism with no increase in harm.
- They are much easier to use than warfarin due to more predictable pharmacodynamics.
- NOACs available in Australia are the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban and apixaban.

syndrome. The evidence supporting the Therapeutics Goods Administration (TGA)-approved indications for dabigatran, rivaroxaban and apixaban is reviewed in this article.

NOACs for stroke prevention in atrial fibrillation

AF is the most common sustained arrhythmia and its prevalence increases with advancing age, with more than one-third of patients being 80 years or older.[1] Nonvalvular AF is associated with a five-fold increased risk of stroke.[2] Strokes due to AF are associated with a higher risk of death and disability than other causes of stroke, and stroke prevention is a major component of the management of patients with this condition. Individuals in whom oral anticoagulation (OAC) should be used to prevent stroke are identified by assessing their stroke and bleeding risks.

Stroke risk stratification in patients with nonvalvular AF can be performed using the CHADS2 and CHA2DS2-VASc scores. Although the CHADS2 score is accurate in identifying patients with a high risk of stroke, it is poor at identifying those with a very low risk of stroke. The CHA2DS2-VASc score, however, is highly sensitive, and the annual stroke rate for patients with a score of 0 is negligible (Tables 1 and 2).[3] OACs can therefore safely be withheld in patients with a CHA2DS2-VASc score of 0 and are recommended in those with a score of 1 or more (unless the only risk factor is female sex). For this reason, CHA2DS2-VASc is now the preferred scoring system.

The HAS-BLED score helps quantify bleeding risk (Table 3). The main utility of this score is to identify modifiable risk factors for bleeding, the correction of which may make OAC use safer. An example of this is that uncontrolled hypertension has a higher risk of bleeding during OAC than treated hypertension, so severe hypertension should be controlled prior to the commencement of an OAC. A high HAS-BLED score (over 3) is not a contraindication to OAC.

Warfarin has proven benefit in patients with AF and increased stroke risk, with relative risk reductions of stroke and death

TABLE 1. CHA2DS2-VASC SCORE

Risk factor	Score (maximum 9)*
C – Congestive heart failure	1
H – Hypertension	1
A2 – Age 75 years or older	2
D – Diabetes mellitus	1
S2 – Stroke, transient ischaemic attack or thromboembolism	2
V – Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
A – Age 65 to 74 years	1
Sc – Sex category (i.e. female)	1

* Maximum score is 9; for age, either the patient is 75 years or older and gets two points, is between 65 and 74 and gets one point, or is under 65 years and does not get any points.

TABLE 2. CHA2DS2-VASC SCORE AND STROKE RATE

CHA2DS2-VASc score	Stroke rate (% per year)
0	0
1	1.3
2	2.2
3	3.2
4	4
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

of 64% and 25%, respectively.[4] These results hold true in the elderly: the BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) study evaluated the efficacy of warfarin compared with the antiplatelet agent aspirin among patients aged over 75 years and showed that warfarin was superior in preventing stroke or systemic embolism without a significant increase in bleeding risk.[5]

Three large randomised controlled trials (RE-LY, ROCKET-AF and ARISTOTLE) compared adjusted-dose warfarin with dabigatran, rivaroxaban and apixaban, respectively (Box).[6-8] The salient results of each study are presented in Figure 1.

Direct comparison of these trials is difficult because their design and end-point definitions varied and differences in sample sizes provided different powers to detect statistical significance. However, the trial results are remarkably concordant, showing that NOACs are at least noninferior to warfarin for prevention of stroke and systemic embolism and at least as safe. It is therefore reasonable in clinical practice to use any of these drugs at the recommended doses shown in Table 4; dabigatran, rivaroxaban and apixaban are PBS listed for use in Australia for prevention of stroke and systemic embolism in patients with nonvalvular AF and at least one additional risk factor for stroke. When these trials were meta-analysed, NOAC use was found to be associated with less stroke, important bleeding and death than warfarin use. A major benefit of NOAC use is a substantial protection against haemorrhagic stroke. It is important to be aware that when bleeding occurs, it is most likely to involve the gastrointestinal tract. NOACs are renally excreted and should not be used if the calculated creatinine clearance is less than 30 mL/min for dabigatran and rivaroxaban and 25 mL/min for apixaban.

Patients with valvular AF (mechanical heart valves or haemodynamically significant mitral stenosis) were excluded from all three major trials; therefore, these patients should be managed with warfarin. The RE-ALIGN trial, which compared dabigatran with warfarin in patients with mechanical heart valves, was ceased because of increased strokes, MI and valvular

TABLE 3. HAS-BLED SCORE

Risk factor	Score (maximum 9)
H – Hypertension (systolic BP over 160 mmHg)	1
A – Abnormal liver or renal function (1 point each)	1 or 2
S – Stroke	1
B – Bleeding history	1
L – Labile INRs	1
E – Elderly (age over 65 years)	1
D – Drugs* or alcohol (1 point each)	1 or 2

* Concomitant use of drugs that promote bleeding.
Abbreviations: BP = blood pressure; INR = international normalised ratio.

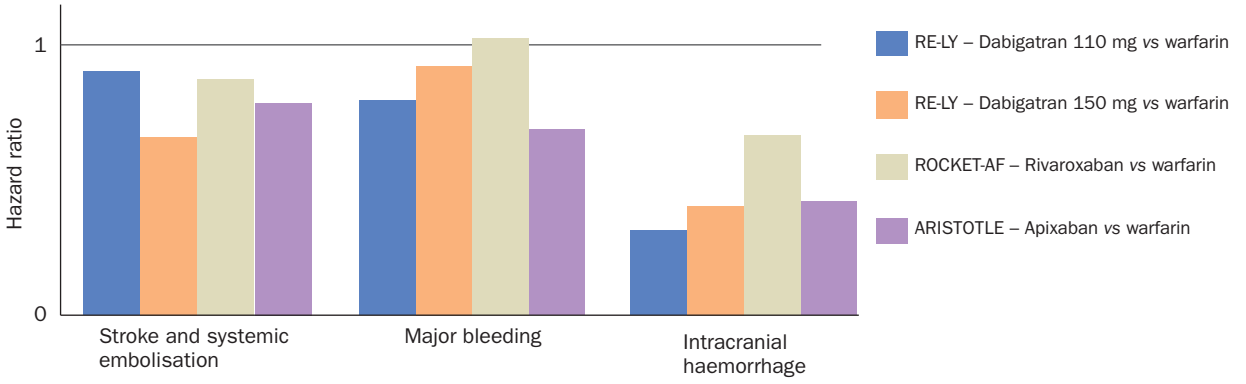

Figure 1. Trials of NOACs versus warfarin in nonvalvular atrial fibrillation: relative risk of outcomes (hazard ratios).[6-8] Use of a NOAC for prevention of stroke or systemic embolism is associated with less stroke, important bleeding and death than use of warfarin.

Abbreviation: NOAC = nonvitamin K antagonist oral anticoagulant.

thrombosis in the dabigatran group, confirming that warfarin remains the optimal therapy for these patients (Box).[9]

NOACs for VTE prophylaxis after hip or knee replacement

Numerous randomised trials and meta-analyses have compared the efficacy and safety of factor Xa and direct thrombin inhibitors with conventional VTE prophylaxis in patients following total hip or knee replacement.[10,11] These studies show that NOACs are slightly more efficacious in preventing VTE than standard therapy with low molecular weight heparin, with no increase in major bleeding but with a trend towards more clinically relevant bleeding. Extending thromboprophylaxis for up to 35 days is recommended for patients undergoing hip replacement.[12] NOACs have the advantage over the parenteral agent heparin of being easier to administer and therefore have better patient acceptability during the outpatient

1. NOAC TRIALS

- AMPLIFY
  - 'Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy' trial[21]
- AMPLIFY-EXT
  - apixaban compared with placebo for extended treatment of VTE[26]
- ARISTOTLE
  - 'Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF' trial; compared adjusted-dose warfarin with apixaban[8]
- EINSTEIN-DVT
  - 'Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients with Acute Symptomatic Deep Vein Thrombosis – The EINSTEIN DVT Study'[19]
- EINSTEIN-PE
  - 'Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients with Acute Symptomatic Pulmonary Embolism – The EINSTEIN PE Study'[20]
- EINSTEIN-EXT
  - rivaroxaban compared with placebo after symptomatic VTE for extended treatment of VTE[19]
- RE-COVER I
  - compared six months of treatment with dabigatran and adjusted-dose warfarin in the treatment of acute VTE[17]
- RE-COVER II
  - same as RE-COVER I[18]
- RE-LY
  - 'Randomised Evaluation of Long-term Anticoagulant Therapy' trial; compared adjusted-dose warfarin with dabigatran[6]
- RE-MEDY
  - dabigatran compared with warfarin for extended treatment of VTE[27]
- RE-SONATE
  - dabigatran compared with placebo for extended treatment of VTE[27]
- ROCKET-AF
  - 'Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF'; compared adjusted dose warfarin with rivaroxaban[7]

Abbreviations: AF = atrial fibrillation; DVT = deep vein thrombosis; NOAC = nonvitamin K antagonist oral anticoagulant; PE = pulmonary embolism; VTE = venous thromboembolism.

phase of extended duration prophylaxis. The recommended doses of NOACs for VTE prophylaxis are shown in Table 5; dabigatran, rivaroxaban and apixaban are PBS listed for use in Australia for prevention of VTE after total hip or knee replacement.

Trials performed in medically ill patients have compared extended-duration rivaroxaban and apixaban with enoxaparin for VTE prophylaxis.[13,14] Although the NOACs were noninferior to subcutaneous enoxaparin for VTE prevention, the risk of clinically relevant bleeding was significantly higher and hence they are not recommended in medical patients.

TABLE 4. RECOMMENDED NOAC DOSAGE REGIMENS FOR STROKE PROPHYLAXIS IN PATIENTS WITH NONVALVULAR AF (PBS-LISTED DRUGS)*

Drug	Dose	Dose reduction
Dabigatran	150 mg twice daily	110 mg if age ⩾75 years or CrCl 30 to 50 mL/min
Rivaroxaban	20 mg daily	15 mg daily if CrCl 30 to 49 mL/min
Apixaban	5 mg twice daily	2.5 g twice daily in patients with two or more of: age ⩾80 years, weight ⩽60 kg or serum creatinine ⩾133 µmol/L

* PBS Authority Required (streamlined) category.
Abbreviations: AF = atrial fibrillation; CrCl = creatinine clearance; NOAC = nonvitamin K antagonist oral anticoagulant; PBS = Pharmaceutical Benefits Scheme.

NOACs for acute VTE treatment

VTE develops in one to two adults per 1000 annually.[15,16] About one-third of patients with symptomatic VTE present with pulmonary embolism (PE) and the remainder with deep vein thrombosis (DVT). Anticoagulation with initial low molecular weight heparin followed by warfarin is the conventional standard of care for patients with acute VTE.

Treatment of acute VTE with dabigatran, rivaroxaban and apixaban were compared with conventional treatment in

the RE-COVER I and II, EINSTEIN-DVT and PE and AMPLIFY trials, respectively (Box).[17-21] The salient results are shown in Figure 2. Dabigatran was administered after an initial course of at least five days of low molecular weight heparin; rivaroxaban and apixaban were used as monotherapy, with no initial low molecular weight heparin, which greatly simplifies treatment.

The consistency of findings across the trials is reassuring and suggests that, as a class, NOACs are noninferior to conventional therapy for treatment of patients with acute VTE. The rates of recurrent VTE during six months of treatment – the primary outcome of the trials – with the NOACs are similar to those with conventional therapy in patients with PE or DVT. Regarding the safety outcomes of the trials, rates of major bleeding are significantly lower with rivaroxaban and apixaban than with conventional therapy, and with the exception of rivaroxaban, the rates of the composite of major or clinically relevant nonmajor bleeding also are significantly lower with the NOACs than with conventional therapy. These positive findings, coupled with their marked ease of use, have made NOACs the first-line choice of treatment for patients with acute VTE in many centres.

TABLE 5. RECOMMENDED NOAC DOSAGE FOR VTE PROPHYLAXIS AFTER TOTAL HIP OR KNEE REPLACEMENT (PBS-LISTED DRUGS)*

Drug	Dose	Duration
Dabigatran	110 mg twice daily; 75 mg twice daily for CrCl 30 to 50 mL/min	10 days for knee replacement; 28 to 35 days for hip replacement
Rivaroxaban	10 mg daily	Up to 2 weeks for knee replacement; up to 5 weeks for hip replacement
Apixaban	2.5 mg twice daily	10 to 14 days for knee replacement; 32 to 38 days for hip replacement

* PBS Authority Required (streamlined) category.
Abbreviations: CrCl = creatinine clearance; NOAC = nonvitamin K antagonist oral anticoagulant; PBS = Pharmaceutical Benefits Scheme; VTE = venous thromboembolism.

Both rivaroxaban and apixaban are TGA approved for the treatment of acute VTE but only rivaroxaban is listed on the PBS for this use. The dosing schedule for rivaroxaban is shown in Table 6.

Patients with acute VTE requiring systemic or catheter-directed thrombolytic therapy were excluded from trials of treatment with NOACs and hence should not receive NOACs. Patients with active cancer or the antiphospholipid syndrome are a high-risk group that had insufficient representation in the NOAC trials; these patients should generally be treated with conventional anticoagulation until further data become available.

NOACs – for extended VTE treatment

Studies have shown that within one year of stopping anticoagulant therapy, the cumulative incidence of recurrent VTE events is approximately 3% when VTE occurs in association with a major, removable risk factor (usually defined as recent major surgery, major trauma or fracture, pregnancy, puerperium or hormonal therapy), 15% when unprovoked and up to 27% when VTE is associated with active cancer.[22-24] Hence, current clinical practice guidelines recommend anticoagulation for the following periods:[12]

- three months for patients with VTE

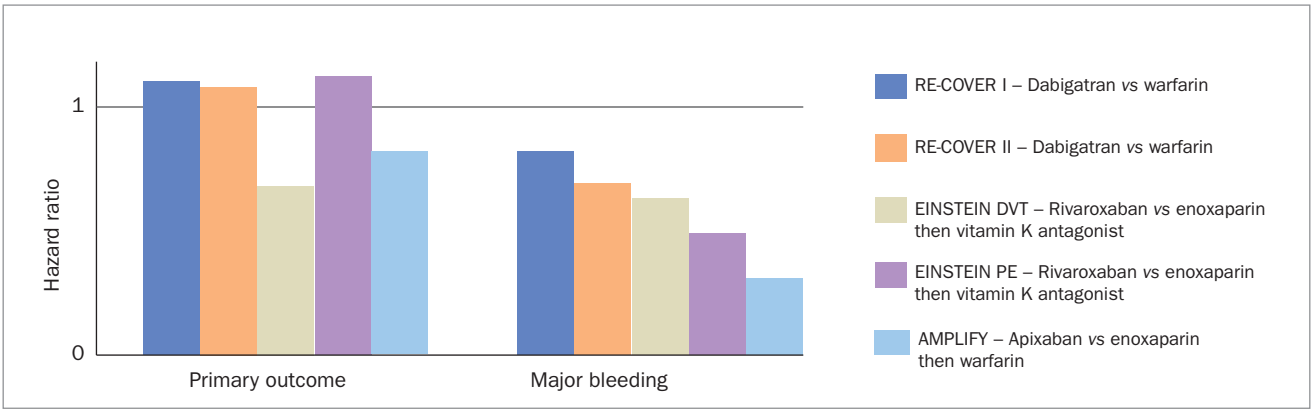

Figure 2. Trials of NOACs versus warfarin in acute VTE: relative risk of outcomes (hazard ratios).[17-21] Rates of recurrent VTE (primary outcome) with the NOACs are similar to those with conventional therapy, and rates of major bleeding (one of the safety outcomes) are significantly lower with rivaroxaban and apixaban than with conventional therapy.
Abbreviations: NOAC = nonvitamin K antagonist oral anticoagulant; VTE = venous thromboembolism.

TABLE 6. RECOMMENDED NOAC DOSAGE FOR VTE TREATMENT (PBS-LISTED DRUGS)*

Drug	Dosage
Acute treatment	
Rivaroxaban	15 mg twice daily for 3 weeks†
Extended treatment	
Rivaroxaban	20 mg daily

PBS Authority Required (streamlined) categories.
† Then 20 mg daily.
Abbreviations: NOAC = nonvitamin K antagonist oral anticoagulant; PBS = Pharmaceutical Benefits Scheme; VTE = venous thromboembolism.

associated with a transient risk factor
- indefinitely in the presence of a permanent risk factor (e.g. cancer, antiphospholipid syndrome)
- at least three months but possibly indefinitely (based on the individual risk–benefit profile) in patients with unprovoked VTE.

According to these recommendations, a substantial proportion of patients with VTE should receive extended treatment, given that up to 50% of VTE events remain classified as unprovoked and 10 to 20% are associated with cancer.[23,25]

Rivaroxaban, apixaban and dabigatran were compared with placebo in the double-blind EINSTEIN-EXT, AMPLIFY-EXT and RE-SONATE trials, respectively (Box).[19,26,27] Dabigatran is the only agent to be compared with warfarin for extended VTE treatment – in the RE-MEDY trial.[27] The salient results are shown in Figure 3.

Dabigatran, rivaroxaban and apixaban are greatly superior to placebo for the prevention of recurrent VTE and are associated with low rates of major bleeding. The risk reduction for recurrent VTE with the NOACs is far superior to that achieved with aspirin, which has been shown in two recent trials to have a weak but definite effect in this situation. Dabigatran was noninferior to warfarin for extended VTE treatment in the RE-MEDY trial, and was associated with less bleeding.[27]

Only rivaroxaban is listed on the PBS for the extended treatment of VTE and its dosing schedule is shown in Table 6.

Future directions

Many studies are ongoing to further define the value of the NOACs. These include studies in patients with acute coronary syndromes, stable atherosclerotic disease and cancer-associated VTE, and studies of prophylaxis in medical patients and those undergoing dialysis. It is anticipated that there will be a significant expansion in the indications for and availability of NOACs in Australia in the next few years.

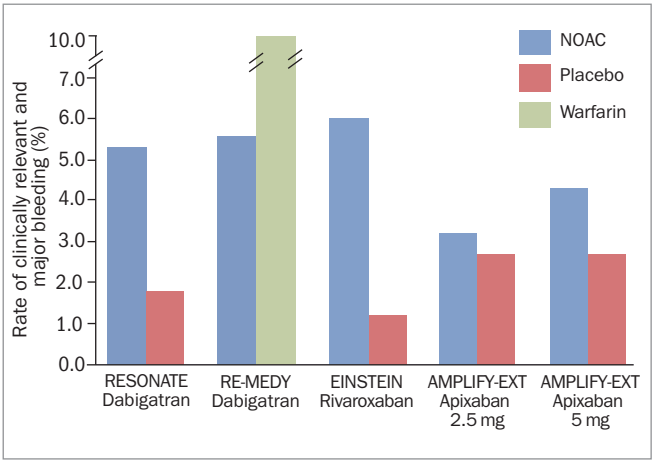

Figure 3. Trials of NOACs in extended VTE treatment: rates of clinically relevant or major bleeding.[19,26,27]

Abbreviations: NOAC = nonvitamin K antagonist oral anticoagulant; VTE = venous thromboembolism.

Conclusion

NOACs are available for use in Australia in a range of thrombotic conditions. The data supporting their use is strong and they offer an alternative to VKAs such as warfarin. Their efficacy, safety, ease of use and favourable pharmacokinetics are likely to see their use expanded in Australia. MT

References

A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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References

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285: 2370-2375.
2. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998; 82(8A): 2N-9N.
3. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. Thromb Haemost 2012; 107: 1172-1179.
4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007; 146: 857-867.
5. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007; 370: 493-503.
6. Connolly SJ, Ezekowitz MD, Yusuf S, et al.; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-1151.
7. Patel MR, Mahaffey KW, Garg J, et al.; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883-891.
8. Granger CB, Alexander JH, McMurray JJ, et al.; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981-992.
9. Van de Werf F, Brueckmann M, Connolly SJ, et al. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: the randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN). Am Heart J 2012; 163: 931-937.e1.
10. Nieto JA, Espada NG, Merino RG, González TC. Dabigatran, rivaroxaban and apixaban versus enoxaparin for thomboprophylaxis after total knee or hip arthroplasty: pool-analysis of phase III randomized clinical trials. Thromb Res 2012; 130: 183-191.
11. Neumann I, Rada G, Claro JC, et al. Oral direct factor Xa inhibitors versus low-molecular-weight heparin to prevent venous thromboembolism in patients undergoing total hip or knee replacement: a systematic review and meta-analysis. Ann Intern Med 2012; 156: 710-719.
12. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ, American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141(2 Suppl): 7S-47S.
13. Cohen AT, Spiro TE, Spyropoulos AC, MAGELLAN Steering Committee. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med 2013; 368: 1945-1946.
14. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al.; ADOPT Trial Investigators. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med 2011; 365: 2167-2177.
15. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost 2000; 83: 657-660.
16. Spencer FA, Emery C, Lessard D, et al. The Worcester Venous Thromboembolism study: a population-based study of the clinical epidemiology of venous thromboembolism. J Gen Intern Med 2006; 21: 722-727.
17. Schulman S, Kearon C, Kakkar AK, et al.; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009; 361: 2342-2352.
18. Schulman S, Kakkar AK, Goldhaber SZ, et al.; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014; 129: 764-772.
19. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363: 2499-2510.
20. EINSTEIN–PE Investigators, Büller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012; 366: 1287-1297.
21. Agnelli G, Buller HR, Cohen A, et al.; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013; 369: 799-808.
22. Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. Arch Intern Med 2010; 170: 1710-1716.
23. Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica 2007; 92: 199-205.
24. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Büller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol 2000; 18: 3078-3083.
25. Lee AY, Levine MN. Venous thromboembolism and cancer: risks and outcomes. Circulation 2003; 107(23 Suppl 1): 17-21.
26. Agnelli G, Buller HR, Cohen A, et al.; PLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013; 368: 699-708.
27. Schulman S, Kearon C, Kakkar AK, et al.; RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013; 368: 709-718.