



Australian Government

Department of Health and Ageing

**Issues and Options Paper:
Review of Anticoagulation Therapies in Atrial
Fibrillation**

Paper-based publications

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Stakeholders can provide comment on this Issues and Options Paper through two avenues: the stakeholder forum; and/or written comment.

The stakeholder forum is being held in Canberra on 4 July 2012. To register your interest to attend or for further details please visit www.pbs.gov.au.

If you would like to comment in writing please:

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Acronyms and abbreviations

AF	atrial fibrillation
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
CADTH	Canadian Agency for Drugs and Technologies in Health
CHADS ₂	score for stratification of stroke risk based on: cardiac failure, hypertension, age 75 years or over, diabetes mellitus, prior stroke or transient ischaemic attack (2 points)
CHA ₂ DS ₂ -VASc	score for stratification of stroke risk based on: cardiac failure, hypertension, age of 75 years or over (2 points), diabetes mellitus, prior stroke or transient ischaemic attack (2 points), vascular disease, age 65–74 years, sex (female)
COX-2	cyclooxygenase two
CrCL	creatinine clearance
cTTR	centre's mean TTR (time in therapeutic range)
CYP	cytochrome P450
FDA	United States Food and Drug Administration
HAS-BLED	score for stratification of bleeding risk based on: hypertension; abnormal renal and liver function (1 point each); stroke; bleeding; labile INRs; elderly (e.g. age 65 years or over); drugs or alcohol (1 point each)
ICH	intracranial haemorrhage
INR	international normalised ratio
MBS	Medicare Benefits Schedule
NOAC(s)	novel/new oral anticoagulant(s)
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
RE-LY	Randomised Evaluation of Long-Term Anticoagulation Therapy (pivotal trial of dabigatran)
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
TGA	Therapeutic Goods Administration
TTR	time in therapeutic range
VKORC1	vitamin K epoxide reductase complex subunit 1

Executive summary

In September 2011, the Australian Government announced a review of options for improving the health outcomes of people treated for atrial fibrillation (AF) with anticoagulation therapies — the Review of Anticoagulation Therapies in Atrial Fibrillation (the Review).

AF is a common form of irregular heart beat (cardiac arrhythmia). It has been estimated that, in Australia, between approximately 240,000 and 400,000 people have this condition. AF increases the risk of ischaemic stroke by around five-fold; strokes in patients with AF are more severe than other types of ischaemic stroke, and result in greater morbidity and mortality. Therefore, an important aspect of the management of AF is the management of stroke risk. For many years, this has been achieved predominantly by prophylactic anticoagulant therapy with warfarin. Although this therapy is effective and cost-effective, there are some drawbacks (including the need for monitoring and the increased risk of bleeding). However, recently, new oral anticoagulants have been developed.

The purpose of the Review is to inform the government of options for optimising the use of currently available treatments in Australia (i.e. warfarin), as well as options for the future use of newer therapies.

The announcement of the Review followed a Pharmaceutical Benefits Advisory Committee (PBAC) recommendation in 2011 that a new oral anticoagulant, dabigatran, was suitable for inclusion on the Pharmaceutical Benefits Scheme for the prevention of stroke or embolism in certain groups of people with AF. However, in making their recommendation, PBAC noted a number of cost implications and other clinical issues in relation to the use of dabigatran. These issues prompted the Review.

From December 2011 to February 2012, the Australian Government Department of Health and Ageing invited interested parties and individuals to provide written submissions to the Review, and received 64 submissions.

Many of the submissions identified that the current anticoagulation therapy for AF, warfarin, is highly effective at preventing strokes. A number of the submissions identified the increasing prevalence of AF in Australia. They also highlighted that a large number of people are not currently being diagnosed or treated with anticoagulant therapy, even though warfarin has been shown to be highly effective.

The inconvenience of regular monitoring with warfarin was identified as an issue. Options to address this included government subsidisation of point-of-care testing in anticoagulation clinics, general practice surgeries, residential aged-care facilities and/or pharmacies, particularly in rural areas. Some submissions also suggested subsidising other agents that do not require regular blood monitoring.

Underuse of warfarin was also raised as a major issue. Options to address this included the development of national guidelines, improved patient and prescriber education of the relative risks and benefits of warfarin therapy prescriber incentives and consumer support programs, including targeting pharmacist home medicines reviews to patients receiving warfarin.

Other issues identified with warfarin were the reported medicine and food interactions, the intra- and intersubject variability of patient response, the reluctance or refusal of patients to take warfarin and the number of patients with contraindications to warfarin.

Another issue raised in submissions was the incidence of bleeding within the brain (intracranial haemorrhage) and the trial evidence supporting a reduction in intracranial haemorrhage with the new oral anticoagulants. Intracranial haemorrhage was seen as a ‘catastrophic’ side effect.

Submissions identified a number of issues with the new oral anticoagulants, mainly focusing on safety. For example, many submissions raised concerns about the adverse event profiles of the new anticoagulants in the long term and in the clinical (nontrial) patient population, which may be different to those patients selected for clinical trials. The use of dabigatran in patients with reduced kidney function and the lack of antidote for bleeding with dabigatran were also raised in many submissions. Options identified by submitters to address these concerns included improved postmarket surveillance and a cautious approach to the introduction of new agents.

This Issues and Options Paper is not a technical paper, and does not contain any recommendations. Its purpose is to collate the issues that were identified in the submissions and the options that were proposed to address these issues. To assist readers prepare a response to these issues and options, this paper also provides a series of focus questions. Responses to the focus questions will inform the development of recommendations for the final report of the review.

PART 1

Background

1 About the review

1.1 Review of Anticoagulation Therapies in Atrial Fibrillation

On 30 September 2011, the Australian Government announced that it would commission Emeritus Professor Lloyd Sansom AO, the former chair of the Pharmaceutical Benefits Advisory Committee (PBAC), to inform the government on options for improving the health outcomes of people treated for atrial fibrillation (AF) with anticoagulation therapies. The purpose of the Review of Anticoagulation Therapies in Atrial Fibrillation (the Review) is to inform the government of options for optimising the use of currently available treatments in Australia (i.e. warfarin) as well as options for the future use of newer therapies, such as dabigatran (Pradaxa[®]), in the treatment of AF. Further details are on the Review website.*

1.1.2 Terms of reference for the Review

The terms of reference for the Review are:

- a. To report on current and future options for improving the health outcomes of patients with AF treated with oral anticoagulants.
- b. To report on modes of health system delivery that may be used to optimise the use of currently available anticoagulants.
- c. To report to what extent optimisation of the use of currently available anticoagulant treatments used in patients with AF would improve health outcomes and at what cost.
- d. To examine the future role of newer anticoagulant therapies for AF.
- e. To report on any other matter relevant to items a–d above and on any other matters referred to it by the minister.

1.2 PBAC consideration of dabigatran

In March 2011, PBAC recommended that a new oral anticoagulant, dabigatran, was suitable for inclusion on the Pharmaceutical Benefits Scheme (PBS) for the prevention of stroke or embolism in certain groups of people with AF. However, in making their recommendation, PBAC noted that:

- dabigatran represented a cost-effective therapy and its use could lead to reductions in morbidity
- the opportunity cost to the Australian Government of listing dabigatran would be significant
- dabigatran derived its advantages when compared to warfarin when warfarin is used suboptimally
- a number of people who are reluctant to take warfarin because of stringent monitoring requirements and interactions with other medicines and foods — but who should be taking oral anticoagulation — would now be treated with dabigatran, which would likely lead to additional benefits and costs not measured in the trial
- low-risk people currently managed on aspirin or no treatment may be unnecessarily transferred to dabigatran.

* <http://www.pbs.gov.au/info/publication/factsheets/shared/anticoagulation-review>

Comprehensive details of PBAC's recommendation in relation to dabigatran can be found in the public summary document on the Australian Government Department of Health and Ageing website.[†]

1.3 Stakeholder submissions

The Australian Government Department of Health and Ageing invited interested parties and individuals to provide written submissions to the Review. The submission period was between 22 December 2011 and 23 February 2012. At this time, the only new oral anticoagulant that had been considered by PBAC was dabigatran. The department received 64 submissions.

A variety of views were put forward in the submissions by a range of stakeholder groups, and there was some consistency in issues and options identified by particular stakeholder groups:

- 15 submissions were from consumers, all of whom were taking dabigatran
- 20 submissions were from health care professionals, with many of these supportive of listing dabigatran on the PBS, primarily due to the inconvenience of regular warfarin monitoring
- 22 submissions were from organisations (such as the Consumers' Health Forum, the National Stroke Foundation, the Royal Australian College of General Practitioners and the Pharmaceutical Society of Australia), the majority of which supported cautious uptake of dabigatran
- 7 submissions were from commercial organisations: 3 submissions from sponsors of new anticoagulants, 1 from the sponsor of warfarin, 2 from manufacturers of point-of-care (portable) warfarin monitors and 1 from a data company.

1.4 Reference group

A reference group has been established to assist in the consideration of matters arising during the review, including in the provision of comments and advice on this Issues and Options Paper and the final report. The reference group consists of experts in the fields of cardiology, haematology, geriatrics, general practice, pharmacy practice, and a nominee from each of Consumers Health Forum and the National Stroke Foundation.

1.5 Structure of this paper

This Issues and Options Paper has three parts:

- **Part 1: Background**
This part includes background information about the review (this Section 1) and an overview of the clinical issues associated with the management of AF, including the risk of stroke (Section 2).
- **Part 2: Current anticoagulant therapies**
This part includes general information about warfarin (Section 3), and a discussion of issues and options for the use of warfarin anticoagulation therapy in AF (Section 4).
- **Part 3: New oral anticoagulants**
This part includes general information about new oral anticoagulants (NOACs; Section 5), and a discussion of issues and options for the use of NOAC therapy in AF (Section 6).

This is not a technical paper and does not contain any recommendations. Rather, its purpose is to collate the issues that were identified in submissions, and the options that were proposed in submissions to address these issues. The paper also provides a series of focus questions that are

[†] <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-dabigatran-march11>

prompts for the reader to consider whether the relevant issues have been identified, and to consider the options outlined in the context of their applicability to the Australian health system, as well as their cost and cost-effectiveness. Responses to the focus questions will inform the development of recommendations for the final report of the Review.

The paper also cross-references the relevant articles that have been identified as part of supporting literature reviews.

2 About atrial fibrillation and stroke

2.1 Atrial fibrillation

AF is a common form of irregular heart beat (cardiac arrhythmia). Approximately 90% of AF patients are considered to have nonvalvular AF with varying risk of strokes.¹ It is noted that the new oral anticoagulants (NOACs) are registered for stroke reductions in patients with nonvalvular AF. People with nonvalvular AF generally present with palpitations, dyspnoea, chest pain, presyncope and syncope (fainting), although approximately 10–30% have no symptoms.² It has also been estimated that around 10–30% of AF cases are undiagnosed.³⁻⁴

AF increases the risk of stroke by about five-fold.⁵ It has been estimated that AF is implicated in 15–25% of all ischaemic strokes and in as many as 35% of strokes in patients over the age of 80.⁶ Other factors have also been identified that further increase the risk of stroke (discussed later).

Strokes in patients with AF are more severe than other types of ischaemic stroke, and result in greater morbidity and mortality.⁶⁻⁷

2.2 Stroke

Stroke is a collection of diseases:

- **small vessel disease**, which is probably best prevented by blood pressure lowering and smoking cessation
- **large vessel disease**, which is best prevented by cholesterol and blood pressure lowering, smoking cessation and antiplatelet therapy
- **cardioembolic stroke**, which is best prevented by anticoagulation therapy
- **other determined conditions**, which are best prevented by treating the index condition (such as vasculitis, syphilis or thrombophilia)
- **haemorrhagic stroke**, which is best prevented by intensively lowering blood pressure and smoking cessation.

The two types of stroke relevant to this review are cardioembolic stroke and haemorrhagic stroke. The latter can be caused by anticoagulants.

2.3 Prevalence of atrial fibrillation

The prevalence of AF is estimated to be between 1% and 2%, and the number of people with stroke has been predicted to grow significantly as the population ages;^{2, 8-10} this was identified in a number of submissions.^{3-4, 11-12} It is estimated that 1 in 20 people over the age of 65 have nonvalvular AF, and this proportion increases to 1 in 10 for people over the age of 75.⁵ The median age of patients with nonvalvular AF is 75 years and 84% of patients with nonvalvular AF are over 65 years old.¹³ Estimates of the prevalence of nonvalvular AF in particular age groups are shown in Table 2.1.

Table 2.1 Prevalence of nonvalvular atrial fibrillation (AF) by age group (including patients who are diagnosed and undiagnosed)

Age group (years)	Prevalence (%) of nonvalvular AF (diagnosed and undiagnosed) ¹⁴	Estimate of total number of people in Australia with nonvalvular AF (at June 2010, includes undiagnosed)
50–59	1.3	36,353
60–69	3.8	80,638
70–79	9.8	123,682
80 and over	13.3	111,392

Source: Adapted from: *Deloitte Access Economics Report, Off Beat: The Case for 21st Century Stroke Prevention*.¹⁴
Total number of people with AF in age group was calculated using Australian Bureau of Statistics data series A3201 (release of June 2010).

It has been estimated that, in Australia, between approximately 240,000 and 400,000 people have AF.⁴ In the United States, it has been projected that there will be a 50% increase in the incidence of AF between 2012 and 2030.¹⁵ Based on these data, it could be projected that there will be 750,000 people in Australia with AF by 2030, with a growing impact on health care services and costs.

2.4 Management of atrial fibrillation

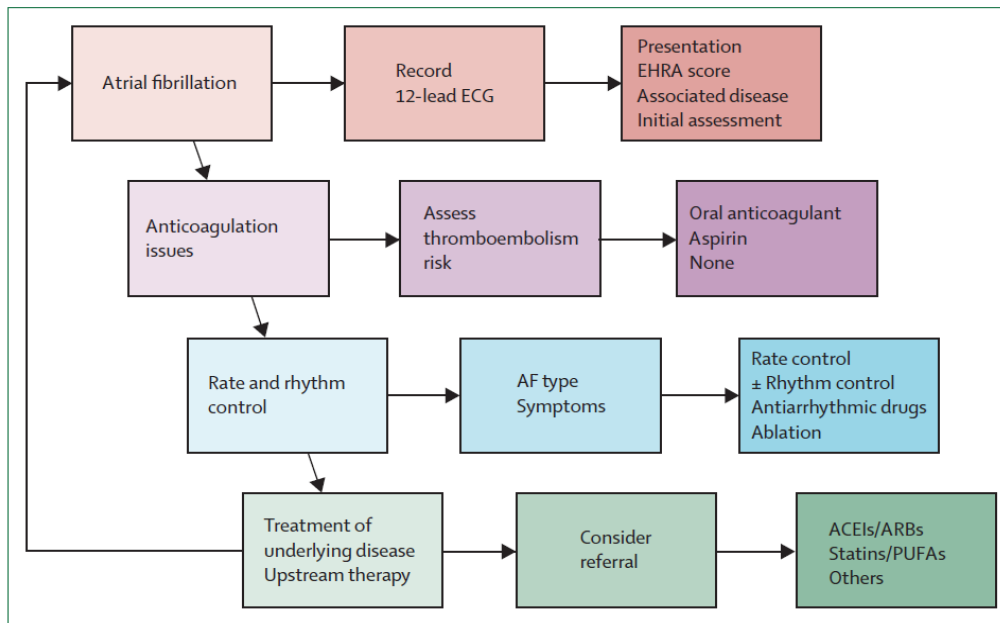
Comprehensive management of AF requires early identification and treatment of predisposing factors and concomitant disorders (such as hypertension and hypercholesterolaemia), which also increase a patient’s risk of stroke and other cardiovascular conditions.¹⁶ Thus, the use of ‘upstream therapies’ (antihypertensives including angiotensin converting enzyme inhibitors and angiotensin-receptor antagonists, and cholesterol-lowering therapies such as statins) may be appropriate.¹⁶ Hypertension is the most common causal risk factor for AF.¹⁶

In addition, overall management of AF may involve consideration of three components, depending on the subtype of a patient’s AF and/or the severity of their AF-related symptoms:

- controlling the heart rate
- controlling the heart rhythm
- stroke prevention.¹⁶

Although stroke prevention is the subject of this review, the management of heart rhythm and/or rate are also important considerations, and these can be controlled with medications, cardioversion or ablation.

A management cascade for patients with AF is shown in Figure 2.1.



ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin-receptor blocker; ECG = electrocardiogram; EHRA = European Heart Rhythm Association; PUFA = polyunsaturated fatty acid
Source: Lip et al (2012)¹⁶

Figure 2.1 Management cascade for patients with atrial fibrillation

2.5 Stroke risk stratification

The magnitude of the increase in stroke risk in patients with AF depends on the presence of other risk factors. Approximately 90% of AF patients have at least one or more additional risk factors for stroke.¹⁷ These additional risk factors can be used to stratify patients into categories of stroke risk, using risk scales such as the CHADS₂ score. The risk factors used to calculate this score are shown in Table 2.2.¹⁸ The higher a patient's CHADS₂ score, then the greater their risk of stroke is, as shown in Table 2.3.

Table 2.2 Calculation of CHADS₂ score

Risk factor	Score
Cardiac failure	1
Hypertension	1
Age of 75 years or over	1
Diabetes mellitus	1
Prior stroke or transient ischaemic attack (TIA)	2
Maximum	6

Source: Adapted from Gage et al (2001)¹⁸

Table 2.3 Stroke risk as a function of CHADS₂ score

CHADS ₂ score	Adjusted stroke rate (% per year without antithrombotic treatment) ^a	Stroke risk
0	1.9	Low
1	2.8	Moderate
2	4.0	High
3	5.9	High
4	8.5	High
5	12.5	High
6	18.2	High

^a The European Society of Cardiology explained the adjusted stroke rate as being 'derived from the multivariable analysis assuming no aspirin usage; these stroke rates are based on data from a cohort of hospitalised AF patients, published in 2001, with low numbers in those with a CHADS₂ score of 5 and 6 to allow an accurate judgment of the risk in these patients. Given that stroke rates are declining overall, actual stroke rates in contemporary non-hospitalized cohorts may also vary from these estimates'.

Source: Adapted from Gage et al (2001)¹⁸, Lip et al (2010)¹⁹ and the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (2010)²⁰

A more recent classification, the CHA₂DS₂-VASc score, incorporates the additional risk factors of vascular disease, age between 65 and 74 years and sex (female), which enables greater stratification at lower levels of risk.²¹ This scale is outlined in Table 2.4 and the associated stroke risk is presented in Table 2.5.

Table 2.4 Calculation of CHA₂DS₂-VASc score

Risk factor	Score
Cardiac failure	1
Hypertension	1
Age of 75 years or over	2
Diabetes mellitus	1
Prior stroke or transient ischaemic attack (TIA)	2
Vascular disease	1
Age 65-74 years	1
Female	1
Maximum	9

Source: Adapted from Lip et al (2010)²¹

Table 2.5 Stroke risk as a function of CHA₂DS₂-VASc score

CHA ₂ DS ₂ -VASc score	Adjusted stroke rate (% per year without antithrombotic treatment) ^a	Stroke risk
0	0.0	Low
1	1.3	Moderate
2	2.2	High
3	3.2	High
4	4.0	High
5	6.7	High
6	9.8	High
7	9.6	High
8	6.7	High
9	15.2	High

^a These are the theoretical thromboembolic event rates without therapy, assuming that warfarin provides a 64% reduction in thromboembolic event risk.

Source: Adapted from Lip et al (2010)¹⁹ and the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (2010)²⁰

These risk stratifications can assist in the determination of which patients to target for anticoagulation therapy balanced against the risk of bleeding with all anticoagulation therapies. For example, of the three major international AF management guidelines identified by Wasmer et al,²² all recommend that patients with low stroke risk (i.e. CHADS₂ = 0 or CHA₂DS₂-VASc = 0) receive either no therapy or aspirin. Anticoagulation therapy is reserved for patients at higher risk (i.e. CHADS₂ or CHA₂DS₂-VASc of 1 or more). Table 2.6 compares the recommendations of the three major international guidelines for patients at different risks of stroke.

Table 2.6 Comparison of recommendations for stroke prophylaxis across three international guidelines

Score	American College of Cardiology Foundation, American Heart Association and Heart Rhythm Society ²³	Canadian Cardiovascular Society ²⁴	European Society of Cardiology ²⁰
CHADS ₂ score = 0	Aspirin	Aspirin or none (no prophylaxis may be appropriate in selected young patients with no stroke risk factors)	Evaluate further with CHA ₂ DS ₂ -VASc score; none or aspirin
CHADS ₂ score = 1	Aspirin or warfarin/dabigatran	Dabigatran/warfarin or aspirin (with dabigatran preferred in most patients)	Evaluate further with CHA ₂ DS ₂ -VASc score
CHADS ₂ score ≥2	Warfarin or dabigatran	Dabigatran or warfarin (with dabigatran preferred in most patients)	Anticoagulation
CHA ₂ DS ₂ -VASc score	Not used	Not used	0 = none 1 = anticoagulation or none >1 = anticoagulation

Source: Wasmer and Eckardt (2011)²²

The CHA₂DS₂-VASc score will identify a greater proportion of the population who are at risk of stroke and for whom anticoagulation therapy would be recommended.²⁵

2.6 Bleeding risk stratification

With any anticoagulation therapy, there is a balance between the risk of stroke and the risk of bleeding. Management approaches to stroke prevention in patients with AF should take account of not only a patient's stroke risk (e.g. through CHADS₂ and CHA₂DS₂-VASc), but also their bleeding risk.²⁶⁻²⁷

One algorithm for calculating bleeding risk is the HAS-BLED score, which is shown in Table 2.7.²⁸⁻³⁰ A HAS-BLED score of 3 or more indicates a high risk of bleeding.

Table 2.7 Clinical characteristics comprising the HAS-BLED score

Risk factor	Score
Hypertension	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (e.g. >65 years)	1
Medicines or alcohol (1 point each)	1 or 2
Maximum	9 points

INR = international normalised ratio

Source: Adapted from Pisters et al (2010)³⁰

It has been stated that ‘the formal assessment of bleeding risk allows informed decision making and makes clinicians think about the correctable risk factors for bleeding (for example concomitant aspirin use or poorly controlled hypertension) that can be modified to reduce bleeding risk’.¹⁶

The difficult balance between reducing stroke and minimising the risk of bleeding is exemplified by the fact that the HAS-BLED algorithm contains common elements with the CHADS₂ and CHA₂DS₂-VASc stroke risk prediction scores. The common elements are hypertension, prior stroke and age.

2.7 Anticoagulation therapy

Reduction in stroke risk associated with AF by the use of anticoagulant or antiplatelet agents has been standard clinical practice for many years, although the percentage of eligible patients actually treated has significantly increased during the past decade.

The most common anticoagulant used in Australia is warfarin, but for patients at a low risk of stroke, or those not able or willing to take warfarin, low-dose aspirin can be used. Newer agents have recently become available as an alternative to warfarin. The use of warfarin is described in detail in Part 2; the use of new anticoagulants is described in Part 3.

PART 2
Current anticoagulation therapy using warfarin

3 About warfarin

Coumarins (a group of medicines, of which warfarin is used in Australia) have been used clinically since the 1950s and are likely the most widely studied medicines currently in clinical use.³¹ Literally thousands of papers have been published relating to warfarin's medical use and ways of optimising therapy.

3.1 Mechanism of action of warfarin

Warfarin is a mixture of two compounds, each a mirror image form of the other (called a racemic mixture). The two compounds are called the R-enantiomer (the 'right hand' molecule) and the S-enantiomer (the 'left hand' molecule). The S-enantiomer is approximately four-fold more potent than the R-enantiomer. The dominant determinant of anticoagulant activity is the plasma concentration of the unbound S-enantiomer.

Warfarin is metabolised (or 'converted') in the body into inactive, or largely inactive, substances by liver enzymes. The liver enzymes that metabolise warfarin are from the cytochrome P450 (CYP) family. As shown in Figure 3.1, particular enzymes are specific for the S and R enantiomers.

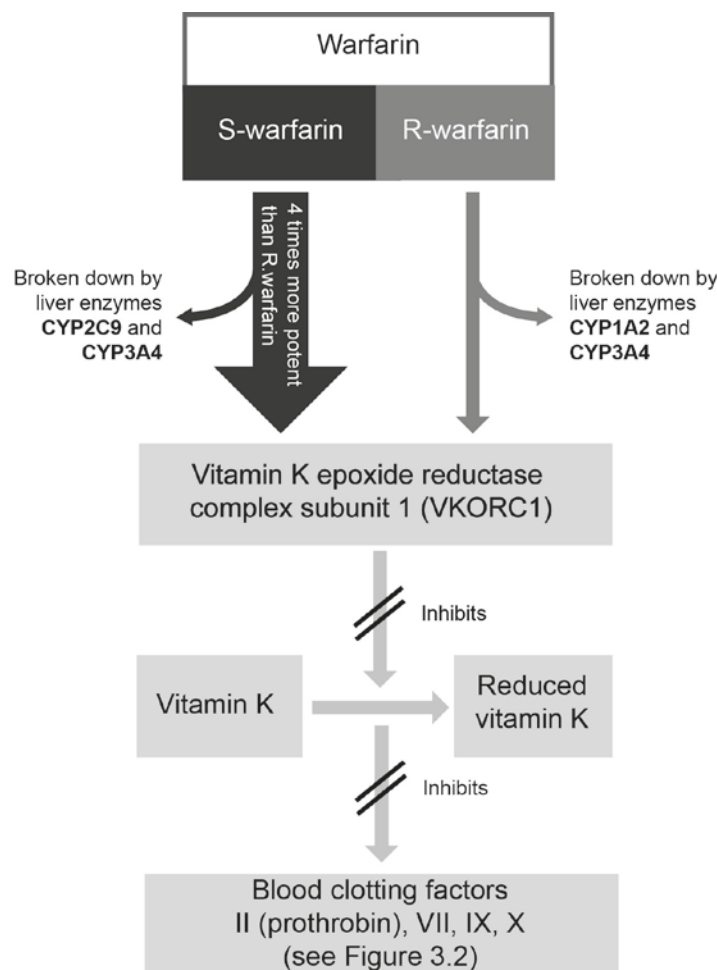
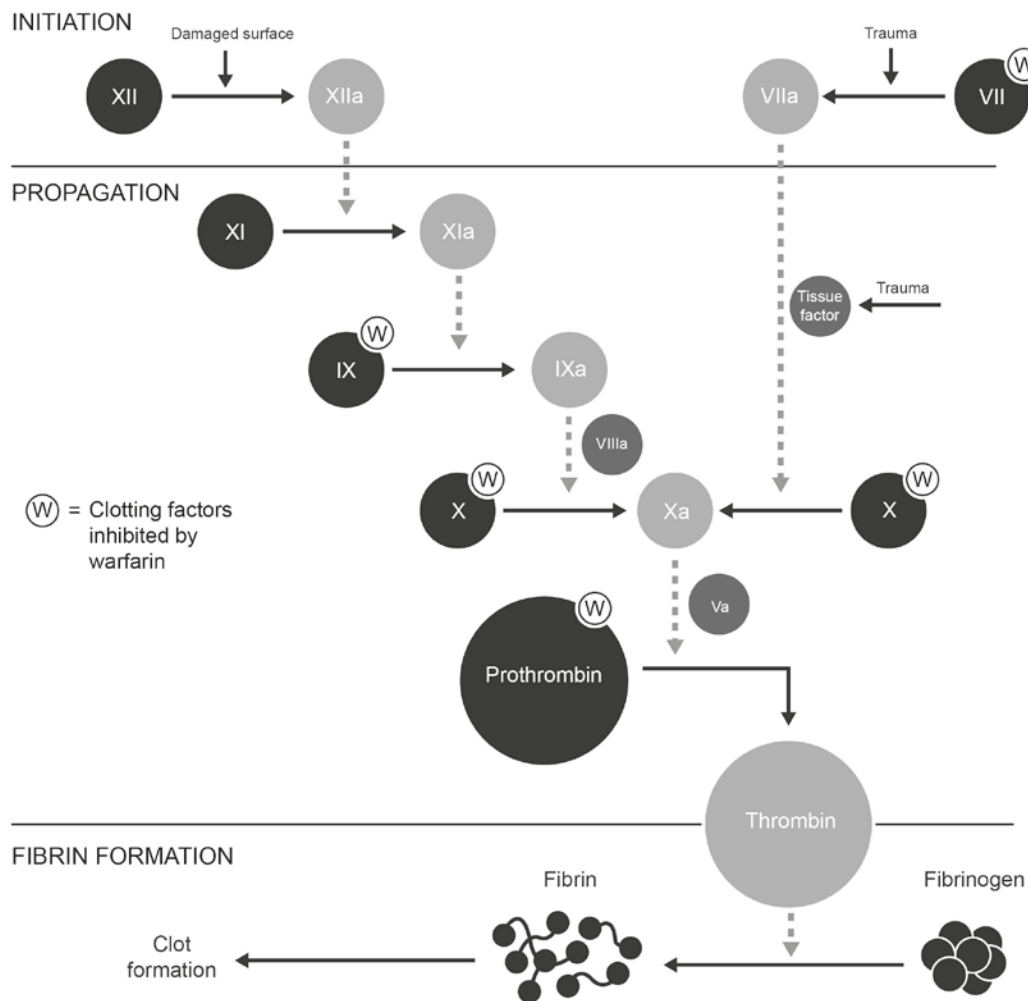


Figure 3.1 Metabolism of warfarin

Warfarin acts by inhibiting vitamin K epoxide reductase complex subunit 1 (VKORC1), which is the enzyme that regenerates vitamin K into a usable form (reduced vitamin K) in the vitamin K cycle.

In response to trauma or damage, a cascading series of events is triggered that results in the formation of a clot. Reduced vitamin K is a critical cofactor in the generation of the specific blood clotting factors II (prothrombin), VII, IX and X.³²⁻³³ As shown in Figure 3.2, inhibition of the reduction of vitamin K results in a reduction in the conversion of fibrinogen to fibrin, which in turn reduces clot formation.



Source: Adapted from BPAC NZ (2011)³⁴

Figure 3.2 Warfarin's effect on the clotting cascade

The vitamin K–dependent clotting factors whose synthesis is blocked by warfarin have varying half-lives (e.g. six hours for factor VII and three days for factor II). This means that a change to a patient's blood level of warfarin (e.g. through a dosage change) will not be immediately translated into a clinical response.

Warfarin has an elimination half-life of approximately 40 hours, and this means that it takes 5–7 days to reach steady state when warfarin is started or when the dosage is adjusted. Importantly, the action of warfarin is modified by vitamin K. This means:

- variable dietary intake of vitamin K may alter the extent of the anticoagulation effect of warfarin
- vitamin K can be used as an antidote to reverse the effects of warfarin.

In addition, the liver enzymes that metabolise warfarin (see Figure 3.1) are commonly involved in the metabolism of other medicines, and their activities can be modified by concomitantly administered medicines. As a consequence, metabolic medicine interactions have been reported for warfarin.

3.2 Warfarin efficacy

Warfarin is highly effective in reducing the incidence of stroke in patients with AF, regardless of the patient's stroke risk level. An updated meta-analysis demonstrates that, when compared to placebo, adjusted-dose warfarin reduces stroke risk by 64% and antiplatelet agents reduce stroke risk by 22%.³⁵ The data indicate that adjusted-dose warfarin is more effective than antiplatelet therapy, but it doubles the risk of major extracranial bleeding and intracranial haemorrhage.³⁵

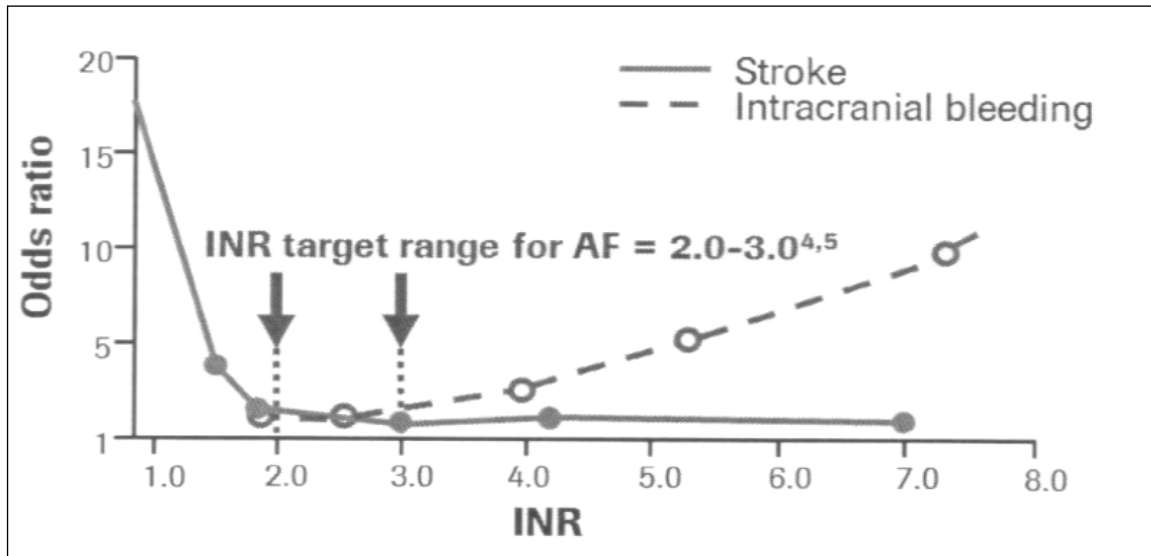
A Cochrane Review examined the effectiveness of antiplatelet therapy in reducing strokes, and found a reduction of approximately 20%,³⁶ although other papers argue that this result is driven by one study.³⁷ Another study suggested that warfarin and aspirin gave similar risk of ischaemic stroke and haemorrhagic stroke (4.6% and 4.3% per year, respectively) in patients over the age of 75.³⁸ The aspirin dose in this study was 325 mg daily and the INR target was 2.0–4.5. The impact that this dose or the wider range of INR (i.e. compared to the accepted therapeutic index for this indication of 2–3) has on these results is uncertain.

A combination of clopidogrel and aspirin reduced the rate of ischaemic stroke by 28% compared to aspirin alone, with an incidence of major bleeds equal to that of warfarin.³⁹

3.3 Therapeutic range of warfarin

Warfarin has a narrow therapeutic index. Its effectiveness and safety is a tight balance between stroke risk and bleeding risk, and it requires careful dose titration and monitoring. Monitoring a patient's response to warfarin is measured by their international normalised ratio (INR), a measure of the extent of anticoagulation.

In AF, the clinical benefits of warfarin are highly dependent on maintaining the INR within the therapeutic range of between two and three.^{40–42} As shown in Figure 3.3, INRs below this range increase the risk of stroke, while INR values above three or four are associated with increased bleeding rate.⁴³



AF = atrial fibrillation; INR = international normalised ratio

Source: Fuster et al (2006)⁴³

Figure 3.3 Maintaining INR in the therapeutic range is crucial to prevent strokes and avoid bleeding

A measure of anticoagulant control during a specified period of time is the time in therapeutic range (TTR).⁴⁴ In those patients where TTR is poor (i.e. TTR less than 60%), the annual mortality rate is higher (4.2% versus 1.7%), major bleeding is higher (3.9% versus 1.6%) and stroke and systemic embolism is higher (2.1% versus 1.1%) compared to patients with good control (i.e. greater than 70% TTR).⁴⁵ Retrospective studies have shown that a 6.9% improvement in TTR significantly reduced major haemorrhage by one event per 100 patient-years of treatment.⁴⁶

The TTR varies significantly among individuals, with estimates in the Australian community-based practice in the range of 50–68%.⁴⁷ A systematic review of international studies cited TTRs ranging from 29% to 75% and reported that randomised controlled studies result in higher TTRs than retrospective studies, which indicates that higher TTRs (and therefore better outcomes) can be achieved with structured anticoagulation control programs.⁴⁶

4 Issues and options for the use of warfarin

4.1 Management of stroke prevention in atrial fibrillation

4.1.1 A significant percentage of the population with atrial fibrillation is undiagnosed

Many patients with AF have no symptoms and, in submissions to the review, respondents estimated that around 10–30% of AF cases are undiagnosed.³⁻⁴

KEY ISSUE: Because of the higher prevalence of AF in elderly patients, in combination with the demographics of an ageing population, an increased awareness of AF and greater attention to detection of AF need to be considered.⁴

4.1.2 Co-existing conditions and concomitant medicines complicate treatment

In Australia, approximately 40% of the aged population have a minimum of three comorbidities (unpublished data, Veterans' Medicines Advice and Therapeutics Education Services, University of South Australia, Adelaide, 2012).

A number of submissions identified that it is common for patients with AF to have a wide range of comorbid conditions (and concomitant medicines) and that this can complicate treatment options for people with AF.⁴⁸ Factors besides ageing that predispose people to AF include coronary heart disease, hypertension, diabetes mellitus, obesity, sleep apnoea, renal disease and thyroid disease.² These factors, in particular hypertension, renal disease and diabetes, are very common in the aged population, and this further complicates management of AF.

As part of its submission, the Royal Australian College of General Practitioners conducted an audit of patients aged 65 and over with AF, and found that 68% were taking eight or more medicines.⁴⁸ Similarly, a recent survey of the Australian Government Department of Veterans' Affairs database indicated wide use of anti-inflammatory agents (nonsteroidal anti-inflammatory agents) and COX-2 inhibitors, proton pump inhibitors and antiplatelet agents in patients with AF (unpublished data, Veterans' Medicines Advice and Therapeutics Education Services, University of South Australia, Adelaide, 2012). (See Section 4.4 for further information on medicine interactions.)

KEY ISSUE: The management of AF is influenced by the other comorbid medical conditions that are common in the elderly, particularly heart disease, cognitive disorders, diabetes and musculoskeletal disorders. For example, these comorbidities may increase the absolute risk of stroke (e.g. cardiac disease and diabetes), increase the risk of bleeding by concomitant use of nonsteroidal anti-inflammatory agents and antiplatelet medicines, and increase the probability of medicine interactions.

KEY ISSUE: Patients who have a degree of cognitive impairment but are responsible for their own medication management may have difficulty with the routine of anticoagulant monitoring and/or dealing with multiple medications. The current treatment algorithms do not provide detailed advice in regard to dealing with patients with comorbidities. Although the pivotal trials of the newer agents included patients with diabetes and heart failure, there has been no comprehensive analysis of the risk–benefit in subjects with concurrent disease.

KEY ISSUE: Although the focus of this review is anticoagulation, this is only one component of stroke risk mitigation. For example, consideration also needs to be given to heart rate and rhythm control and ‘upstream’ management of other stroke risk factors, such as hypertension and high cholesterol.

4.1.3 Guidelines and management algorithms

In recent years, a number of international guidelines on the management of AF have been published, which include detailed discussions on the management of anticoagulation therapy. These include guidelines developed by the American College of Cardiology Foundation, the American Heart Association and the Heart Rhythm Society;²³ the Canadian Cardiovascular Society;²⁴ the European Society of Cardiology;⁴⁹ the National Institute for Health and Clinical Excellence (NICE);⁵⁰ the Japanese Circulation Society⁵¹ and the American College of Chest Physicians.⁵² None of these guidelines explicitly take into account the cost or cost-effectiveness of management options, nor do they discuss management in patients with multiple conditions.

A number of submissions raised the issue that no recent, comprehensive Australian guidelines exist.^{4, 53} Resources available in Australia include a position statement on AF from 2001⁵⁴ and the recent cardiovascular edition of the *Therapeutic Guidelines* (2012), which includes a discussion on treatment options and other management issues for the prevention of stroke in patients with AF.⁵⁵

In its submission to the review, the Cardiac Society of Australia and New Zealand stated that assessment of bleeding risk in clinical practice is usually a subjective assessment and that risk scores for bleeding (such as HAS-BLED) ‘are not widely used in clinical practice’.²

KEY ISSUE: There are no recent comprehensive and consistent Australian clinical guidelines for the management of AF. Comprehensive guidelines should consider overall management of anticoagulation, including detection of AF, a standard methodology for stroke risk and bleeding risk calculations, discussion of dosage considerations (such as dosage initiation and adjustment), and guidelines for monitoring anticoagulation (including the issue of comorbidities).

KEY ISSUE: Managing bleeding risk is an important part of the management of AF and should occur in a systematic way.

4.1.4 Noncompliance with guidelines and undertreatment of patients with AF

A number of submissions raised the issue that undertreatment of AF patients is a ‘significant’ cause of preventable stroke.^{3, 12, 56-57} The *National Stroke Audit — Acute Services Clinical Audit Report 2011* found that only 30% of patients with known and pre-existing AF are treated with anticoagulation therapy when presenting with a stroke to participating audited hospitals.⁵⁸ A recently published Australian audit of medical records of hospital inpatients found that of those patients deemed ‘eligible’ for anticoagulant therapy, only 55% were actually prescribed this treatment on discharge.⁵⁹ Clinicians will often make decisions to not begin treatment based on clinical and social reasons.

Several submissions raised the issue that some patients who are at moderate to high risk of stroke, and who are therefore eligible for anticoagulation therapy under the international guidelines outlined in Section 4.1.3, are not being anticoagulated, but are instead being treated with less effective antiplatelet therapy (such as aspirin). This is an issue because warfarin is significantly more effective at reducing the risk of stroke and offers a net benefit — even when taking into account the increased bleeding risk.³⁵

Submissions identified a range of factors contributing to underuse of anticoagulation therapy, including barriers, or perceived barriers, to a clinician’s prescribing of anticoagulation therapy.⁶⁰⁻⁶² One submission pointed to the results of a survey in which Australian general

practitioners were asked about factors that they consider when deciding whether or not to prescribe warfarin.^{4,63} The results are summarised in Table 4.1.⁶²

Table 4.1 Barriers to anticoagulant prescribing from a survey of Australian general practitioners (n = 596)

Barriers: How often does each reason apply to your patients with NVAF when considering whether or not to prescribe warfarin?	Never or rarely number (%)	Sometimes number (%)	Usually or always number (%)
Patient reluctance to take warfarin	173 (29.0)	324 (54.4)	92 (15.4)
Patient refusal to take warfarin	276 (46.3)	181 (30.4)	133 (22.3)
Regular monitoring of INR levels will be too impractical or inconvenient for the patient	352 (59.1)	177 (29.7)	60 (10.1)
Risk of adverse events will be unacceptably high	57 (26.3)	237 (39.8)	195 (32.7)
You feel the patient would be unable to comply with requirements for regular follow-up	212 (35.6)	251 (42.1)	127 (21.3)
The patient has contraindications to warfarin	163 (27.3)	185 (31.0)	242 (40.6)
Patient risk of falls	153 (25.7)	293 (49.2)	(4.0)

INR = international normalised ratio; NVAF = nonvalvular atrial fibrillation
Source: Gattellari et al (2008)⁶²

Table 4.1 shows that patient reluctance and/or refusal to take warfarin is a relatively common barrier to anticoagulant prescribing. Factors that contribute to patient reluctance and refusal may include consideration of dietary factors, (perceived) inconvenience of regular monitoring and a lack of venous access. Patient decisions about starting anticoagulation therapies must be informed decisions — taking into account the risks and benefits of such medicines.

It is interesting to note that several of the barriers outlined in Table 4.1 may equally apply to all anticoagulants irrespective of whether regular monitoring is required. Further, regular monitoring is also required for many other medicines, including tests for renal function, haematological side effects or for continuation of Pharmaceutical Benefits Scheme (PBS) subsidy.

A study from the United States also identified a number of factors influencing warfarin use. A summary is shown in Table 4.2.⁶¹ Similar to the Australian study above, many of the factors will be applicable to any anticoagulant therapy and not just to warfarin.

Table 4.2 Factors influencing a reduction in warfarin use or increasing warfarin use

Factors influencing reduction in warfarin use	Factors increasing warfarin use
Alcohol and medicine use	Congestive heart failure
Increasing age	Cerebrovascular accident
Contraindications to warfarin	Male gender
Dementia	Perceived appropriateness of warfarin
Falls	Atrial fibrillation frequency
Gastrointestinal bleeding	
History of bleeding	
Hepatic impairment	
Intracranial bleeding	
Perceived barriers to compliance	
Renal impairment	
Perceived and actual risk of bleeding	

Source: Baczek et al (2012)⁶¹

A number of submissions identified that, in addition to the factors mentioned in tables 4.1 and 4.2, some cases of underuse of anticoagulation therapies are due to an inappropriate perception

of risk versus benefit by both prescribers and patients.²⁻⁴ Many submissions identified that fear of bleeding often dominates prescriber decision making.^{2-4, 11, 63-64}

The European Society of Cardiology Working Group on Thrombosis position document on bleeding risk assessment and management in AF patients states that ‘in most patients, thromboembolic rates without anticoagulation are markedly higher than bleeding rates. Therefore, most patients with AF — including the majority of patients at high bleeding risk — are in need of anticoagulant therapy’.²⁹ Therefore, even though there is an increase in risk of bleeding in patients receiving anticoagulants, this is generally outweighed by the benefit of anticoagulation treatment in reducing stroke.

KEY ISSUE: A significant proportion of people who have been diagnosed with AF are not receiving pharmacotherapy in accord with existing treatment paradigms:

- It is estimated that only 40–60% of patients who are appropriate candidates for oral anticoagulation receive anticoagulation treatment.
- It is further estimated that a percentage of patients with moderate to high risk of stroke (for whom current anticoagulation therapy would be appropriate) are inappropriately receiving antiplatelet medicines (such as aspirin) as monotherapy.

KEY ISSUE: Untreated and undertreated patients are considered to be a major source of preventable strokes. Removal or reduction of some of the barriers to anticoagulant use has the potential to result in a significant health gain.

KEY ISSUE: Several studies have reported the reluctance or refusal of patients to take warfarin as a major barrier to its use. The issue is whether these patients have an appropriate understanding of the risk versus benefit of anticoagulation — particularly when the risk reduction in stroke incidence generally exceeds the increased risk of bleeding.

KEY ISSUE: There is uncertainty as to which of the identified barriers to the use of anticoagulation therapy would be addressed by other anticoagulation management options, since many of those barriers identified will also apply to anticoagulant therapy in general.

OPTIONS AND QUESTIONS FOR THE REVIEW

Options for management of stroke prevention

- Develop and maintain best practice, evidence-based Australian clinical guidelines for the detection and appropriate management of AF, including decision support that incorporates the use of risk calculators integrated within medical software (e.g. CHA₂DS₂-VASc and HAS-BLED) and management of comorbidities.^{2, 11, 48, 53, 65} The AF management guidelines must take into account the cost and cost-effectiveness of therapies, as well as patient factors.
- Improve the diagnosis and management of AF through a program to bring about evidence-based changes in clinical behaviour. The program should use a multifaceted approach incorporating changes at the professional, organisational, consumer, regulatory and financial levels.⁴ For example, this could include:
 - multiple education and support programs for clinicians and patients discussing the risks versus benefits of anticoagulation^{2, 4, 64, 67}
 - roles for allied health professionals in identifying patients suitable for anticoagulation therapy^{2, 11}
 - disease management programs⁶⁸
 - incentives for prescribers and more consultation time between health care professionals and patients.^{2, 4, 67}

Focus questions

1. Will algorithms for the calculation of stroke risk and bleeding risk assist in the decision-making process around anticoagulation management and how should these be incorporated into the practice environment?
2. What is the best process for the development of national, readily accessible Australian guidelines? Who should take responsibility for its development? Which partners need to be involved? Are current overseas guidelines applicable to the Australian health care system? Should specific guidelines be developed for consumers regarding management and other patient-relevant issues?
3. What should guidelines contain to be most useful to prescribers and other stakeholders, and how should these be accessible; for example, through electronic means including mobile phone technology and/or incorporated into decision-support systems? Should there be a nationally endorsed algorithm for managing dosage adjustments in response to INR values?
4. What sorts of intervention programs to reduce barriers to anticoagulant use are the most effective at driving behavioural changes, and what are the costs associated with such programs?

4.2 Warfarin monitoring and maintaining an INR within the therapeutic range

4.2.1 Warfarin has a narrow therapeutic index

The clinical benefit of warfarin in the reduction of stroke in patients with AF is highly dependent on maintaining the INR within the therapeutic range of between two and three.^{42, 69-70}

KEY ISSUE: Warfarin is a medicine of narrow therapeutic index, and a patient's INR must be maintained in the range of two to three to have the optimum balance between stroke reduction (INR above two) and minimising the risk of major haemorrhage (INR less than three).

4.2.2 Warfarin requires regular monitoring to maintain a therapeutic INR

The need for regular monitoring of the effect of warfarin, through a patient's INR, was identified in a number of submissions as a major inconvenience to patients, carers and general practitioners.^{3-4, 12, 56, 71-74}

Although INR monitoring is generally required approximately once per month (with more frequent monitoring required at the initiation of therapy or when a dosage adjustment is made), one report has suggested that the average number of INR tests per Australian patient on warfarin is 1.7 tests per month.⁷⁵ This is greater than reported recently in the ARISTOTLE trial of apixaban, and also an Australian trial that found an average of 9.3 INR tests per person per year.⁷⁶

The frequency of INR monitoring was raised as an issue in a number of submissions. Some submissions suggested that some stabilised patients who have a low bleeding risk may only require INR testing once every 12 weeks.^{2, 11}

Currently, to be eligible for Medicare Benefits Schedule (MBS) subsidy, an INR test must be conducted by an accredited laboratory using blood obtained by venipuncture. Point-of-care testing is currently not covered under Medicare arrangements.

A number of submissions identified issues with the current approach of monitoring INR based on venipuncture results, and examples of these issues include:

- the availability of laboratory facilities in rural areas^{48,2, 64, 77,78}
- the time between the taking of a blood sample for INR monitoring and when the subsequent action regarding change of management (if required) is protracted⁶⁷⁻⁶⁸
- INR management can be time consuming for health professionals⁶⁷
- whether the current MBS rebates for primary practitioners to provide care for patients on warfarin represent adequate incentives^{2, 4, 66}
- obtaining venous access in some patients^{67, 71, 79}
- patient time and travel costs^{4, 80}
- overall patient costs^{2, 73, 80}
- difficulty in accessing INR testing facilities when travelling⁷⁷
- the impact on patient job and employment^{12, 56}
- impact on patient quality of life.^{4, 12, 81}

KEY ISSUE: The frequency of INR monitoring is likely to be greater during initiation or when dosage adjustments are made. For patients who are able to maintain a relatively constant INR,

less frequent monitoring is recommended, particularly if they have a low bleeding risk as determined by measures such as HAS-BLED.

KEY ISSUE: The need for regular INR monitoring and management of patients receiving warfarin has been reported to pose a difficulty for some health professionals, patients and carers, including inconvenience, potential delays to dosage adjustment, and access issues in rural and remote areas.

4.2.3 A range of models are used for monitoring INR in Australia and internationally

INR monitoring during warfarin therapy has been managed within a variety of practice settings and processes. The list below outlines some of the models currently used for INR testing, both in Australia and internationally. Some of these processes involve point-of-care testing devices, which are hand held, provide immediate results and use blood from a finger prick rather than by venipuncture. The following settings and processes are used:

1. The patient's primary medical practitioner or practice nurse takes the blood sample by venipuncture and forwards the sample to an external accredited laboratory. The INR result is then communicated to the medical practitioner who contacts the patient if a dosage adjustment or other action is required.
2. The patient presents to a laboratory service centre to have a blood sample taken by venipuncture and the sample is transported to the accredited laboratory. The results are then either communicated to the patient's medical practitioner who responds to the result as appropriate; or the laboratory contacts the patient directly and makes recommendations in regard to any required dosage adjustment, or other action. In the latter case, the laboratory representative takes control of the patient's warfarin management. Several of these programs are available in Australia, for which an additional fee is charged to the patient that is not subsidised by the Australian Government.⁶⁶
3. The patient's primary medical practitioner or practice nurse conducts point-of-care testing, and any required action can be undertaken quickly.⁸²
4. Point-of-care testing occurs in other health care settings. For example, the patient presents to an accredited pharmacy to have point-of-care INR testing and the pharmacist makes recommendations regarding any required dosing adjustments using an agreed management algorithm in a framework of a shared-care model with the patient's designated medical practitioner. This model was recently trialled in New Zealand, and was successful in improving the TTR of patients.⁸³ More examples include point-of-care testing in residential aged-care facilities⁶⁷ and using point-of-care-testing by domiciliary nurses undertaking home visits.
5. The patient presents to a designated anticoagulation clinic where INR monitoring and warfarin management is undertaken. These centres are not widely available in Australia, but have been used for many years in the United States of America and throughout Europe.⁸⁴
6. The patient self-monitors their INR values at home using point-of-care devices. If the INR is outside the accepted range they either contact their health care practitioner for advice on appropriate action to be taken (self-monitoring) or manage any dosage adjustments themselves using an agreed management algorithm (self-management).

Processes 1–3 are the most commonly practised in Australia.

International experience suggests that programs can be successfully implemented to improve time in therapeutic range (TTR), so that a TTR > 75% can be achieved.⁸⁵ TTR has been shown to be statistically significantly higher in patients managed in anticoagulation clinics and clinical trials compared to patients managed in community practice.⁸⁶

KEY ISSUE: There is a lack of appropriate infrastructure and funding arrangements in Australia for more convenient INR monitoring arrangements, including point-of-care INR testing, and patient self-monitoring and self-management.

KEY ISSUE: The cost of point-of-care testing using technology requiring finger-prick blood sampling is a barrier to its wider uptake because this service is currently not covered under Medicare services.

KEY ISSUE: The ability of personnel involved in INR monitoring and anticoagulant patient management to access a current health record, including comorbidities, current medication and INR history, limits the quality of some anticoagulant services. The use of a personally controlled electronic health record by patients receiving anticoagulants may address some of these issues.

OPTIONS AND QUESTIONS FOR THE REVIEW

Options for warfarin monitoring and maintaining patient INR

- Examine alternative options for warfarin management, including INR monitoring, that provide greater convenience for patients, and more consistent and timely responses to INR results. For example, the role of point-of-care INR testing using finger-prick techniques could be investigated in regard to accuracy, convenience, clinical outcomes, patient convenience, cost and cost-effectiveness.^{11, 82, 48} Other systems for warfarin INR monitoring that could be examined include:
 - specialised anticoagulant clinics, which are common in many countries^{11, 53, 87} patients could be referred to such a clinic for management within a multidisciplinary shared-care model^{53, 87}
 - a shared-care model for anticoagulant therapy similar to that currently in place for the prescribing and management of antiglaucoma PBS-subsidised medications by optometrists
 - the use of ‘anticoagulant-accredited’ pharmacists (and other allied health professionals, including domiciliary care service providers) under shared-care models with medical practitioners using point-of-care testing⁸⁷
 - an accredited program for the National Health Call Centre Network to provide appropriate advice on the management of anticoagulant therapy
 - provision of point-of care devices to suitable patients for self-monitoring and/or self-management⁴⁸
 - subsidised anticoagulant management services including dosage-adjustment recommendations provided by pathology laboratories⁶⁶ that are part of a shared-care model using an endorsed management algorithm.
- Develop a nationally endorsed warfarin dosing algorithm, which could include advice with regard to frequency of INR monitoring, and appropriate dosage adjustments or other management options. This resource should be available in multiple formats, including paper-based (hard copy), IT-based (such as a computer-based decision tool) and mobile phone applications.
- To explore and evaluate innovative ways to assist selected patients to improve their management of warfarin, including their ability to self-monitor and self-manage, and dosage-adjustment or collaborative models between health professionals and consumers.

Focus questions

5. What would be the impact of, and the opportunities that arise from, developing a model of multiple mechanisms/programs for the monitoring of anticoagulant therapy on the uptake and acceptance of anticoagulant therapy?
6. What would a multidisciplinary shared-care model look like? What are the barriers to creating a shared-care model? Are there existing models that could form a framework? What funding arrangements would be needed to support such a model? How would patient information be accessed to ensure appropriate care?
7. With regard to patient reluctance and/or refusal to take warfarin because of perceived inconvenience resulting from the need for monitoring, what would the willingness to pay by the consumer be to avoid monitoring in the context of having a test that allows their risk of under- or overcoagulation to be monitored, and appropriate action taken to minimise the risk of an adverse outcome?
8. Which patients could be considered for anticoagulant self-monitoring or self-management? What would be the criteria for patient selection?
9. What is the cost and cost-effectiveness of the various models?
10. What opportunities arise from the establishment of a nationally endorsed anticoagulant treatment algorithm for use by health professionals, including those operating within a shared-care model?

4.3 Initiation of warfarin

Several reports indicate that people experience greater difficulties in maintaining a stable INR in the first three months after warfarin initiation.⁸⁹ Adverse event rates with warfarin are higher in this period, with bleeding and recurrent thromboembolic events occurring more frequently.⁸⁹⁻⁹⁰

Management algorithms for the initiation of warfarin are available. However, it has been suggested that the commonly employed starting dose of 5mg daily would lead to over-anticoagulation in 82% of women and 65% of men who are older than 70 years.⁹¹

It is estimated that 50% of warfarin initiations occur in hospitals. A particular issue occurs when warfarin is initiated in hospital and the patient is discharged before a stable INR is achieved. In this case, completion of the INR stabilisation becomes the responsibility of the patient's general practitioner, who may not have received the postdischarge summary. Further, it may not be possible for the patient to obtain an appointment with their general practitioner in an appropriate timeframe. If the general practitioner does not have point-of-care testing, a critical delay in obtaining INR results can occur. This scenario demonstrates the critical importance of continuity of care between hospitals and the community.

For patients newly initiated on warfarin in hospital, postdischarge services have been trialled in Australia, including services where INR monitoring occurs in the patient's home using point-of-care devices.⁹²⁻⁹⁵ Note that a hospital-referred pathway for home medicine reviews is in the process of being established.

KEY ISSUE: Bleeding and INRs outside the therapeutic range are more common in the first three months of therapy and immediately after discharge from hospital.

KEY ISSUE: There are no systematic processes in place to assist initiation of warfarin therapy in either the hospital or community setting.

OPTIONS AND QUESTIONS FOR THE REVIEW

Options for initiation of warfarin

- Investigate collaborative health care team approaches that build on existing programs and structures, such as home medicine reviews^{11, 64, 67, 88} and practice incentive programs.
- Promote continuity of care for patients who start warfarin therapy in hospital^{3, 53, 87} and comparable models for patients who start their therapy in the community setting.
- Provide standardised patient information and education to every new patient starting warfarin therapy, and for those already taking warfarin who may not have received sufficient information when they started their therapy.

Focus questions

11. What are the potential models for a collaborative approach to managing anticoagulation therapy among health professionals immediately postdischarge?
12. What current processes/programs are in place that may be expanded to include a postdischarge anticoagulation service? Could these process or programs be integrated with a similar service for patients who are initiated on warfarin therapy in the community setting?
13. Could the infrastructures currently in place in Australia be used to facilitate development of these collaborative arrangements; for example, Medicare Locals and hospital-initiated home medicine reviews?

4.4 Inpatient variability in response to warfarin

A theme both in submissions and the literature is inpatient variability — the variability in INR values seen within a patient. Such variability makes patient management problematic and unstable INR values increase bleeding risk, as demonstrated by its inclusion as a risk factor in the HAS-BLED algorithm.

A number of submissions from consumers raised the issue of unstable INR blood test results,⁹⁶⁻⁹⁷ and prescribers outlined particular patients for whom maintaining an INR within an acceptable range was difficult to achieve⁷⁸ or whose usually stable INR changed markedly for no apparent reason.⁷¹

This inpatient variability is problematic with patients having periods of under- and over-anticoagulation, and patients needing multiple dosage adjustments, which can lead to confusion and a ‘chasing the dose’ phenomenon of frequent dosage adjustments. If dosage adjustment is required, there is no nationally endorsed, readily available Australian algorithm to help clinicians adjust warfarin doses depending on INR values.

Further, physician fear of erratic INRs due to concerns regarding bleeding risk can potentially lead to a conservative underdosing approach to warfarin management and therefore a reduction in the efficacy of warfarin.

Inpatient variability of the anticoagulation effect of warfarin, as measured by its impact on INR, may result from a number of factors, including:

- medicine interactions
- patient adherence and compliance
- plasma vitamin K levels
- concurrent illness.

Each of these issues is discussed further below.

4.4.1 Medicine interactions

A number of submissions identified the issue of medicine interactions in the management of patients on warfarin.^{3, 64, 98-99} Further, one submission identified that medicine interactions with warfarin are ‘often poorly understood by general practitioners and patients’.¹¹

The literature often refers to the fact that warfarin has multiple medicine interactions and lists of medicines reported to interact with warfarin have been published.¹⁰⁰ However, many of the examples of warfarin medicine interactions given within the literature are not well supported by robust clinical evidence and, in fact, a significant proportion of these examples rely on single case reports.¹⁰¹ In addition, for many of these case reports, the reported medicine interactions have no obvious or plausible biological mechanism.

Further, of those interactions which have been validated some of the interacting medicines (e.g. rifampicin) have a restricted clinical place and are often used in specialised units, therefore the number of patients potentially exposed to such interactions is likely to be small and appropriate dosage adjustments can be made.

Many medicine interactions with warfarin can be avoided or their impact minimised. For example:

- For many of the clinically confirmed medicine interactions, alternative medicines of comparable efficacy are often available that do not interact with warfarin. Therefore,

appropriate monitoring of a patient's medication record (including using decision-support tools) and prescribing medicines that are known not to interact with warfarin (where an alternative exists) could help minimise the impact of warfarin medicine interactions.

- Predicting dosage requirements before starting interacting agents such as amiodarone (dosage reduction is likely to be 25%) can minimise the risk of adverse outcomes.
- Active patient counselling about over-the-counter products and their interaction with warfarin (e.g. paracetamol and complementary medicines).

Co-administration of medicines that have the potential to cause bleeding in their own right (such as nonsteroidal anti-inflammatory medicines) is likely to result in increased bleeding independent of the anticoagulant used, including newer oral anticoagulants. This is clinically relevant because data provided by the Australian Government Department of Veterans' Affairs indicate that around 30% of veterans with AF are taking nonsteroidal anti-inflammatory medicines or COX-2 inhibitors (unpublished data, Veterans' Medicines Advice and Therapeutics Education Services, University of South Australia, Adelaide, 2012). This figure is higher than reported in the pivotal trials with the newer agents.

4.4.2 Patient compliance and adherence

As with other chronic medications, patient compliance can be a significant factor in achieving optimal outcomes from warfarin. Many factors can impact on patient compliance. The Cardiac Society of Australia and New Zealand identified a range of factors, including dose frequency, patient perception of treatment benefits, patient–physician communication, patient motivation, socioeconomic background, family and social support, and age.²

Warfarin has a long half-life (40 hours) and is administered once per day.

It has been suggested that the requirement for regular INR monitoring, and the routines around this, may improve patient compliance with their warfarin therapy.⁷⁶

However, problems with warfarin compliance can be exacerbated by frequent dosage changes and the use of multiple tablets of different strengths, particularly because warfarin is used in a mainly elderly population who are likely to be taking multiple medications.

In addition, patient compliance with warfarin may be influenced by patient confusion regarding the two different brands of warfarin (Coumadin[®] 1, 2, and 5 mg, and Marevan[®] 1, 3 and 5 mg). The *Warfarin: Important Information for Patients* booklet states that the different brands are 'NOT the same' and they should not be interchanged based on the fact that they have not been shown to be bioequivalent.¹⁰² This statement may lead to the belief that warfarin is poorly absorbed and as such is subject to variability in absorption contributing to variability in response. In fact, warfarin is 100% bioavailable¹⁰³ (this contrasts with dabigatran, which is 6% bioavailable). Further, it is highly unlikely that the brands would not be bioequivalent (provided the dissolution rates are appropriate). The fact that the medicine has a narrow therapeutic index is a factor to be considered, but absorption of warfarin is unlikely to be a clinically relevant issue in variability of response.

It is interesting to note that in the pivotal ARISTOTLE trial of apixaban in AF, the only strength of warfarin used were the 2 mg tablets.¹⁰⁴ This presumably required half tablets to be used in dosage adjustment. This approach — that is, changing dose by half or whole tablets rather than having multiple strengths of different brands — may cause less patient confusion.

4.4.3 Changes in blood and tissue levels of vitamin K

Variable vitamin K intake has the potential to influence the level of anticoagulation seen with warfarin.

The majority (90%) of vitamin K is obtained from the diet, particularly from green leafy vegetables.¹⁰⁵ Less than 10% is obtained from nondietary sources, menaquinones, which are largely synthesised by colonic bacteria.¹⁰⁵ Therefore, changes in diet are likely to have a greater impact on plasma vitamin K levels than changes in menaquinone levels.

Consumer submissions stated that they have been told to follow 'strict diets' and are unable to eat particular foods containing vitamin K. Some submissions identified that sometimes advice given to patients is inconsistent with best practice, particularly in relation to the omission of vitamin K from the diets of patients on warfarin.⁷⁷

There is strong evidence that significant variability in dietary vitamin K intake can manifest itself in wide variability in INR values in patients receiving warfarin, particularly in patients with low vitamin K levels.¹⁰⁶⁻¹¹² The tissue stores of vitamin K are limited and can be readily depleted.¹⁰⁵ Some studies have achieved stable INRs through regular daily administration of low dose vitamin K, which is thought to maintain relatively constant plasma/tissue levels.¹¹³⁻¹¹⁴ Patients with higher dietary vitamin K intake, and thus higher 'baseline' plasma/tissue levels of vitamin K, have significantly more stable INR values than patients with lower intakes of vitamin K.¹⁰⁶⁻¹¹² It has been proposed that patients with high baseline levels of vitamin K are less susceptible to changes in anticoagulation activity in response to periodic dietary changes.¹⁰⁶⁻¹¹²

4.4.4 Concurrent illness

Concurrent illnesses such as diarrhoea have been reported to result in a four-fold increase in the risk of having an INR greater than six.¹¹⁵ This has been suggested to be due to the malabsorption of vitamin K (that is, the body may not absorb vitamin K optimally when a patient has diarrhoea). Because changing vitamin K levels have the potential to influence a patient's INR this could lead to greater anticoagulation effect with the same dose of warfarin. However, there is an absence of high-quality evidence to support this hypothesis.¹¹⁶ It is possible that a more plausible explanation is that dietary vitamin K intake changes during periods of illness such as diarrhoea, and thus the impact is influenced by baseline vitamin K levels.

Decompensated heart failure has also been associated with an increase in INR values.⁸⁶

KEY ISSUE: Inpatient variability in INR values can make warfarin management problematic, and may be a reason for ceasing therapy. The most probable reasons for this variation are dosage issues (patient compliance and adherence), changes in patient vitamin K levels (being dependent on baseline vitamin K levels) and concurrent illness such as diarrhoea.

OPTIONS AND QUESTIONS FOR THE REVIEW

Options for management of inpatient variability of response to warfarin

- Develop and implement strategies, health-delivery models and support systems that promote quality use of warfarin to improve health outcomes.
- Develop a nationally endorsed management algorithm that can be used for amending the warfarin dose during maintenance therapy in response to changes in INR.
- Develop comprehensive education strategies each for health professionals and patients to improve understanding and acceptance of anticoagulation therapy. This could include developing comprehensive yet simplified anticoagulant food, medicine and disease-state interaction tables; guidelines for patient counselling; and advice for clinicians regarding appropriate actions. These could be made available in multiple formats, including mobile phone applications.
- Develop a resource for alternative therapies (i.e. medicines that do not interact with warfarin) to medicines shown to interact with warfarin, and include this resource within prescribing/dispensing software and other systems.
- Ensure that plasma and tissue concentrations of vitamin K are adequate so that any relative changes in vitamin K dietary intake will have minimum effect on the INR value. Literature suggests that this may be achieved through appropriate dietary advice and/or vitamin K supplementation.
- Consider reducing the number of different strength products used in a patient's warfarin management to lessen the risk of patient confusion.

Focus questions

14. Which medicine, food and disease-state interactions with warfarin have a strong evidence base and how can these interactions be best managed?
15. Which medicine interactions with warfarin are the most problematic, particularly due to a lack of appropriate alternatives that do not interact with warfarin? What advice can be given about pre-emptive dosage changes when interacting medicines are needed to be added to a patient's regimen?
16. What impact does the need for regular monitoring have on patient compliance?
17. Should plasma vitamin K levels be measured at the time of warfarin initiation to identify those patients with low levels — who are therefore at greatest risk of INR fluctuations due to dietary vitamin K intake?
18. Should appropriate dietary advice be received by patients initiating warfarin? Simply issuing tables of vitamin K content of foods could infer that those with the highest content should be avoided. What is the best way to provide dietary advice to patients?
19. What would be the likely benefits and risks of low-dose vitamin K supplementation for patients on warfarin?

4.5 Interpatient variability in response to warfarin

Interpatient differences in warfarin dosage requirements are considered to be less of a clinical issue than inpatient variability because dose requirements can be monitored by INR measurements. Interpatient variability is likely to be more important at the initiation of warfarin therapy and requires consideration at the titration phase of therapy.

A number of submissions raised the issue of significant interpatient variability in warfarin dose requirements.^{57, 71, 99, 117} This is predominantly due to genetic differences between patients, with up to 40% of the interpatient variability seen in warfarin dose requirements attributable to genetic differences in two particular enzymes:¹¹⁸

- **CYP2C9.** This liver enzyme metabolises the more potent S-warfarin into its inactive, or largely inactive, form. The clinical implications of genetic mutations in this enzyme are that some patients require lower doses of warfarin, take longer to reach a constant therapeutic blood warfarin level ('steady state'), and are at greater risk of elevated INR values.¹¹⁹ It is estimated that this genetic variation, which results in a reduced clearance rate of warfarin, affects 2–14% of patients¹²⁰
and/or
- **Vitamin K epoxide reductase complex subunit 1 (VKORC1).** This enzyme regenerates vitamin K into a usable form. VKORC1 mutations result in a requirement for lower dosages of warfarin to maintain the INR in the therapeutic range.¹²¹

A number of studies have found that a combination of age, weight and height, and CYP2C9 and VKORC1 genotype, could explain a significant proportion (60%) of the interpatient variability in warfarin dosage requirements.¹²²⁻¹²³ Dosing algorithms that are based on genetic tests incorporating patient age, weight, height and sex have been shown to be beneficial for warfarin dosing, especially in the initiation phases.^{119, 124-128} In August 2007, the United States Food and Drug Administration approved a change on warfarin labels, which now state that 'lower initiation doses should be considered in patients with certain genetic variations in CYP 2C9 and VKORC1 enzymes'.

Studies have found that pharmacogenetic testing results in a reduction in bleeding events in the initial months of warfarin therapy, with one study finding that patients who underwent a genetic test before warfarin therapy experienced 28% fewer hospitalisations for bleeding or thromboembolism during the six-month followup period.¹²⁶ However, the cost-effectiveness of such an approach has not consistently been shown to be favourable in overseas trials and may depend on a range of variables.¹²⁹⁻¹³⁰

Patients with severe renal impairment (i.e. a creatinine clearance test [CrCL] value of < 30 mL/min) have been reported to require significantly lower doses of warfarin, exhibit more labile INR values and have a two-fold increase in the risk of major haemorrhage compared to patients with lesser degrees of renal impairment.¹³¹

KEY ISSUE: Genetic polymorphisms in CYP2C9 and VKORC1 make a significant contribution to an individual patient's dosage requirements.

KEY ISSUE: It is not yet clear whether testing for genetic polymorphisms is cost-effective and whether it provides better health outcomes than programs of appropriate INR monitoring, especially during the beginning stages of warfarin therapy.

KEY ISSUE: Routine INR monitoring may need to be more frequent in patients with a reduced renal function (i.e. CrCL < 30 mL/min).¹³²

OPTIONS AND QUESTIONS FOR THE REVIEW

Options for management of interpatient variability of response to warfarin

- Examine screening for the genetic polymorphisms associated with interpatient variability of warfarin.
- Develop a nationally endorsed management algorithm for warfarin therapy,⁶⁶ which includes advice about therapy initiation, particularly in view of the impact of genetic polymorphisms on dosage requirements. The guidelines would also need to address additional therapies to cover stroke risk in those patients with a very high risk during the therapy initiation phase.
- If genetic testing was to be implemented, consider the use of computer-based or other dosing algorithms for dose initiation that take into account genetic variability, patient demographics and the co-administration of interacting agents.

Focus questions

20. What is the national availability, efficacy, cost and cost-effectiveness of pharmacogenetic testing to aid warfarin therapy initiation in Australia? Would other interventions be able to achieve similar results at a lower cost?
21. What is an accepted dosage and monitoring algorithm for warfarin therapy initiation? What patient factors should be taken into account in deciding a starting dose? What should be the INR testing rate, and/or the rate of dosage changes in the initiation phase of warfarin therapy? How should an algorithm be available (e.g. integration within prescribing software/mobile phone applications)?
22. What is the appropriate advice for the stroke risk reduction in a high-risk patient during the warfarin therapy initiation phase?

4.6 Warfarin and intracranial haemorrhage

A number of submissions raised particular concerns about the issue of the risk of intracranial haemorrhage (ICH)[‡] associated with warfarin.⁴ The National Stroke Foundation described ICH as a ‘catastrophic outcome’.⁴ ICHs are generally more severe than ischaemic strokes, causing greater morbidity and mortality.^{70, 133} The three-month mortality of patients on warfarin at the time of ICH has been reported to be 52.0% compared to 25.8% for those not taking warfarin.⁷⁰ It is the fear of inducing an ICH that is often given for not giving high-risk patients warfarin or keeping the INR at a lower range, which increases the risk of thrombotic strokes.

ICH occurs eight to ten times more frequently in anticoagulated patients compared to patients not on anticoagulation,¹³⁴ and 5–12% of ICHs are related to anticoagulant use.¹³⁵ One reason proposed for the increased rate and severity of ICH in anticoagulated patients is the unmasking of bleeding that would otherwise remain asymptomatic.¹³⁶

Although reversal agents are available for warfarin, their benefits in patient outcomes in ICH are unclear.¹³⁷

A consistent finding in all the pivotal studies of the new oral anticoagulants (NOACs) is the reduction in the incidence of ICH compared to patients on warfarin.^{104, 138-139} A number of submissions identified that this was an important, clinically relevant difference between warfarin and the newer agents.⁴ The biological plausibility for the difference between warfarin and the NOACs in regard to ICH is not known, but it has been proposed that the difference may be associated with factor VII availability¹⁴⁰ or due to the greater impairment of thrombin generation in the propagation phase of coagulation with warfarin than the NOACs.¹⁴¹ Risk factors for warfarin-associated ICH include:

- poorly controlled warfarin management with an increased incidence of ICH in patients whose INR is greater than three^{70, 133}
- increasing age¹³⁵
- hypertension (systolic blood pressure > 160 mmHg)¹³⁵
- history of cerebrovascular disease¹³⁵
- co-administration of warfarin with antiplatelet therapy.¹³⁵

Better INR control may reduce both the incidence and severity of warfarin-associated ICH, as seen in a longitudinal population-based study in Finland.¹³³ However, although there is an association between high INRs and an increase in the risk of ICH,^{70, 142} many ICHs occur in patients with an INR less than three.^{70, 142} In fact, some studies have shown that more than 60% of all warfarin-associated ICHs occur at an INR of three or less.^{70, 142}

Patients who are at risk of falling pose a clinical dilemma for managing the risk of stroke and the risk of bleeding.^{2, 77, 143} One study found that patients at high risk of falls are at greater risk of ICH, especially traumatic ICH.¹⁴³ However, the study concluded that ‘because of their high stroke rate, they appear to benefit from anticoagulant therapy if they have multiple stroke risk factors’.¹⁴³ The European Medicines Agency recently issued an advisory warning regarding intracranial bleeding following falls in patients receiving dabigatran.

KEY ISSUE: Morbidity and mortality following anticoagulant-associated ICH are greater than ICHs in those patients not receiving anticoagulants. Clinician concerns regarding the risk of inducing an ICH with warfarin therapy is one of the common reasons given for the lack of appropriate warfarin use in patients with AF.

‡ An ICH is sometimes referred to as a ‘haemorrhagic stroke’ because the stroke is caused by bleeding. This is different to an ischaemic stroke, which is due to clotting.

KEY ISSUE: There is a clinical trade-off between the risk of ischaemic strokes due to AF and the increase in ICH (and other serious bleeds) associated with anticoagulation therapy. The pivot point for the decision to begin anticoagulants, which agent and the intensity of anticoagulation, needs to be better understood.

OPTIONS AND QUESTIONS FOR THE REVIEW

Options for reducing the risk of intracranial haemorrhage

- Consider education programs and support infrastructure for health professionals and consumers, including development of decision-support tools, to enable the relative risks of ischaemic stroke and serious bleeds (especially ICH) to be better assessed. This will involve wider understanding of the available tools, including CHADS₂, CHA₂DS₂-VASC and HAS-BLED. Education programs would be designed to ensure that other risk factors known to increase the incidence of ICH are addressed as part of a patient's total management.
- Develop education strategies for consumers to improve both the uptake and quality use of anticoagulants.
- Consider the use of anticoagulants that are associated with a lower risk of ICH.

Focus questions

23. What is the impact of the risk of ICH on the decision to start warfarin therapy? Is there a specific patient group or patient characteristic(s) that are more dominant in that decision?
24. Is the reported reduction in ICH with the newer agents a result of these agents being less likely to produce an over-anticoagulated state (that is, a coagulation state equivalent to a warfarin INR above three)? Is a component of the reported reduction in ICH with the NOACs that therapy with these agents essentially 'removes or minimises' the subset of patients on warfarin who have an elevated INR (more likely with poorer INR control) and associated increased risk of ICH?

PART 3
New oral anticoagulants

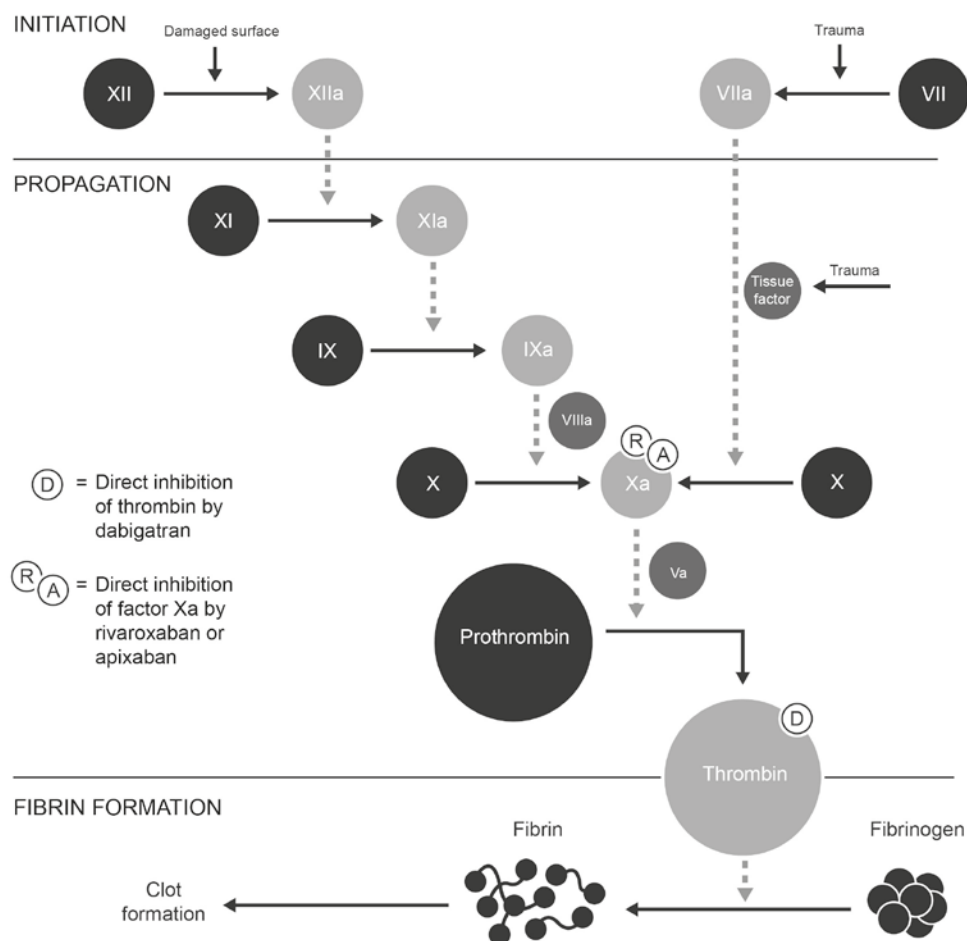
5 About new oral anticoagulants

A number of new or novel oral anticoagulants (NOACs) have been developed in recent years. Dabigatran was the first NOAC available for clinical use in Australia more than 50 years ago.

Dabigatran and rivaroxaban are Therapeutic Goods Administration (TGA)-registered for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF) and at least one other risk factor for stroke. Sponsors have applied to use apixaban for this indication in a number of countries. There are other NOACs in development internationally, such as edoxaban, although major clinical trials of these agents are ongoing.

5.1 Mechanism of action

The new agents act on different parts of the clotting cascade to warfarin, as shown in Figure 5.1.



Source: Adapted from BPAC NZ (2011)³⁴

Figure 5.1 The effect on the clotting cascade of new oral anticoagulants

The publicly available information is much greater for dabigatran than for the other agents due to its earlier introduction into the Australian market.

The characteristics of the NOACs are outlined in Appendix 1, Table A1. Note that Appendix 1 only includes those NOACs that have completed a major, multicentre randomised clinical trial evaluating its efficacy compared to warfarin in the prevention of stroke in patients with AF and at least one other risk factor for stroke.

5.2 Clinical trials

The tables in Appendix 1 outline the baseline characteristics of the participants of the three pivotal trials for dabigatran (RE-LY), rivaroxaban (ROCKET-AF) and apixaban (ARISTOTLE) (Table A2), and the key elements and differences in the design of these trials (Table A3).

Table A2 demonstrates that populations for the RE-LY and ARISTOTLE trials were more similar than patients who were included in the ROCKET-AF trial.

Note that all three trials were multinational and recruited patients from approximately 40 different countries. The proportion of the total populations from various regions varied among the trials as shown in Table 5.1. It should also be noted that the standard of care is likely to be different between and within regions, as has been demonstrated in the significant variation in time in therapeutic range (TTR) results in the warfarin arm of the studies in certain countries or regions.

Table 5.1 Trial participants by region (per cent)

Trial	Asia	South America	United States and Canada	Western Europe	Eastern/central Europe	Others (Australia, Israel, South Africa)
RE-LY (dabigatran) ¹⁴⁴	15.4	5.3	36.1	25.7	11.7	5.9
ROCKET (rivaroxaban) ¹⁴⁵	14.8 (Asia-Pacific)	13.2	18.8	14.8	38.6	(reported under Asia-Pacific)
ARISTOTLE (apixaban) ¹⁴⁶	14.3	19.0	24.7	16.2	21.8	4.1

There have been no head-to-head (direct comparison) randomised trials of the three NOACs, and differences between the three pivotal trials make indirect comparisons between the agents problematic. The European Sub-Committee Working Group on Thrombosis summarised these differences as:⁴⁹

- ‘the moderate-risk populations in RE-LY and ARISTOTLE trials with dabigatran and apixaban are different from the high-risk population included in the ROCKET-AF trial with rivaroxaban’ (see Appendix 1; in particular, note that the baseline characteristics of participants in the ROCKET-AF trial had higher CHADS₂ scores, were older, and had a higher incidence of heart failure, hypertension, diabetes and previous stroke than participants in the other two trials)
- ‘the studies have a different distribution of participating countries, with more patients from the ROCKET-AF trial being from lower income countries with a lower average level of TTR, and possibly other differences in the standards of care
- ‘it cannot be excluded that the open-label design of the RE-LY trial may have led to some advantages concerning individualised warfarin dosing and INR control and disadvantages concerning blinding of event evaluation compared with the double-blind ROCKET-AF and ARISTOTLE trials

- ‘differences in follow-up periods because only the ROCKET-AF trial included events up to 30 days after study medicine discontinuation
- ‘the ROCKET-AF trial prespecified an on-treatment analysis instead of the conventional intention-to-treat analysis for the primary testing of noninferiority
- ‘the end-of-study treatment differed among the trials: most dabigatran-treated patients in the RE-LY trial continued with the same blinded dose of the medicine as part of the RELY-ABLE (Long-Term Multicenter Extension of Dabigatran Treatment in Patients With Atrial Fibrillation Who Completed RE-LY Trial) trial, whereas there was a switch from the double-blind study medicine to open-label vitamin K antagonists in the ROCKET-AF and ARISTOTLE trials’.⁴⁹

In addition, definitions of the endpoint of major bleeding differed between the trials.¹⁴⁷ The ROCKET-AF and ARISTOTLE trials allocated patients to the higher strength of the trial medicine based on renal function (ROCKET-AF), and renal function, age and/or weight (ARISTOTLE), while the RE-LY trial randomised patients into strengths of dabigatran.

These important differences between the trials should be borne in mind when considering the tables in this part of the paper. Of particular note are the differences between the ROCKET-AF trial of rivaroxaban and the other two trials.

The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a Therapeutic Review of the NOACs, *Safety and Effectiveness of New Oral Anti-coagulants Compared to Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients with Atrial Fibrillation* (CADTH Review),¹⁴⁷ which is referred to throughout this part of the paper. This review does not take into account the impact of any heterogeneity among the trials, and CADTH caution that these differences should be borne in mind when interpreting the results.

6 Issues and options for the use of new oral anticoagulants

6.1 Efficacy of new oral anticoagulants compared to warfarin

The efficacy outcomes of the NOACs compared to warfarin in pivotal trials are shown in Table 6.1.

Table 6.1 Efficacy outcomes of NOAC trials

Trial (medicine) RR/HR	Hazard ratio (HR) or relative risk (RR) (95% confidence interval)							
	Total stroke and systemic embolism		Ischaemic stroke		Haemorrhagic stroke		Systemic embolism	
RE-LY (dabigatran) RR ¹⁴⁸	<u>110 mg</u> 0.90 (0.74, 1.10)	<u>150 mg</u> 0.65 (0.52, 0.81)	<u>110 mg</u> 1.11 (0.88, 1.39)	<u>150 mg</u> 0.76 (0.59, 0.97)	<u>110 mg</u> 0.31 (0.17, 0.56)	<u>150 mg</u> 0.26 (0.14, 0.49)	<u>110 mg</u> NA	<u>150 mg</u> NA
ROCKET (rivaroxaban) RR ¹³⁸	0.79 (0.66, 0.96) ITT: 0.88 (0.75, 1.03)		0.91 (0.73, 1.27)		0.59 (0.37, 0.93)		0.23 (0.09, 0.60)	
ARISTOTLE (apixaban) HR ¹⁰⁴	0.79 (0.66, 0.95)		0.92 (0.74, 1.13)		0.51 (0.35, 0.75)		0.87 (0.44, 1.75)	

ITT = intention to treat; NA = not available

Note: Numbers are bolded where they are statistically significant.

These data show that:

- dabigatran 150 mg was the only agent to demonstrate a statistically significant reduction in ischaemic stroke compared to warfarin
- dabigatran 110 mg was noninferior to warfarin in relation to total stroke and systemic embolism
- all the NOACs were associated with a statistically significant reduction in haemorrhagic stroke.

Table 6.2 shows the number of events that would be caused (positive numbers) or avoided (negative numbers) per 100,000 patients per year who are put on:

- therapy with warfarin instead of aspirin (based on a meta-analysis)
- therapy with NOACs instead of warfarin (based on the differences in the event rates from the individual trials).

Note that these numbers should be treated as indicative only given the heterogeneity among the trials.

The greatest benefit in stroke/systemic embolism reduction occurs when patients move from aspirin to warfarin. However, it should be noted that this switch will cause an increase in the rate of intracranial haemorrhage (ICH).

Further, data from the New Zealand experience with dabigatran use in a clinical (nontrial) setting demonstrate a 50:50 split of dabigatran 150 mg and dabigatran 110 mg doses.¹⁴⁹ This means that the reduction in strokes/systemic embolism with dabigatran compared to warfarin would be around 390 per 100,000 patients per year in a nontrial setting.

Statistically significant benefits in the reduction of ischaemic stroke compared to warfarin were only seen in the dabigatran 150 mg arm of the RE-LY trial.

The difference in the rate of stroke/systemic embolism between the NOACs and warfarin is driven by difference in haemorrhagic stroke, which is consistent across all trials.

Table 6.2 Absolute risk reduction per 100,000 patients per year (including 95% confidence intervals, where available)[§]

	Stroke or systemic embolism (includes haemorrhagic, ischaemic and unknown stroke)	Haemorrhagic stroke	Ischemic or unknown stroke	Mortality (all causes)	Intracranial haemorrhage
Warfarin vs aspirin ^a	-1400	NA	NA	-500	+200
Dabigatran 110 mg vs warfarin	-170 (-440, +170)	-260 (-320, -170)	+130 (-150, +470)	-370 (-830, +120)	-510 (-590, -390)
Dabigatran 150 mg vs warfarin	-600 (-820, -320)	-280 (-330, -190)	-290 (-500, -40)	-500 (-950, 0)	-440 (-540, -300)
Dabigatran average usage based on 50:50 split of 110 mg and 150 mg	-390	-270	-80	-440	-480
Apixaban vs warfarin	-340 (-540, -80)	-230 (-310, -120)	-80 (-270, +140)	-430 (-790, -10)	-460 (-560, -340)
Rivaroxiban vs warfarin	-290 (-600, +70)	-180 (-280, -30) ^b	-90 (-360, +240) ^b	-330 (-60, +40) ^b	-230 (-370, -50) ^b

+ = more events; - = fewer events; NA = not available

a The absolute risk reduction figures for warfarin versus aspirin are indicative only and are based on the results of a meta-analysis, whereas the absolute risk reduction figures for the NOACs compared to warfarin are based on individual trial results.

b Safety on treatment (as ITT not available).

Note that there is significant heterogeneity between the trials, particularly the ROCKET-AF trial of rivaroxaban.

Sources: Connolly et al (2010),¹⁴⁸ Granger et al (2011),¹⁰⁴ Patel et al (2011)¹³⁸

Table 6.3 shows a similar analysis conducted by CADTH.

[§] The absolute risk reduction per 100,000 patients per year and associated 95% confidence intervals (CIs) was calculated using the following method: All estimates of absolute risk reduction and confidence intervals for the NOACs compared to warfarin are based on results reported in papers that originally reported the research and the absolute risk reduction is calculated $(1 - \text{the relative risk or hazard ratio reported}) \times 100,000$. This is equivalent to a relative risk improvement per patient per year estimate $\times 100,000$. The CIs are based on the relative risk or hazard ratio CIs reported in the underlying research. The average dabigatran estimates (point estimate and CIs) are approximate and are a simple average of the point estimates, and each upper and lower boundary of the CIs (this assumes a 50:50 split of dabigatran 110 mg and dabigatran 150 mg). For warfarin versus aspirin, the absolute risk reduction estimates per 100,000 patients are based on the absolute risk reduction percentage per year reported in the meta-analysis.

Table 6.3 Summary of individual study results — absolute risk reduction per 1000 patients treated each year (95% confidence interval)

	Mean follow-up	Stroke/systemic embolism	Major bleeding	All-cause mortality	Intracranial bleeding	Major gastrointestinal bleeding	Myocardial infarction
Apixaban 5 mg twice daily	1.8 years	3 fewer (1 fewer, 5 fewer)	8 fewer (6 fewer, 11 fewer)	4 fewer (0 fewer, 8 fewer)	4 fewer (3 fewer, 5 fewer)	1 fewer (1 more, 2 fewer)	1 fewer (1 more, 2 fewer)
Dabigatran 110 mg twice daily	2 years	2 fewer (2 more, 4 fewer)	7 fewer (2 fewer, 11 fewer)	3 fewer (2 more, 8 fewer)	5 fewer (4 fewer, 6 fewer)	1 more (4 more, 1 fewer)	2 more (5 more, 0 more)
Dabigatran 150 mg twice daily	2 years	6 fewer (3 fewer, 8 fewer)	2 fewer (3 more, 6 fewer)	4 fewer (0 more, 9 fewer)	4 fewer (3 fewer, 5 fewer)	4 more (8 more, 1 more)	2 more (5 more, 0 more)
Rivaroxaban 20 mg twice daily	1.9 years ITT 1.6 years SOT	3 fewer (1 more, 6 fewer)	1 more (6 more, 3 fewer)	4 fewer (2 more, 8 fewer)	3 fewer (1 fewer, 4 fewer)	8 more (13 more, 4 more)	2 fewer (1 more, 4 fewer)

ITT = intention-to-treat; SOT = safety on treatment
Source: CADTH Review¹⁴⁷

6.2 Safety of new oral anticoagulants compared to warfarin

The TGA Safety Advisory (5 October 2011) *Dabigatran (Pradaxa): Risk of Bleeding Relating to Use* advised that ‘in clinical trials the risk of bleeding (major or minor) per year of treatment with dabigatran was 16.6% (1 in 6 patients) when taking 150 mg twice daily, and 14.7% (1 in 6.8 patients) taking 110 mg twice daily) compared to 18.4% (1 in 5.4 patients) for warfarin’.¹⁵⁰

However, as shown in Table 6.4, the distribution of types of bleeding events is different between the NOACs and warfarin. All NOACs showed lower rates of ICH than warfarin, while dabigatran and rivaroxaban showed higher rates of gastrointestinal bleeding than warfarin.

Table 6.4 Odds ratios for bleeding events — NOACs compared to warfarin (95% confidence interval)

Event	Odds ratio			
	RE-LY (dabigatran)		ROCKET-AF (rivaroxaban) ^a	ARISTOTLE (apixaban)
	110 mg	150 mg		
Major bleeding	0.80 (0.70, 0.93)	0.93 (0.81, 1.07)	1.04 (0.90, 1.20)	0.69 (0.60, 0.80)
Major gastrointestinal bleeding	1.08 (0.85, 1.38)	1.48 (1.18, 1.85)	1.60 (1.29, 1.98)	0.88 (0.67, 1.14)
Intracranial haemorrhage	0.30 (0.19, 0.45)	0.41 (0.28, 0.60)	0.65 (0.46, 0.92)	0.42 (0.30, 0.58)
All-cause mortality	0.91 (0.80, 1.03)	0.88 (0.77, 1.00)	0.92 (0.82, 1.04)	0.89 (0.79, 0.997)

^a Safety on treatment

Note: Numbers are bolded where they are statistically significant.

Sources: Connolly et al (2010),¹⁴⁸ Granger et al (2011),¹⁰⁴ Patel et al (2011)¹³⁸

As shown in Table 6.4, there was a statistically significant increase in major gastrointestinal bleeding with both dabigatran 150 mg and rivaroxaban compared to adjusted-dose warfarin. There was a statistically significant reduction in major bleeding with both dabigatran 110 mg and apixaban compared to warfarin. Apixaban also demonstrated a statistically significant reduction in all-cause mortality compared to warfarin. It is uncertain if the concomitant use of nonsteroidal anti-inflammatory medicines in patients receiving NOACs (particularly those receiving dabigatran or rivaroxaban) will exhibit a greater degree of gastric bleeding.

As shown in Table 6.4, the reduction in ICH is a consistent finding across all the pivotal trials of the NOACs, and this was raised as a key benefit in a number of submissions.^{2, 4, 12, 63-64} Whether the magnitude of reduction in ICH would be reduced by an improvement in TTR, especially due to a reduction in INR values above three, is unknown.

The National Stroke Foundation stated that ‘not all bleeding events are clinically equivalent and clinicians may be most concerned with the small but important incidence of ICH’.⁴

The underlying mechanism for the variations in sites of bleeding with different anticoagulants has not been established, although a number of theories have been put forward, particularly in regard to the reduction in ICH (some of these are discussed in Section 4.6).

An issue raised by the National Stroke Foundation was the ‘high concomitant aspirin use’ (which is known to increase bleeding, including ICHs, with all anticoagulant therapy) in these trials, which the National Stroke Foundation described as ‘unusual and probably important’.⁴

6.2.1 Safety data from regulatory agencies

The Institute for Safe Medication Practices produces details of adverse event cases reported to the United States Food and Drug Administration (FDA). The institute recently reported that dabigatran ‘accounted for 3781 domestic, serious adverse events overall in 2011 (both manufacturer and direct reports), including 542 patient deaths. It surpassed all other regularly monitored drugs in reports of haemorrhage (2367 cases), acute renal failure (291), and stroke (644). It was also suspect in 15 cases of liver failure’.¹⁵¹ In this same period (2011), warfarin ranked second highest in terms of number of adverse events reported to the regulatory agency, and it accounted for 1106 cases overall in 2011, including 72 deaths.¹⁵¹

The limitations of spontaneous adverse event reporting data must be emphasised and the reporting biases inherent in this type of data are well established. The report stated that the difference in the number of events reported with dabigatran compared to those reported for warfarin ‘could be at least partly explained by differences in the reporting rate for an older generic drug with many manufacturers, and a newly launched brand name drug being promoted by a large sales force. What is clear, however, is that the FDA’s system is receiving a strong signal about this safety issue. A large share of the dabigatran reports (79%) come from health professionals, suggesting that despite this well-known drug risk, the bleeding was unexpected or unusually severe’.¹⁵¹

Further, the report stated that ‘the primary feature of dabigatran that has helped its rapid uptake into the market has been the perception that it is easier to use than warfarin... Whether anticoagulation can be managed safely without individualizing the dose remains an unanswered question’.¹⁵¹ These types of sentiments were also raised in a number of submissions to the review.^{53, 79, 88, 152}

The FDA is currently evaluating postmarketing reports of bleeding events in patients taking dabigatran.

The European Medicines Agency’s Committee for Medicinal Products for Human Use assessed the available data on dabigatran and found that the frequency of occurrence of fatal bleedings with dabigatran seen in postmarketing data ‘was significantly lower than what was observed in the clinical trials that supported the authorisation of the medicine, but considered that this issue should nonetheless be kept under close surveillance’.¹⁸⁴ The committee recommended an update to the European patient and prescriber information for dabigatran to provide clearer guidance to doctors and patients on how to reduce and manage the risk of bleeding associated with dabigatran.

Clinical (nontrial), postmarket surveillance data are not yet available for rivaroxaban and apixaban.

6.3 Factors impacting on safety and efficacy of new oral anticoagulants compared to warfarin

A number of analyses (including the CADTH Review) have investigated the impact of various factors on the relative efficacy of the NOACs compared to warfarin, such as the quality of warfarin management in the control arm and patient characteristics such as age, renal impairment and stroke/bleeding risk.

6.3.1 Impact of trial centre's average TTR on efficacy and safety of NOACs compared to warfarin

A subgroup analysis of the RE-LY trial analysed the efficacy and safety of dabigatran in relation to each trial centre's mean time in therapeutic range (cTTR) for the warfarin population.¹⁵³ Individual patient TTR levels are not available, although these would have been informative. The analysis found no significant interaction between cTTR and the prevention of stroke and systemic embolism, or between cTTR and the incidence of ICH. However, a significant outcome-by-cTTR interaction was observed for major bleeding events (for the 150 mg twice-daily dose), total mortality and on the composite of all cardiovascular events.¹⁵³

These statistically significant interaction terms indicate that the advantages of dabigatran for these outcomes compared to warfarin were greater at trial sites with poor international normalised ratio (INR) control than those with better control, indicating that local standards of care can affect the relative risks and benefits of dabigatran versus warfarin.

Although the outcome-by-cTTR interaction for stroke/systemic embolism is not statistically significant, the hazard ratio for the 150 mg twice-daily dose versus warfarin is statistically significant for cTTR values up to 65.5%, but not at TTR values $\geq 65.5\%$. Tables 6.5 and 6.6 show the hazard ratios for various endpoints as a function of cTTR from the RE-LY trial for dabigatran 150 mg and 110 mg, respectively.

Table 6.5 Hazard ratios (with 95% confidence intervals) for various endpoints as a function of cTTR for dabigatran 150 mg from RE-LY¹⁵³

cTTR (%)	Stroke/systemic embolism	Mortality	Composite efficacy ^a	Major bleeding	Intracranial haemorrhage
<57.1	0.57 (0.37, 0.88)	0.67 (0.53, 0.85)	0.64 (0.50, 0.80)	0.71 (0.52, 0.96)	0.53 (0.25, 1.15)
57.1–65.5	0.50 (0.33, 0.77)	0.92 (0.71, 1.18)	0.80 (0.62, 1.04)	0.81 (0.62, 1.05)	0.45 (0.24, 0.88)
65.5–72.6	0.69 (0.44, 1.09)	0.98 (0.75, 1.28)	0.94 (0.72, 1.22)	1.13 (0.87, 1.48)	0.35 (0.15, 0.82)
>72.6	0.95 (0.61, 1.48)	1.08 (0.81, 1.44)	1.19 (0.90, 1.57)	1.16 (0.88, 1.54)	0.39 (0.18, 0.84)
Interaction P-value	0.20	0.052	0.006	0.03	0.89

cTTR = centre's mean time in therapeutic range

^a Composite of stroke, systemic embolism, pulmonary embolism, cardiovascular death and myocardial infarction.

Note: Numbers are bolded where they are statistically significant.

Table 6.6 Hazard ratios (with 95% confidence intervals) for various endpoints as a function of cTTR for dabigatran 110 mg from RE-LY¹⁵³

cTTR (%)	Stroke/systemic embolism	Mortality	Composite efficacy ^a	Major bleeding	Intracranial haemorrhage
<57.1	1.00 (0.68, 1.45)	0.73 (0.58, 0.92)	0.83 (0.67, 1.04)	0.65 (0.48, 0.89)	0.43 (0.19, 1.00)
57.1–65.5	0.81 (0.56, 1.17)	0.97 (0.75, 1.24)	0.99 (0.78, 1.27)	0.82 (0.63, 1.06)	0.31 (0.15, 0.66)
65.5–72.6	0.89 (0.58, 1.36)	0.86 (0.65, 1.13)	0.97 (0.74, 1.25)	0.83 (0.62, 1.11)	0.20 (0.07, 0.58)
>72.6	0.92 (0.59, 1.45)	1.18 (0.89, 1.57)	1.27 (0.97, 1.67)	0.90 (0.67, 1.21)	0.27 (0.11, 0.66)
Interaction P-value	0.89	0.066	0.14	0.50	0.71

cTTR = centre's mean time in therapeutic range

a Composite of stroke, systemic embolism, pulmonary embolism, cardiovascular death and myocardial infarction.

Data for the outcomes from the ARISTOTLE trial of apixaban as a function of cTTR are also available and are presented in Table 6.7.¹⁴⁶ No significant outcome-by-cTTR interaction was observed in the outcomes below; however, a significant interaction was observed for the endpoint of major and clinically relevant bleeds.¹⁴⁶

Table 6.7 Hazard ratios (95% confidence interval) for various endpoints as a function of cTTR for apixaban from ARISTOTLE¹⁴⁶

cTTR (%)	Stroke/systemic embolism	Mortality	Composite efficacy ^a	Major bleeding	Haemorrhagic stroke ^b
<58	0.77 (0.56, 1.06)	0.83 (0.68, 1.03)	0.81 (0.67, 0.97)	0.53 (0.39, 0.72)	0.52 (0.27, 1.00)
58–65.7	0.80 (0.56, 1.15)	0.91 (0.73, 1.12)	0.93 (0.77, 1.12)	0.60 (0.43, 0.82)	0.35 (0.16, 0.75)
65.7–72.2	0.79 (0.54, 1.13)	0.84 (0.68, 1.05)	0.85 (0.71, 1.03)	0.93 (0.71, 1.21)	0.72 (0.35, 1.47)
>72.2	0.81 (0.52, 1.26)	1.04 (0.82, 1.33)	0.96 (0.79, 1.18)	0.72 (0.55, 0.93)	0.50 (0.15, 1.66)
Interaction P-value	0.29	0.39	0.27	0.10	0.51

cTTR = centre's mean time in therapeutic range

a Composite of stroke, systemic embolism, death and myocardial infarction.

b Haemorrhagic stroke is reported here (cf. intracranial haemorrhage in Tables 6.5 and 6.6)

Note: Numbers are bolded where they are statistically significant.

The available data for rivaroxaban also demonstrated no significant outcome (total stroke) by cTTR.

The CADTH Review reported on the absolute risk reduction for particular outcomes per 1000 patients treated per year with each of the NOACs, by cTTR less than 66% and by cTTR greater than or equal to 66%; the results are shown in Table 6.8. For example, the table shows that, per 1000 patients treated with apixaban 5 mg twice daily per year (compared to being treated with warfarin in a centre with an average TTR less than 66%) there would be four fewer strokes/systemic emboli (with a 95% confidence interval of between nil and seven fewer strokes/systemic emboli).

The report found that for stroke/systemic embolism:

- for cTTRs less than 66%, the absolute risk reduction ranged from 2 to 9 fewer strokes/systemic emboli per 1000 patients treated in a year, but was only statistically significant for dabigatran 150 mg
- for cTTRs greater than or equal to 66% the absolute risk reduction of stroke/systemic embolism ranged from one to five fewer per 1000 patients.

The report found that for major bleeding:

- for cTTRs less than 66%, the absolute risk reduction ranged from two to eleven fewer major bleeds per 1000 patients treated in a year, with apixaban and both strengths of dabigatran showing a statistically significant outcome compared to warfarin
- for cTTRs greater than or equal to 66%, the absolute risk reduction for major bleeding ranged from 11 more to 6 fewer major bleeds per 1000 patients treated in a year, but was only statistically significant for apixaban.

Table 6.8 Summary of individual study results by TTR — absolute risk reduction per 1000 patients treated each year (95% confidence interval)

NOAC and dosage	Reference case		TTR <66%		TTR ≥66%	
	Stroke/ systemic embolism	Major bleeding	Stroke/ systemic embolism	Major bleeding	Stroke/ systemic embolism	Major bleeding
Apixaban 5 mg twice daily	3 fewer (1 fewer, 5 fewer)	8 fewer (6 fewer, 11 fewer)	4 fewer (0 more, 7 fewer)	11 fewer (8 fewer, 14 fewer)	3 fewer (1 more, 5 fewer)	6 fewer (0 more, 10 fewer)
Dabigatran 110 mg twice daily	2 fewer (2 more, 4 fewer)	7 fewer (2 fewer, 11 fewer)	2 fewer (4 more, 6 fewer)	9 fewer (3 fewer, 14 fewer)	1 fewer (3 more, 5 fewer)	4 fewer (2 more, 10 fewer)
Dabigatran 150 mg twice daily	6 fewer (3 fewer, 8 fewer)	2 fewer (3 more, 6 fewer)	9 fewer (5 fewer, 12 fewer)	9 fewer (2 fewer, 14 fewer)	3 fewer (2 more, 6 fewer)	5 more (13 more, 2 fewer)
Rivaroxaban 20 mg twice daily	3 fewer (1 more, 6 fewer)	1 more (6 more, 3 fewer)	3 fewer ^a (0 more, 6 fewer)	2 fewer (3 more, 6 fewer)	5 fewer ^a (2 more, 10 fewer)	11 more (25 more, 0 more)

TTR = time in therapeutic range

^a Safety of treatment population for rivaroxaban subgroups — intention-to-treat data were not available for TTR subgroups.

Source: CADTH Review¹⁴⁷

KEY ISSUE: The absolute risk change of stroke/systemic embolism per 1000 patients treated for a year declines from –2 to –9 at a cTTR less than 66% to –1 to –5 at a cTTR greater than or equal to 66%, indicative of a lack of TTR-stroke/systemic embolism interaction. However there is a trend towards a declining benefit with improved cTTR.

The absolute risk change for major bleeding per 1000 patients treated for a year declined from –2 to –11 at TTR less than 66% to –6 to –11 at TTR greater or equal to 66%. These analyses indicate that overall the reduction in major bleeding observed in the pivotal trials is dependent on the cTTR and improvement in the TTR removes the evidence of benefit for this outcome.

6.3.2 Impact of patient stroke and bleeding risk on efficacy and safety of NOACs compared to warfarin

In clinical judgment regarding the use of anticoagulants, there is a balance between the consideration of reducing the incidence of ischaemic strokes and systemic embolism, and the increasing risk for ICH caused by anticoagulation.

There is a strong correlation between the CHADS₂ score and the rate of stroke and systemic embolism, with a 1.5-fold increase with every one point increase in CHADS₂ for patients not receiving anticoagulants (see Section 2, Table 2.3).

A subgroup analysis of the RE-LY trial data investigated the impact of the CHADS₂ score on clinical outcomes.¹⁵⁴ The rates of stroke or systemic embolism, major and intracranial bleeding, and vascular and total mortality increased as the CHADS₂ score increased in all arms of the trial. For stroke and systemic embolism, the 150 mg twice-daily dose of dabigatran was superior to warfarin at all CHADS₂ scores, while both doses of dabigatran were superior to warfarin in regard to ICH across all CHADS₂ risk groups.

A similar analysis was conducted for apixaban, which found that apixaban was only statistically significantly superior to warfarin in the reduction of stroke/systemic embolism at CHADS₂ scores of three or more. At all levels of CHADS₂ scores, apixaban was statistically significantly superior to warfarin for the outcome of major bleeds, but was not statistically significantly superior to warfarin for all-cause mortality at any of the levels of the CHADS₂ score reported.¹⁵⁵

Banerjee et al calculated the net clinical benefit, balancing the risk of ischaemic stroke and the risk of ICH, in patients at varying levels of stroke risk (measured by CHADS₂ and CHA₂DS₂-VASc) and bleeding risk (HAS-BLED).¹⁵⁶ The modelling analysis used patient data from the Danish National Patient Registry and outcome data from the recent clinical trials of the NOACs.

The Banerjee et al¹⁵⁶ model found that:

- when both the risk of stroke and bleeding are high, all the NOACs are superior to warfarin in terms of net clinical benefit
- in patients with CHADS₂ or CHA₂DS₂-VASc scores of greater than or equal to one or two, respectively, the three NOACs appear better than warfarin for net clinical benefit, regardless of risk of bleeding. This is likely to be predominately due to the reduction in ICH seen with all three NOACs.

Note that this model only accounted for ischaemic and haemorrhagic strokes. Outcomes may have been different if other outcomes, such as major bleeding, were included.

The CADTH Review summarised the absolute risk reduction for particular outcomes per 1000 patients treated per year with each of the NOACs, using patients with CHADS₂ score less than two, and CHADS₂ score of two or more (Table 6.9).

Note that the ROCKET-AF trial of rivaroxaban only included patients that had a CHADS₂ score of two or more.

The report found that for stroke/systemic embolism:

- for CHADS₂ less than two the absolute risk reduction ranged from nil to four fewer strokes/systemic emboli per 1000 patients treated in a year, but was only statistically significant for dabigatran 150 mg
- for CHADS₂ greater than or equal to two, the absolute risk reduction of stroke/systemic embolism ranged from two to six fewer strokes/systemic emboli per 1000 patients treated in a year, and was statistically significant for apixaban and dabigatran 150 mg.

The report found that for major bleeding:

- for CHADS₂ less than two the absolute risk reduction ranged from seven to ten fewer major bleeds per 1000 patients treated in a year; the dabigatran 150 mg results were not statistically significant
- for CHADS₂ greater than or equal to two the absolute risk reduction ranged from one more to eight fewer major bleeds per 1000 patients treated in a year; apixaban was the only agent that showed a statistically significant result.

Table 6.9 Summary of individual study results by CHADS₂ score — absolute risk reduction per 1000 patients treated each year (95% confidence interval)

NOAC and dosage	Reference case		CHADS ₂ <2		CHADS ₂ ≥2	
	Stroke/systemic embolism	Major bleeding	Stroke/systemic embolism	Major bleeding	Stroke/systemic embolism	Major bleeding
Apixaban 5 mg twice daily	3 fewer (1 fewer, 5 fewer)	8 fewer (6 fewer, 11 fewer)	1 fewer (3 more, 4 fewer)	9 fewer (5 fewer, 13 fewer)	4 fewer (1 fewer, 7 fewer)	8 fewer (4 fewer, 12 fewer)
Dabigatran 110 mg twice daily	2 fewer (2 more, 4 fewer)	7 fewer (2 fewer, 11 fewer)	0 more (6 more, 4 fewer)	10 fewer (3 fewer, 15 fewer)	2 fewer (2 more, 6 fewer)	5 fewer (1 more, 10 fewer)
Dabigatran 150 mg twice daily	6 fewer (3 fewer, 8 fewer)	2 fewer (3 more, 6 fewer)	4 fewer (0 more, 7 fewer)	7 fewer (1 more, 12 fewer)	6 fewer (3 fewer, 9 fewer)	0 more (7 more, 5 fewer)
Rivaroxaban 20 mg twice daily ^a	3 fewer (1 more, 6 fewer)	1 more (6 more, 3 fewer)	NA	NA	3 fewer ^a (1 more, 7 fewer)	1 more ^a (6 more, 3 fewer)

NA = not available

^a Safety of treatment population for rivaroxaban subgroups — intention to treat data were not available for CHADS₂ subgroups.

Source: CADTH Review¹⁴⁷

6.3.3 Impact of age on efficacy and safety of new oral anticoagulants compared to warfarin

In its Safety Advisory of 3 November 2011, TGA noted that being over 75 years old is a risk factor for bleeding with dabigatran.¹⁵⁰ This increased bleeding risk in the elderly was also raised as an issue in a number of submissions,^{4, 157} and is particularly important since approximately 50% of patients with AF are over 75 years old.¹⁵⁷

The Australian product information for dabigatran states that 110 mg twice daily should be used in patients over 75 years old to prevent strokes in patients with AF and at least one other risk factor for stroke.¹⁵⁸

The CADTH Review summarises the absolute risk reduction for particular outcomes per 1000 patients treated per year with each of the NOACs by age (< 75 years old or ≥ 75 years old) (Table 6.10).

Table 6.10 Summary of individual study results by age — absolute risk reduction per 1000 patients treated each year (95% confidence interval)

NOAC and dosage	Reference case		Age < 75		Age ≥ 75	
	Stroke/ Systemic embolism	Major bleeding	Stroke/ systemic embolism	Major bleeding	Stroke/ systemic embolism	Major bleeding
Apixaban 5 mg twice daily	3 fewer (1 fewer, 5 fewer)	8 fewer (6 fewer, 11 fewer)	2 fewer (1 more, 4 fewer)	6 fewer (2 fewer, 8 fewer)	6 fewer (1 fewer, 10 fewer)	15 fewer (8 fewer, 21 fewer)
Dabigatran 110 mg twice daily	2 fewer (2 more, 4 fewer)	7 fewer (2 fewer, 11 fewer)	1 fewer (3 more, 4 fewer)	11 fewer (7 fewer, 15 fewer)	2 fewer (4 more, 7 fewer)	1 more (10 more, 7 fewer)
Dabigatran 150 mg twice daily	6 fewer (3 fewer, 8 fewer)	2 fewer (3 more, 6 fewer)	5 fewer (2 fewer, 7 fewer)	9 fewer (4 fewer, 13 fewer)	7 fewer (2 fewer, 11 fewer)	8 more (18 more, 0 more)
Rivaroxaban 20 mg twice daily	3 fewer (1 more, 6 fewer)	1 more (6 more, 3 fewer)	1 fewer (5 more, 6 fewer)	2 fewer (4 more, 8 fewer)	6 fewer (1 more, 11 fewer)	5 more (14 more, 2 fewer)

Source: CADTH Review¹⁴⁷

Similar to the CADTH analysis, a significant treatment-by-age interaction for major bleeding was also observed in a subanalysis of the RE-LY (dabigatran) trial population data:

- dabigatran 110 mg twice daily compared to warfarin was associated with a lower risk of major bleeding in patients less than 75 years old and a similar risk in those over 75 years old
- dabigatran 150 mg twice daily compared to warfarin was associated with a lower risk of major bleeding in those aged less than 75 years and a trend towards a higher risk of major bleeding in those over 75 years old
- the interaction-by-age was also seen for extracranial bleeding but not for intracranial bleeds, which were reduced independent of age for both doses of dabigatran.¹⁴⁰

Recent data on the clinical (nontrial) use of dabigatran in New Zealand (in the six-month period July to December 2011) shows that 78% of patients receiving 110 mg twice daily are over 75 years old while only 20% of those receiving 150 mg twice daily are over 75 years old.¹⁴⁹ Further, patients over 75 years old represented 50% of the total number of patients receiving dabigatran. These data indicate that prescribers are favouring the use of the lower dose in patients over 75 years old. Based on the analyses by Eikelboom et al¹⁴⁰ and the CADTH Review, this would indicate that in regard to this cohort of patients (> 75 years old), the benefit of a reduction in major extracranial bleeding compared to warfarin reported in the overall RE-LY population may not be seen. The New Zealand experience to date indicates that patients receiving dabigatran are older than those patients in the pivotal trials — the mean age was 71 years in RE-LY, 73 years in ROCKET-AF and 70 years in ARISTOTLE.

KEY ISSUE: Further exploration of the place in therapy of the 110 mg twice-daily dose of dabigatran may be required. The data above indicates that the use of 110 mg twice daily in patients 75 years old and over leads to a nonsignificant outcome for both stroke/systemic embolism and major bleeding compared to warfarin. The benefit in regard to ICH remains. Further, the use of dabigatran 150 mg twice daily in patients 75 years old and over leads to a reduction in stroke/systemic embolism but an increase in major bleeding compared to warfarin. This contrasts to data from the ARISTOTLE trial of apixaban, which indicated no influence of age on either stroke risk or major bleeding compared to warfarin.

KEY ISSUE: Some of the reported benefits of NOACs versus warfarin could be modified by certain factors including TTR and age (i.e. > 75 years old). Thus, the actual magnitude of the reported overall net benefits of NOACs in practice may be different from those observed in the trials, particularly if the TTR is higher (as exhibited by Australian participants in the trials) and if the average age of patients is greater. This remains an area of uncertainty. However, a consistent observation, independent of potential identified confounders, is the lower rate of ICH seen with the new agents and is perhaps the outcome of greatest certainty.

KEY ISSUE: Some further exploration is required, such as the extent to which an improvement in TTR and use in a population older than the one used in the pivotal trials will influence the various outcomes and impact any changes may have on the cost-effectiveness of the NOACs.

6.3.4 Impact of renal function

Dabigatran is predominately cleared by renal excretion (80%) unlike warfarin, which is 100% cleared by the hepatic metabolism. This means that dabigatran blood levels will be influenced by the extent of renal impairment and a number of submissions raised the issue that careful consideration of renal function will be required before prescribing dabigatran.^{2, 4, 11, 53, 79, 82}

On 3 November 2011, the TGA issued advice to health professionals and consumers that, 'following further evaluation of international reports of bleeding with Pradaxa[®], new recommendations for assessing kidney function before starting this medicine and during its use are now in place' and the summary of these new recommendations is provided in Box 6.1.¹⁵⁹

Box 6.1 Dabigatran (Pradaxa[®]) and the risk of bleeding: new recommendations for monitoring kidney function

Summary of the new recommendations:

- Kidney function should be assessed in all patients before beginning dabigatran therapy.
- Patients with severe kidney impairment (i.e. CrCL < 30 mL/min) should not take dabigatran.
- While on treatment, kidney function should be assessed in clinical situations where a decline in kidney function is suspected. Such situations include low blood volume, dehydration and when certain medications are taken at the same time.
- In elderly patients (> 75 years old) or in patients with moderate kidney impairment, kidney function should be assessed at least once a year.
- Kidney function should be assessed by measuring the CrCL.

Source: TGA Safety Advisory of 3 November 2011

The Australian product information for dabigatran states that 'in patients with moderate renal impairment (CrCL 30–50 mL/min) a reduced daily dose of 220 mg given as a 110 mg capsule twice daily may be considered'; this is to reduce the incidence of bleeding.¹⁵⁸

However, the FDA noted that patients with poor renal function (glomerular filtration rate 30–50 mL/min) have a similar bleeding risk independent of dosage, but have an increased incidence of stroke and systemic embolism at dosages of 110 mg twice daily compared to 150 mg twice daily. This suggests that reducing the dabigatran dosage from 150 mg twice daily to 110 mg twice daily in patients with renal impairment may not reduce the bleeding risk, but does reduce the efficacy in regard to the primary outcome.

One submission noted that, in New Zealand, a number of cases of haemorrhage in patients on dabigatran were in patients who were overdosed because of renal impairment.¹⁵⁷

6.3.5 Estimation of renal function

A number of submitters felt that, in some cases, appropriate estimation of renal function may be an issue; for example, in patients with low body weight¹⁵⁷ or where renal function is not appropriately calculated by prescribers (pathology renal function results need to be adjusted for the patient's age, weight and height, by using calculations such as the Cockcroft-Gault formula).⁶³

A patient's renal function may change over time, particularly in elderly patients who may experience gradual deterioration of renal function, potentially leading to inpatient variability in response to NOACs. Because medicine and/or coagulation measures are not monitored with NOACs, declining renal function may not be identified until the patient's next renal function test, which — according to the TGA guidelines — would be once per year. In the ROCKET-AF trial, patients randomised to rivaroxaban received the lower dose if their renal function was < 50 mL/min.¹⁶⁰ Similarly, in the ARISTOTLE trial, patients randomised to apixaban received the lower dose if they had two or more of the following risk factors: reduced renal function, age > 80 years and/or weight < 60 kg.¹⁰⁴

KEY ISSUE: The impact of declining renal impairment, which results in increased systemic exposure of dabigatran, on stroke prevention and haemorrhagic risk requires further investigation and seems to be confounded by other factors.

Patients who are on a lower dosage of dabigatran (110 mg twice a day) appear to have a similar bleeding risk as patients receiving 150 mg twice daily, particularly for patients with a moderate degree of renal impairment despite the lower systemic exposure.

Public comments on the impact of renal function on bleeding risk and recommendations regarding dosage in patients with renal impairment are not strongly supported by data from the RE-LY trial. Further, the impact of systemic exposure on the stroke/systemic embolism outcome in patients with renal impairment is also uncertain and requires further investigation.

KEY ISSUE: Care is required when considering beginning NOAC treatment in patients who may have reduced renal function, and this involves appropriate calculation of a patient's renal function.

OPTIONS AND QUESTIONS FOR THE REVIEW

Options for optimising safety and efficacy

- Investigate the relationship between renal function and bleeding risk and stroke risk reduction, with a view to better understand the relationship between systemic exposure and clinical outcomes. The aim will be to improve use in the elderly population, who have decreasing renal function.
- Development and promotion of clinical guidelines in relation to the use of NOACs in patients with, or at risk of, reduced renal function.⁵³ This could include overall clinical education strategies to improve awareness and use of the appropriate calculation of a patient's glomerular filtration rate, potentially through integrating the formula into user-friendly interfaces such as prescriber software.

Focus questions

25. Is the dabigatran dose–response (efficacy and safety) in patients with impaired renal function expected? What factors may be influencing the observation that similar systemic exposure gives different outcome rates? Is this dose–response relationship likely to occur with other NOACs?
26. Does reducing the dose of dabigatran in patients with impaired renal function reduce the major bleeding rate compared to warfarin?

6.4 Monitoring new oral anticoagulants

6.4.1 Regular monitoring

A number of submissions discussed that an advantage of the NOACs is that regular monitoring of their therapeutic effect is not required.^{2-4, 56, 63, 73, 78-79, 81, 96-99, 117, 161-162} This was identified as being of particular advantage in some groups of patients, including patients for whom warfarin INR monitoring may limit work opportunities,⁵⁶ patients with poor venous access, rural patients and patients who are travelling.

6.4.2 Validated test for anticoagulation intensity

In contrast to warfarin, at present there is no routinely available, validated test that will allow estimation of over/under-anticoagulation for the NOACs. This may be important since effectiveness will depend on renal function (in particular dabigatran), medicine interactions (all agents) and patient compliance (all agents). Other situations in which monitoring would be of clinical benefit are in overdose or serious bleeding,^{64,162} emergency surgery^{79, 82} or in patients at the extremities of size.¹⁵²

Some coagulation assays have been identified that provide a linear, dose-dependent correlation to the plasma concentration of the specific anticoagulant, such as the HEMOCLOT Thrombin-Inhibitors assay for dabigatran.¹⁶³⁻¹⁶⁵ However, a relationship such as what exists between INR and clinical outcome for warfarin has not been established or validated for the new agents.¹⁶⁶ In particular, there has been no guidance published linking plasma concentration levels of the NOACs to set therapeutic ranges and/or bleeding risk ranges.¹⁶⁶ Further limitations associated with these assays are lack of commercial availability for some of the assays, lack of standardisation and lack of validation.¹⁶⁶

In an editorial, the chairman of the Board of the Dutch Federation of Anticoagulation Clinics stated that 'it is becoming more and more apparent that the absence of proper lab tests (as well as the lack of antidotes) is a major hurdle in the safe introduction of NOACs.'¹⁶⁷

Measuring INR is an extremely useful tool to monitor extent of anticoagulation in an individual patient. A low INR may indicate, for example, poor compliance or increased dosage requirements; an elevated INR indicates the increased probability of the patient having a bleeding event and appropriate action can be taken (dose omission(s) or dosage reduction) to reduce that probability.

6.4.3 Switching between anticoagulants

Clinical guidelines on the use of anticoagulants in AF would need to include recommendations for switching between anticoagulation agents. This issue was been highlighted in the ROCKET-AF trial of rivaroxaban, where a greater number of strokes/systemic emboli were recorded in people switching from rivaroxaban to warfarin at the end of the trial.¹⁶⁸

KEY ISSUE: Although the absence of the need for monitoring the NOACs is seen as a significant advantage for patients in regard to convenience, the absence of a validated surrogate for the extent of anticoagulant control and bleeding risk with NOACs can also be seen as a disadvantage. This is particularly the case early in the life cycle of the medicine where patient selection, including comorbidities and polypharmacy, may be different from the trial population. There is currently no available measure to monitor an individual patient on NOACs for under- or over-anticoagulation. This may also be an issue in cases of bleeding, overdose, or where emergency surgery or switching between agents is required, particularly as there is no clinically proven antidote to reverse the effects of the new agents.

6.4.4 Variability in response to new oral anticoagulants

Medicine interactions

Many of the reported medicine interactions for the NOACs involve medicines that are common with those reported with warfarin. With NOACs start to have wider clinical use, other medicine interactions will be identified, but in the absence of a suitable, easily monitored surrogate measure, these interactions will not be identified until adverse reactions are seen (i.e. strokes and bleeding). At this stage, there is no ‘efficacy or toxicity safety signal’ — like there is with warfarin — to identify patients who may be at greater risk. For example, if an INR is high in the absence of bleeding, preventative measures such as dosage reduction, cessation or vitamin K administration can be undertaken, thereby reducing the bleeding risk.

Submissions identified that dabigatran has the potential for significant interactions with multiple medicines (e.g. P-glycoprotein inhibitors).^{11, 152, 157} In particular, submitters raised that dabigatran interacts with amiodarone and verapamil, which are both commonly used cardiac medicines.^{2, 11, 79, 152}

Rivaroxaban and apixaban also interact with CYP3A4 inhibitors and inducers, and P-glycoprotein inhibitors.

The pharmacodynamic interactions reported with currently available anticoagulants have also been reported with the NOACs, with increased bleeding observed when NOACs were concomitantly taken with antiplatelets and nonsteroidal anti-inflammatory medicines.¹⁵⁸ Note that the RE-LY (dabigatran) trial protocol strongly discouraged the use of concomitant nonsteroidal anti-inflammatory medicines,¹⁶⁹ while the ROCKET-AF trial protocol prohibited the long-term (i.e. more than two weeks) use of concomitant nonsteroidal anti-inflammatory medicines.¹⁶⁰ As previously mentioned, data from the Australian Government Department of Veterans’ Affairs indicate that around 30% of veterans with AF are taking nonsteroidal anti-inflammatory medicines or COX-2 inhibitors (unpublished data, Veterans’ Medicines Advice and Therapeutics Education Services, University of South Australia, Adelaide, 2012)

A number of submitters also raised that the effects of concomitant medicines on the NOACs have not been studied as extensively as they have for warfarin,^{64, 152} and that this is a ‘particular problem for people taking many medications, a group not included in the clinical trials’.¹⁵²

Patient compliance and adherence

Warfarin is administered once daily. A number of submissions raised that twice-daily dosages (as required for apixaban and dabigatran) requires increased patient adherence.^{2, 82, 88, 152} The Cardiac Society of Australia and New Zealand discussed that several studies have found that compliance declines as dosage frequency increases.²

In its submission, the Cardiac Society of Australia and New Zealand stated that ‘it should be noted that non-adherence to medication is widespread and that these issues are not unique to warfarin, as experience with antihypertensive medicines over many years has shown. It is worth noting that many factors identified as associated with suboptimal compliance in general are also likely to impact adversely upon treatment adherence with anticoagulant drugs’.²

An issue that was raised in a number of submissions is that dabigatran should not be repackaged into dose-administration aids or unit-dose systems (e.g. in hospitals),^{4, 53} because if exposed to moisture, the capsules have the potential to lose potency.

The Society of Hospital Pharmacists of Australia also raised an issue with dabigatran in that the ‘administration method can have a significant impact on clinical effect and bleeding times, for example if the patient spreads the contents of the capsule onto food there is an increased anticoagulant effect’.⁵³ The capsule shell must be left intact.¹⁵⁸ This will be relevant to patients

with dysphagia who may require crushing of medication or removal of the capsule content before administration.

Dabigatran has been reported to cause dyspepsia in a significant number of patients and has been reported as a common reason for discontinuation.^{139, 170}

The National Stroke Foundation discussed the NOAC discontinuation rates seen in the key pivotal trials.⁴ Table 6.11 presents a summary of these trial discontinuation rates.

Table 6.11 Summary of patient discontinuation rates in the pivotal trials for the new agents

	Dabigatran ¹³⁹ (RE-LY)		Rivaroxaban ¹⁷¹ (ROCKET-AF)	Apixaban ¹⁰⁴ (ARISTOTLE)
Warfarin discontinuation rate	16.6%		34.6%	27.5%
Trial agent discontinuation rate	110 mg	150 mg	35.4%	25.3%
	20.7%	21.2%		

Notes:

1. The higher patient discontinuation rates in the ROCKET-AF trial are likely due to the higher risk population enrolled in this trial.

2. There are key differences between the trials, so it is difficult to compare across the trials. For example, the trial of rivaroxaban enrolled patients at higher stroke risk.

KEY ISSUE: There are multiple medicine interactions with the NOACs that need to be managed. Further (as discussed earlier), there is no readily available, clinically validated marker to measure clinical response to interactions, and clinical trial populations may not accurately reflect the community use of concomitant medicines.

KEY ISSUE: Availability of newer agents may not necessarily lead to significant improvements in patient compliance and adherence to anticoagulant therapy. Poor compliance will not be able to be identified as a potential reason for under-anticoagulation by a readily available test such as INR.

KEY ISSUE: The discontinuation rates of the NOACs in the pivotal trials were very similar to those for warfarin. In the RE-LY trial no regular blood taking for INR monitoring was performed in the dabigatran arms of the trial; however, the discontinuation rate was higher than for the warfarin arm.

KEY ISSUE: Dabigatran capsules must be swallowed whole and cannot be repackaged into dose-administration aids, and the capsule cannot be opened for use in patients with severe dysphagia.

6.5 Reversal of bleeding with new oral anticoagulants

6.5.1 Management of bleeding

A recent literature review by the CADTH retrieved ‘limited evidence with uncertain applicability to clinical practice ... regarding strategies to manage over-anticoagulation and bleeding associated with the use of dabigatran and rivaroxaban’.¹⁶⁶ The review acknowledged that reversal strategies for the NOACs are emerging; however, these are currently only supported by anecdotal case reports published as conference abstracts.¹⁶⁶

The Australasian Society of Thrombosis and Haemostasis is currently preparing guidelines for monitoring and reversal of the NOACs with the aim of these becoming national guidelines.

6.5.2 Reversal of dabigatran

Submissions raised concerns regarding the lack of a proven antidote for bleeding with dabigatran^{4, 53, 64, 79, 88, 152, 172} and one submission outlined that this was a particular concern because gastrointestinal bleeds are more frequent with dabigatran than with warfarin.⁶⁴

The Cardiac Society of Australia and New Zealand outlined that ‘apart from ceasing the drug, management is supportive only. There is some evidence that the effect can be reduced by use of certain blood products along with consideration to dialysis’ is the current management approach to serious bleeding with dabigatran.²

Local guidelines for the reversal of dabigatran have been developed in some areas, such as the Queensland Health *Guidelines for Managing Patients on Dabigatran (Pradaxa®) who Present to Hospital*¹⁷³ (see Figure 6.1).

Management of bleeding		
Currently, there is no available antidote for dabigatran. Prothrombin complex concentrates have been shown to be ineffective (in contrast to rivaroxaban studies). Vitamin K and fresh frozen plasma infusion have not been shown to be effective. The effect of Factor VIIa (Novoseven®) is currently unknown.		
Dabigatran associated bleeding		
If a patient is bleeding, discontinue dabigatran therapy and investigate for site of bleeding. Initiate symptomatic treatment and optimise renal function. Review all medications and discontinue all anticoagulants, anti-platelets and NSAIDs. Check for possible drug interactions (see above). Check coagulation screen (APTT, TT and fibrinogen assay); indicate time of last dose on request form. Check full blood count, renal function and electrolytes (including calcium). Organise blood group and hold, and blood group antibody screen.		
Mild bleeding	Moderate to severe bleeding*	Life threatening†
<ul style="list-style-type: none"> Withhold next dose of dabigatran or discontinue treatment as appropriate. Apply local measures and treat any underlying infection. 	<ul style="list-style-type: none"> Discontinue dabigatran. Consult Haematology Service. Mechanical compression, or consider surgical intervention or wound packing. Fluid replacement to maintain good urine output as dabigatran is renally excreted. Consider platelets if levels less than 70-80 x 10⁹/L or patient on anti-platelet agent. Consider anti-fibrinolytic agent, tranexamic acid IV 15-30mg/kg, possibly followed by a continuous infusion at 1mg/kg/hr and continue until bleeding under control. Oral charcoal application if dabigatran ingested in last 2 hours. 	<ul style="list-style-type: none"> Implement all measures for moderate to severe bleeding, and: Recombinant factor VIIa (Novoseven®) IV bolus 50microg/kg may be trialled if critical. Seek Haematology guidance.* Note factor VIIa half life is significantly shorter than dabigatran; may require further dosing of factor VIIa. Haemodialysis (especially if renal failure present) may remove approximately 60% of dabigatran. Charcoal haemofiltration.
<p>* Moderate to severe bleeding: reduction in Hb of greater than or equal to 20g/L, transfusion of greater than or equal to 2 units of red blood cells, or symptomatic bleeding in critical area or organ.</p> <p>† Life-threatening bleeding: symptomatic intracranial bleed, reduction in Hb of greater than or equal to 50g/L, transfusion of greater than or equal to 4 units of red blood cells, hypotension requiring inotropic agents or bleeding requiring surgical intervention.</p> <p>◆ NB: Individual Patient Approval should be obtained as per hospital or District procedure for recombinant factor VIIa 'For the management of life-threatening bleeding and coagulopathy in non-haemophilic patients who have failed to respond to conventional therapy.' (QH LAM , see Appendix 9).</p>		

Source: Queensland Health (2011)¹⁷³

Figure 6.1 Guidelines for the reversal of dabigatran

Some authors have commented that ‘time is an important antidote with the NOACs’ due to their half-lives of less than 12 hours;¹⁷⁴ however, these half-lives are prolonged as renal function declines.

6.5.3 Reversal of other new oral anticoagulants

There is some evidence that prothrombin complex concentrate may reverse anticoagulation with rivaroxaban,¹⁷⁵ and this was identified in some submissions.^{77, 79} However, this evidence is from a trial of 12 healthy volunteers, and effectiveness was measured based on laboratory markers, the clinical meaningfulness of which are uncertain.¹⁶⁶

6.5.4 Reversal of new oral anticoagulants in perioperative settings

The lack of reversal agent for dabigatran was raised as a specific concern in emergency settings¹⁷⁶ and perioperative settings,¹⁷⁷ with the Royal Australasian College of Physicians

stating that ‘in patients with urgent surgery, dabigatran would need to be ceased and surgery deferred if possible’.⁶⁴ One submission raised the example of a case where surgery was delayed for a patient on dabigatran with a fractured neck of femur and gastrointestinal bleed in New Zealand.¹⁵⁷

A recent subgroup analysis of the RE-LY trial indicated that dabigatran and warfarin were associated with similar rates of periprocedural bleeding, although shorter interruption periods were possible with dabigatran because of its shorter elimination half-life.¹⁷⁸

The Cardiac Society of Australia and New Zealand discuss a recent report by Lakkireddy et al¹⁷⁹ that found that, in patients undergoing radiofrequency ablation for AF, ‘periprocedural dabigatran use significantly increased the risk of bleeding or thromboembolic complications compared with uninterrupted warfarin therapy’.²

6.5.5 Cost of reversal

In view of the lack of a commonly available antidote for reversal of life-threatening anticoagulation by NOACs, the recommended use of recombinant factor VIIa, haemodialysis or charcoal haemofiltration can be expensive.

KEY ISSUE: The lack of a clinically proven reversal agent and reversal guidelines for NOACs in clinical use is problematic, notwithstanding the benefits that these agents have in terms of a reduction in the risk of ICH.

OPTIONS AND QUESTIONS FOR THE REVIEW

Options for reversal of bleeding with NOACs

- Ensure that any clinical guidelines around the use of anticoagulants in AF include clear advice regarding the most appropriate monitoring and reversal strategies for any agents being used in practice.
- Ensure that patient and physician education strategies promote awareness of the lack of a marker and antidote for the new agents, so that decision making regarding the new agents is appropriately informed.

Focus questions

27. Within what timeframes is it envisaged that validated, standardised, monitoring tests that provide clinicians with an indication of a patient's risk of haemorrhage will be commercially available for NOACs, and at what cost?
28. If a test(s) becomes available, in what circumstances would clinicians want to use the test(s)? Would the test(s) be used in routine practice to monitor patients? Would patient doses be personalised instead of using the fixed-dose regimes? At what frequency would the test(s) be used? What would be the impact on the cost-effectiveness of NOACs if such a test(s) became routine practice?
29. What value is placed by clinicians and patients on the current availability of a simple INR test to monitor warfarin, which has been validated to predict risk–benefit and allow individual patient dose titration? Is the absence of such a simple monitoring tool for NOACs seen to be a significant clinical management disadvantage?
30. What value do patients and physicians place on the ability to reverse bleeding with anticoagulation therapy?
31. What is the cost of managing a major bleed in patients with NOACs compared to those receiving warfarin? What proportion of the major bleeds due to NOACs need to be actively managed compared to waiting until the medicine is cleared (acknowledging the shorter half-lives of NOACS compared to warfarin)?
32. What is the role of HAS-BLED in decision making and risk management in determining the most appropriate anticoagulant therapy — should a greater emphasis be placed on this score with the newer agents in light of the inability to monitor anticoagulant intensity and reverse bleeding? Or should this also take into account differentials in bleeding risks with each of the anticoagulant therapies?

6.6 Translation of the results of the key pivotal clinical trials of NOACs into practice

A number of submissions outlined that the full safety profile of NOACs in the general community may be different to that observed in the clinical trial scenario, where patients are selected to be enrolled in trials.⁸⁸ Submissions raised concerns about whether the trial participants were representative of the Australian population likely to take the medicine in clinical practice.^{64, 172} For example, one submission stated that the patients in the pivotal clinical trial for dabigatran were ‘younger, larger and with better renal function, and with less comorbidity and co-medication compared to those in whom it is used in clinical practice’.¹⁵²

Submissions also discussed that there is a lack of long-term safety data with the NOACs, with follow-up data limited to two or three years.⁶³⁻⁶⁴

KEY ISSUE: There is uncertainty regarding the translatability of the trial results.

OPTIONS AND QUESTIONS FOR THE REVIEW

Options for translating results of clinical trials of NOACs into practice

- Restrict the use of NOACs until more information is known regarding their safety profile in a clinical practice population.²
- Conduct extensive postmarket surveillance of the NOACs, including through a clinical registry that includes information regarding efficacy and toxicity.^{2,152}

6.7 Miscellaneous

6.7.1 Myocardial infarction

Submissions raised the issue of a recent meta-analysis linking dabigatran to an increased incidence of myocardial infarction (heart attack) and angina (chest pains) compared to warfarin.^{4, 64, 88, 157, 180-181} One submission highlighted that in New Zealand there have been uncertainties regarding management approaches to patients with acute myocardial infarction who are on dabigatran.¹⁵⁷

Similar increases in myocardial infarction in other NOACs have not been reported.

Appendix 1

New oral anticoagulation agents — further information

Table A1 outlines the characteristics and registration status of dabigatran, rivaroxaban and apixaban.

Table A1 Characteristics and registration status of dabigatran, rivaroxaban and apixaban

	Dabigatran	Rivaroxaban	Apixaban
TGA-registered indications	<p>1. The prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement).</p> <p>2. The prevention of stroke and systemic embolism in patients with nonvalvular AF and at least one risk factor for stroke.</p>	<p>1. The prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement).</p> <p>2. The prevention of stroke and systemic embolism in patients with nonvalvular AF and at least one risk factor for stroke.</p> <p>3. Treatment of deep vein thrombosis, and for the prevention of recurrent deep vein thrombosis and pulmonary embolism.</p>	<p>1. The prevention of venous thromboembolic events in adult patients who have undergone elective total hip or total knee replacement surgery.</p>
Mechanism of action (refer to Figure 5.1)	direct thrombin inhibitor	factor Xa inhibitor	factor Xa inhibitor
Clearance	<p>80% eliminated unchanged by renal excretion.</p> <p>Dabigatran etexilate (but not the active dabigatran) is a substrate of P-gp.¹⁵⁸</p>	<p>36% excreted unchanged. 44% liver metabolism via CYP3A4, CYP2J2 and CYP-independent mechanisms involving P-gp transporter systems.¹⁸²</p>	<p>27% excreted unchanged. Major enzymes that metabolise apixaban to inactive metabolites are CYP3A4/5 and sulfotransferase 1A1. Minor contributors are CYP1A2, 2C8, 2C9, 2C19 and 2J2. Substrate of P-gp.¹⁸³</p>

... Continued

	Dabigatran	Rivaroxaban	Apixaban
Oral bioavailability	The bioavailability is low (6%) and the product is formulated using a tartaric acid core to aid dissolution. It is administered as an inactive 'pro-medicine' (dabigatran etexilate) and is converted into its active form (dabigatran). Oral bioavailability increased by about 1.8-fold (+75%) when the pellets are taken without the HPMC capsule shell; therefore, the HPMC capsules should always be preserved in clinical use. ¹⁵⁸	Oral bioavailability of 80–100%. Oral bioavailability is affected by food. Bioavailability of 20 mg tablet is 66% under fasting conditions. ¹⁸²	Oral bioavailability of approximately 50%. ¹⁸³
Half-life	12–14 hours in elderly healthy volunteers; 14–17 hours in surgical patients. ¹⁵⁸	5–9 hours in young patients; 11–13 hours in the elderly. ¹⁸²	12 hours
Dosing frequency	Twice daily	Once daily	Twice daily
Dosage for stroke prevention in patients with AF (TGA-approved unless otherwise indicated)	150 mg twice daily or 110 mg twice daily should be used in patients aged over 75 years and may be considered in the following groups of patients: <ul style="list-style-type: none"> with renal function of 30–50 mL/min and patients with a potentially higher risk of bleeding. 	20 mg once daily or 15 mg for patients with renal function of 30–49 mL/min. ¹⁸²	From ARISTOTLE trial: 5 mg twice daily, or 2.5 mg twice daily in patients with two or more of the following risk factors: <ul style="list-style-type: none"> reduced renal function age over 80 years weight less than 60 kg.
C _{max}	0.5–2.0 hours ¹⁵⁸	2–4 hours ¹⁸²	3–4 hours ¹⁸³
Name of pivotal trial	RE-LY (Randomised Evaluation of Long-Term Anticoagulation Therapy)	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) ¹³⁸	ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) ¹⁰⁴

AF = arterial fibrillation; HPMC = hard gelatin and hypromellose; P-gp = P-glycoprotein; TGA = Therapeutic Goods Administration

Table A2 compares the baseline characteristics of trial participants in the three pivotal trials of novel oral anticoagulants (NOACs).

Table A2 Comparison of baseline characteristics of trial participants for novel oral anticoagulants

Baseline characteristics of study participants (active arm)	RE-LY (dabigatran)		ROCKET (rivaroxaban) (characteristics of ITT population)	ARISTOTLE (apixaban)
	110 mg	150 mg		
Age (years)	71.4	71.5	73.0	70.0
Weight (kg)	82.9	82.5	82.1	82.0
Male sex (%)	64.3	63.2	60.3	64.5
Prior warfarin/VKA (%)	50.1	50.2	62.3	57.1
BP				
Systolic (mmHg)	130.8	131.0	130.0	130.0
Diastolic (mmHg)	77.0	77.0	80.0	82.0
CHADS₂				
Mean	2.1 ± 1.1	2.2 ± 1.2	3.48 ± 0.94	2.1 ± 1.1
0 or 1 (%)	32.6	33.2	NIL	34.0
2 (%)	34.7	35.2	13.0	35.8
3–6 (%)	32.7	32.6	87.0	30.2
Comorbidities				
Prior stroke or TIA (%)	19.9	20.3	54.9	19.2
Prior MI (%)	16.8	16.9	16.6	14.5
With diabetes (%)	23.4	23.1	40.4	25.0
With heart failure (%)	32.2	31.8	62.6	35.5
With hypertension (%)	78.8	78.9	90.3	87.3
Medicines in use at baseline				
Aspirin (%)	40.0	38.7	36.3	31.3
Statin (%)	44.9	43.9	43.0	45.0
PPI or H ₂ -receptor antagonist (%)	17.2	17.9	12.9	18.5
ARB or ACE inhibitor (%)	66.3	66.7	77.7	70.9
Beta-blocker (%)	62.9	63.7	62.1	63.6
Amiodarone (%)	10.4	10.9	–	11.1

– = unknown; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ITT = intention-to-treat; MI = myocardial infarction; PPI = proton pump inhibitor; TIA = transient ischemic attack; VKA = vitamin K antagonist

Table A3 outlines key elements of the design of each of the pivotal trials of the NOACs.

Table A3 Design of NOAC trials

	RE-LY (dabigatran)	ROCKET (rivaroxaban)	ARISTOTLE (apixaban)
Trial design	Compared two doses of dabigatran (110 mg and 150 mg), each administered in a blinded manner with open-label use of warfarin. ¹³⁹	Double-blind, randomised trial that compared rivaroxaban (20 mg daily or 15 mg daily in patients with reduced renal function, as indicated by a CrCL of 30–49 mL/min) to adjusted-dose warfarin. ¹³⁸	Double-blind, randomised trial that compared apixaban (5 mg or 2.5 mg twice daily in patients with two or more of the following risk factors: <ul style="list-style-type: none"> • reduced renal function • >80 years old • weight less than 60 kg) to adjusted-dose warfarin. ^{104, 138}
Number of participants	18,133	14,264	18,201
Number of trial centres	951	1178	1034
Number of countries	44	45	39
Median follow-up (years)	2.0	1.9	1.8
Exclusion criteria — renal function	CrCL <30 mL/min	CrCL <30 mL/min	CrCL <25 mL/min
Inclusion criteria	AF and at least one of the following: <ul style="list-style-type: none"> • previous stroke/TIA • heart failure • >74 years old • 65–74 years old plus diabetes, hypertension or coronary artery disease. 	History of stroke/TIA/SE or 2 or more of: <ul style="list-style-type: none"> • congestive heart failure or LVEF <35% • >74 years old • hypertension • diabetes. The number of participants with only 2 risk factors was capped at 10%.	AF and at least one of the following: <ul style="list-style-type: none"> • previous stroke, TIA or systemic embolism • heart failure • >74 years old • hypertension • diabetes.
Average TTR in warfarin arm (% mean)	64.0	55.0	62.2
Method of warfarin dosing and INR monitoring	Warfarin was adjusted locally. INR was measured at least monthly. TTR values reported back to participating centres with advice for optimal INR control.	PoCT device generated encrypted values that were sent to independent centres to monitor, who provided study sites with either real or sham INR values.	Blinded, encrypted, PoCT device. Warfarin-dose adjustments per algorithm. A program was implemented to improve the quality of INR control through education and feedback at the site and country levels.
Analysis	Intention-to-treat	Per-protocol (found superiority in analysis of patients receiving at least one dose of a study medicine)	Intention-to-treat

CrCL = creatinine clearance rate; INR= international normalised ratio; LVEF = left ventricle ejection fraction; PoCT = point-of-care testing; SE = systemic embolism; TIA = transient ischemic attack; TTR = time in therapeutic range

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