



Australian Government

Department of Health and Ageing

Review of Anticoagulation Therapies in Atrial Fibrillation

Paper-based publications

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Editing and production by Biotext

Foreword

This review was commissioned in September 2011 by the Hon Nicola Roxon, the former Minister for Health and Ageing. The report has been prepared after extensive consultation with stakeholders via the receipt of submissions, the evaluation of the existing literature, the preparation of an Issues and Options paper, a Stakeholder Forum, meetings with individual stakeholders and consultation with an expert reference group.

The terms of reference for the Review were wide ranging and involved a consideration of the current situation and future management options for anticoagulation in patients with atrial fibrillation (AF).

The report is presented as two parts. Part A contains the key issues identified during the review together with recommendations that address the terms of reference. Part B is the supporting evidence for the recommendations. In addition to specific recommendations, the report contains a number of suggested options or suggestions for further consideration by various stakeholders for the development of an improved management of anticoagulation in patients with atrial fibrillation.

AF is a common disease, particularly in the elderly, which affects approximately 300,000 Australians. It is a significant contributor to the incidence of strokes that are associated with high morbidity and mortality. The consequential cost to the health system is large and these costs are anticipated to increase as a result of an ageing population.

A significant proportion of the patients with AF have no symptoms and many of these are undiagnosed but at a high risk of stroke, while a further pool of patients with diagnosed AF are also not being provided with appropriate therapy to minimise their risk of stroke. The Review identifies these people as a major source of preventable strokes and makes recommendations regarding a national approach to the better diagnosis and management of patients with AF. This includes the development of a comprehensive guideline from which professional support and education programs should be developed. In addition a campaign aimed at improving the awareness of AF should be developed for both health professionals and consumers.

The most common antithrombotic medicines that are used for the reduction of stroke risk at the present time are the anticoagulant warfarin, and/or the antiplatelet agents aspirin and/or clopidogrel. Warfarin is more effective than the antiplatelet agents and has been shown to reduce the risk of stroke in AF patients by approximately 65%. However warfarin needs to be closely monitored by the use of regular blood sampling to ensure the appropriate level of anticoagulant control and its response can be variable within and between individuals. For patients receiving warfarin, there is a balance between stroke risk reduction and the risk of bleeding, with the most feared bleeding risk associated with warfarin being haemorrhagic stroke.

The Review has found that by addressing the barriers to the use of warfarin and improving its quality of use, an improvement in health outcomes and patient satisfaction is likely to occur. The Review recommends that a greater range of options for the management of warfarin be made available and that these should be considered in the context of existing programs and/or for government support.

The Review identifies that the new oral anticoagulants (NOACs) provided an additional option to patients with AF and that a consistent and clinically relevant finding from the pivotal clinical trials was a reduction in the event rate of haemorrhagic strokes compared to warfarin. NOACs also provide an alternative to patients who are unable to tolerate existing therapies. The impact of NOACs on ischaemic strokes and bleeding rates compared to warfarin therapy varies between

the various agents and dosage regimens but no direct head-to-head comparative data are available. The Review has identified a number of factors relevant to Australia that have become apparent over the past 18 months that will impact on the uncertainty of the cost-effectiveness of NOACs in wider Australian clinical practice when compared to that calculated from the pivotal clinical trials. These include, but are not limited to, the quality of warfarin management, characteristics of AF patients in Australia compared to the clinical trial population, switching patterns, and the inability to monitor anticoagulant response in patients with comorbidities receiving multiple medications.

The Review recommends that the Minister for Health asks the Pharmaceutical Benefits Advisory Committee to consider the impact of these identified factors to determine if option(s) that might address the resultant uncertainty are required, particularly in view of the high increased total cost of the new agents over current therapies.

An improvement in the management of stroke prevention in patients with AF is required. To address this issue, the Review has identified options that take into account the burden of the disease, the need for better clinical guidance and management options, and the opportunity costs associated with new therapies to ensure optimal cost-effectiveness in clinical practice.

In presenting this Review, I would like to acknowledge the input of stakeholders and the hard work and dedication of the Review team, in particular Ms Maria Donohue, who have supported me in the conduct of the Review.

A handwritten signature in black ink, appearing to read 'L Sansom', with a long horizontal flourish extending to the right.

Emeritus Professor Lloyd Sansom AO

October 2012

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Acronyms and abbreviations

AF	atrial fibrillation
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
ACSOM	Advisory Committee on the Safety of Medicines
AUSPAR	Australian Public Assessment Report
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 75 years or over (2 points), diabetes mellitus, prior stroke or transient ischaemic attack (2 points), vascular disease, age 65–74 years, sex (female)
CI	confidence interval
COX-2	cyclooxygenase two
CrCL	creatinine clearance
CSANZ	Cardiac Society of Australia and New Zealand
C _{ss}	Concentration at steady state
cTTR	centre's mean TTR (time in therapeutic range)
CYP2C9	cytochrome P450 isoenzyme 2C9
CYP3A4	cytochrome P450 isoenzyme 3A4
CYP1A2	cytochrome P450 isoenzyme 1A2
ECG	electrocardiogram
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
GFR	glomerular filtration rate
GI	gastrointestinal
GP	general practitioner
GPRN	General Practice Research Network
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); drugs or alcohol (1 point each)
HDL	high-density lipoprotein
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
ICH	intracranial haemorrhage
INR	international normalised ratio
LMWH	low molecular weight heparin
MBS	Medicare Benefits Schedule
MI	myocardial infarction
MSAC	Medical Services Advisory Committee
NNH	number needed to harm

NNT	number needed to treat
NOAC	new (or novel) oral anticoagulant
NSAID	nonsteroidal anti-inflammatory drug
NSF	National Stroke Foundation
NVAF	nonvalvular atrial fibrillation
OR	odds ratio
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCC	prothrombin complex concentrate
P-gp	P-glycoprotein
PoCT	point-of-care testing
PPI	proton-pump inhibitor
QALY	quality-adjusted life-year
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
RR	relative risk
SPRINT	Stroke Prevention Results In Atrial Fibrillation Therapy
SSRI	selective serotonin reuptake inhibitors
TGA	Therapeutic Goods Administration
TIA	transient ischaemic attack
TTR	time in therapeutic range
VKA	vitamin K antagonist (coumarins; i.e. warfarin in Australia, but internationally, phenprocoumon and acenocoumarol are used)
VKORC1	vitamin K epoxide reductase complex subunit 1

Symbols

<	less than
>	more than
≤	less than or equal to
≥	more than or equal to

Recommendations

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).

Review recommendations

Recommendation 1 — atrial fibrillation awareness

Programs to increase the awareness of atrial fibrillation (AF) (including its prevention and detection) in patients and health professionals should be developed and implemented.

This recommendation should be facilitated by the development of an Australian clinical guideline for AF, and the implementation of a multifaceted educational program (see Chapter 2).

Recommendation 2 — national guidelines

A national guideline for the detection and management of AF should be developed as part of a multifaceted program in order to bring about evidence-based changes in behaviour.

Recommendation 3 — scope of national guidelines

In regard to anticoagulation therapies in the management of AF, the national guideline will need to consider:

- a systematic approach to risk assessment (assessment of stroke risk through algorithms such as CHADS₂ and CHA₂DS₂-VASc, and bleeding risk through algorithms such as HAS-BLED); therapeutic options (including addressing barriers to the optimisation of anticoagulant use); and the cost-effectiveness of therapeutic options
- nationally endorsed dosing and management algorithms for all available anticoagulants; such algorithms would need to cover situations such as initiation, frequency of monitoring for efficacy and for toxicity, adjustment of dosage when required, cessation of therapy and switching between therapies. This should also include recommendations for the calculation and use of time in therapeutic range (TTR) for warfarin
- pre-operative and peri-operative management of bleeding risk
- management of bleeding or over anticoagulation taking into account different healthcare environments and resources available to mitigate or reverse this adverse effect
- consideration of concomitant medicines and comorbid conditions, including development of a resource for alternative treatment options to medicines shown to interact with warfarin or other anticoagulants; and consideration of including this resource within prescribing and dispensing software and other information and communication systems
- the risk–benefit profile of combining anticoagulant and antiplatelet therapies
- guidelines on appropriate provision of patient education, including lifestyle issues (including recommendations regarding vitamin K intake in patients receiving warfarin, as outlined in Recommendation 14)
- overall management of patients on anticoagulants (for example how to monitor patients on NOACs in regard to renal function and signs of over anticoagulation).

Recommendation 4 — dissemination and implementation of guidelines

The national guideline should be widely disseminated. Modules should be developed from the guideline, which can then be integrated into clinical practice through decision-support systems, including prescribing software, and be available from multiple communication platforms, including applications (‘apps’) for mobile phones and tablets.

Recommendation 5 — educational materials

To improve the health outcomes for patients with AF, appropriate resources should be developed from the national guideline and be available in a wide variety of formats. These should be readily accessible to consumers and carers and used in education, training and professional development programs for health professionals.

Recommendation 6 — warfarin initiation

During the initiation period, all patients commenced on warfarin should be included in one or more programs designed to optimise outcomes and minimise risks:

- For patients started on warfarin during a hospital admission, the proportion who participate in a structured initiation program should be considered by the Australian Commission on Safety and Quality in Healthcare as a key performance indicator in its standards for hospital accreditation.
- Medicare Locals should investigate the availability and coordination of community-based anticoagulation support services for patients started on warfarin in the community.

Recommendation 7 — pharmacogenomic screening

Government funding of routine pharmacogenomic screening of patients commencing warfarin therapy is not recommended at this time.

However, a cost-effectiveness analysis of pharmacogenomic testing of CYP2C9 and vitamin K epoxide reductase complex subunit 1 (VKORC1) in AF patients with a high bleeding risk (e.g. HAS-BLED score ≥ 4) commencing warfarin should be undertaken to determine whether, in this subgroup of patients, such an intervention improves health outcomes and is cost-effective.

Recommendation 8 — Warfarin maintenance - optimisation of time in therapeutic range

Optimisation of the time in the therapeutic range (TTR) should be a goal for patients treated with warfarin, and identification of factors that influence TTR should be a key part of a warfarin management plan for each patient.

This recommendation should be facilitated by the development of the Australian clinical guideline for AF and the implementation of a multifaceted educational program (see Recommendation 5).

Advice regarding the measurement and application of a patient’s TTR should be developed as part of the guidelines, and implementation of this could be facilitated through IT (such as Personally Controlled Electronic Health Records, prescribing software or pathology laboratory computer systems).

Recommendation 9 — government support of options for warfarin management

A wider range of options for the management of warfarin patients should be considered for government support. Options that should be considered are those that offer greater convenience and support to patients in a timely, systematic and coordinated fashion, and that incorporate patient education, systematic international normalised ratio (INR) testing, tracking, followup and effective communication of results and dosing decisions to patients.

Recommendation 10 — point-of-care testing

The use of point-of-care testing (PoCT) for the measurement of INR values should be considered as an option for warfarin management, particularly in the community setting. Such testing could be conducted at a medical practice or could involve a collaborative shared-care arrangement between a patient's medical practitioner and other health professionals with whom the patient has regular and convenient contact (e.g. domiciliary and residential care qualified staff, pharmacists). Uptake of PoCT in Australia, as a component of a warfarin management program, should be considered for government support.

Recommendation 11 — shared-care model

A nationally endorsed shared-care model for warfarin monitoring and management between health practitioners should be developed. This will require the development of standard protocols and quality assurance systems and consideration of relevant legislation. Such a model has the potential to significantly improve both health outcomes and patient satisfaction.

Recommendation 12 — pathology laboratory warfarin programs

Consideration should be given to the development of a formalised structure of anticoagulation programs offered by pathology laboratories throughout Australia and to the funding of such a structure. This would need to involve accreditation of such programs as part of a model of shared responsibility, and the development and endorsement of standard operating procedures (including validation of decision algorithms, patient-management protocols and a quality assurance framework).

The Medical Services Advisory Committee should be asked to consider this matter. Introduction of a 'patient warfarin-management fee', or an incentive payment linked to the proportion of patients within a certain INR range, rather than an additional Medicare Benefits Schedule fee per INR test, would address concerns regarding potential overservicing of INR testing.

Recommendation 13 — access to patients' health records

To improve the management of anticoagulation therapies through promoting access to a patients' current health record, patients on anticoagulation therapy and health practitioners involved in their care should be encouraged to register for e-health initiatives such as a Personally Controlled Electronic Health Record.

Recommendation 14 — national vitamin K guideline

The Dietitians Association of Australia should be asked to develop appropriate material regarding dietary intake of vitamin K in patients receiving warfarin, as a component of the national AF clinical management guideline.

Recommendation 15 — new oral anticoagulants

While warfarin will retain a place in the management of stroke risk in patients with atrial fibrillation, new oral anticoagulants (NOACs) offer an important clinical benefit in reducing the incidence of intracranial haemorrhages in AF patients who receive anticoagulants and offer patients who are unable to take warfarin an effective alternative. However, the net overall benefit of NOACs in clinical practice and the subsequent impact on cost-effectiveness is uncertain at this stage, given the further information about dabigatran use that has become available since the Pharmaceutical Benefits Advisory Committee (PBAC) decision regarding this NOAC in 2011.

In view of the uncertainties identified in the Review regarding the magnitude of any incremental clinical and cost-effectiveness benefit of NOACs over other therapies when introduced into widespread clinical practice, and the high total predicted cost, it is recommended that the Minister for Health asks PBAC to review its previous recommendations of NOACs, including consideration of the following options:

- a) The establishment of a managed entry scheme for the PBS availability of NOACs. This would take into account the identified uncertainties while acknowledging the clinical need for effective alternatives to warfarin. In considering a managed entry scheme, PBAC should evaluate the entry price that addresses the uncertainties and what ‘fit for purpose’ evidence would be required to address these to ensure that acceptable cost-effectiveness is achieved in the clinical practice setting once the medicines are subsidised.
- b) The PBS listing of NOACs as a restricted benefit for patients unable to tolerate warfarin therapy and/or who are unable to obtain satisfactory INR control despite specific measures. There would need to be a definition of ‘satisfactory INR control’ together with a price–volume arrangement which addresses the risk to the Australian Government of use beyond any restriction.

The Review notes that PBAC is the statutory committee with the legal responsibility of making recommendations (including advice regarding any restrictions) to the Minister for Health regarding the listing of medicines on the Pharmaceutical Benefits Scheme (PBS), and may make recommendations different to the two options presented above.

About the Review

Background

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 review the use of anticoagulation therapies in people with atrial fibrillation (AF).

The announcement of this review — the Review of Anticoagulation Therapies in Atrial Fibrillation (hereafter, ‘the Review’) — followed a PBAC recommendation in 2011 that a new oral anticoagulant, dabigatran, was suitable for consideration for inclusion on the Pharmaceutical Benefits Scheme (PBS) for the prevention of stroke or systemic embolism in certain groups of people with AF. In making its recommendation, the 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 anticoagulants — would now be treated with dabigatran, which would likely lead to additional benefits and costs not measured in clinical trials
- people at low risk of stroke currently managed on aspirin or no treatment may be unnecessarily transferred to dabigatran.

Terms of reference

The terms of reference of 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.

Overview of key issues

AF is a common form of irregular heart beat (cardiac arrhythmia) and it has been estimated that, in Australia, approximately 240,000 to 400,000 people have the condition. AF increases the risk of ischaemic stroke (a stroke that arises from an occlusion of blood flow to part of the brain) by around five-fold. Also, 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 reduction of stroke risk.

However, management options are complicated by the epidemiology of AF — it is more prevalent in elderly people in whom co-existing conditions and concomitant medicines are common. There is no comprehensive, readily available Australian guideline for anticoagulation in people with AF.

For many years moderate-to-high stroke risk in people with AF has been managed predominantly by prophylactic anticoagulant therapy with warfarin. Warfarin is a highly effective medicine; however, there are barriers to its use including:

- *Regular monitoring of its clinical effect is required.*
Issues identified with warfarin monitoring included inconvenience; patient time and travel costs; availability of facilities in rural areas; and difficulties of taking samples of venous blood. A range of models for monitoring warfarin are used in Australia and internationally and optimisation of these models could reduce or eliminate some of the issues identified above.
- *Inpatient and outpatient variability in response.*
This may result from a number of known factors (e.g. drug and food interactions and genetic polymorphism), some of which can be addressed or modified by appropriate management.
- *Its use is associated with intracranial haemorrhage.*

New oral anticoagulants (NOACs) with mechanisms of action different to that of warfarin are now becoming available for clinical use. These new agents have the potential to offer AF patients alternatives to warfarin therapy. It has been claimed, on the basis of results from clinical trials, that they provide at least the same protection against stroke and major bleeding as warfarin without the need for regular monitoring, and they reduce the risk of intracranial haemorrhage (ICH).

However, a number of factors have been shown to impact on the safety and efficacy of NOACs compared to warfarin in clinical trials, including but not limited to the quality of warfarin management in the control arm; the patient's risk of stroke and/or bleeding; and the patient's age. These factors could mean that the size of the overall benefit of the new agents may vary in Australian practice compared to the clinical trial population. For example, in New Zealand, where dabigatran is subsidised for this condition, and in the dabigatran Product Familiarisation Program in Australia, patients have generally been older than those recruited into the clinical trials. It is stated that NOACs do not require routine monitoring but this has recently been questioned. There is no widely available, standardised and validated test to monitor the bleeding risk of these new agents like there is for warfarin. In addition, there are no readily available reversal agents for NOACs.

Review process

Stakeholder consultation

The Australian Government Department of Health and Ageing invited interested parties and individuals to provide written submissions to the Review between 22 December 2011 and 23 February 2012. At that time, only one NOAC (dabigatran) had been considered by PBAC.

The department received 64 submissions from a range of stakeholders. The submissions put forward a variety of views, but 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 (e.g. Consumers Health Forum, National Stroke Foundation, Royal Australian College of General Practitioners and Pharmaceutical Society of Australia), the majority of which supported cautious uptake of dabigatran
- 7 submissions were from commercial organisations: 3 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.

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

The inconvenience of regular monitoring with warfarin was identified as an issue. Suggestions to address this issue 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 suggested subsidising NOACs as they are promoted as not requiring regular blood monitoring.

Options proposed to address the underuse of warfarin included the development of a national guideline, improved patient and prescriber education of the relative risks and benefits of warfarin therapy, prescriber incentives and consumer support programs, including targeting specific pharmacist home medicines reviews to patients receiving warfarin.

Other issues identified regarding warfarin were the reported medicine and food interactions, intra- and inter-subject 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 NOACs, mainly focusing on safety. For example, many submissions raised concerns about the adverse event profiles of the NOACs 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 renal function and the lack of antidote for bleeding 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.

An Issues and Options Paper was made available for public comment on 29 June 2012 (see Attachment A). The Issues and Options Paper brought together the issues and options relevant to the terms of reference that were raised in submissions to the Review, ongoing literature reviews, stakeholder consultations and discussions of the reference group. Stakeholders were invited to provide written feedback on the paper, and to attend a stakeholder forum, which was held on 4 July 2012. The feedback provided was taken into account in the preparation of this report.

Reference group

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

Structure of this report

This report has two parts:

- **Part A — Review findings and recommendations**
Part A provides a brief summary of the key issues identified in the Review, and recommendations to address these issues. A cross-reference is provided at the end of each chapter in Part A to the relevant details in Part B.
- **Part B — Supporting details and evidence**
Part B provides details of the review, including matters considered in the Review and evidence from the literature and submissions to the Review.

The report has one attachment:

- Issues and Options Paper.

PART A
REVIEW FINDINGS AND RECOMMENDATIONS

1 Atrial fibrillation

1.1 Key issues

- Atrial fibrillation (AF) occurs in 1–2% of Australians overall and is more common in older Australians.
- AF may be categorised as paroxysmal (recurrent episodes that self-terminate, usually within 48 hours), persistent (recurrent episodes that last more than one week), or permanent (ongoing AF).
- AF increases the risk of stroke.
- Management of AF involves consideration of reduction of stroke risk, symptom control, and identification and treatment of predisposing factors and concomitant disorders. Patients with paroxysmal AF should be treated in the same manner as those with persistent or permanent AF.
- Many cases of AF are not diagnosed.

1.2 Review findings and recommendations

1.2.1 Atrial fibrillation affects 1–2% of Australians and is more common in older Australians

AF is a common form of irregular heart rhythm. A minority (10%) of AF cases occur in people with rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair; this is described as *valvular AF*. The other 90% of AF is described as *nonvalvular AF* (NVAF) (Ang et al 1998).

NVAF affects 1–2% of Australians overall (the equivalent of 240,000–400,000 people) (Go et al 2001, Miyasaka et al 2006, Sturm et al 2002)¹ and this percentage increases sharply in older people. It is estimated that 1 in 20 people over the age of 65 years have NVAF, and this proportion increases to 1 in 10 for people aged over 75 (Wolf et al 1991). Based on projections from the United States (Miyasaka et al 2006), it is estimated that there will be 750,000 people in Australia with AF by 2030, which will have an increasing impact on health care services and costs.

Patients with AF commonly have a wide range of comorbid conditions.² Factors that predispose people to AF include coronary heart disease, hypertension, diabetes mellitus, obesity, sleep apnoea, renal disease and thyroid disease.³

1.2.2 Atrial fibrillation increases the risk of stroke

AF increases a person's risk for ischaemic stroke by about five-fold, whether or not symptoms of AF are present (Wolf et al 1991). Ischaemic strokes arise from an occlusion of blood flow to part of the brain. Due to ineffective atrial contraction in AF, stagnation of blood may occur, leading to clot formation. The embolised clot can be transported into the systemic circulation and then to the cerebral circulation where occlusion may occur (a type of ischaemic stroke called cardioembolic stroke).

¹ Submission from: National Stroke Foundation (2012)

² Submission from: Royal Australian College of General Practitioners (2012)

³ Submission from: Cardiac Society of Australia and New Zealand (2012)

Strokes in AF patients are also more severe than other types of ischaemic stroke, and result in greater morbidity and mortality (Béjot et al 2009, Gattellari et al 2011). AF has been implicated in 15–25% of all ischaemic strokes (Gattellari et al 2011).

1.2.3 Management of atrial fibrillation includes reduction of stroke risk, symptom control, and identification and treatment of predisposing factors and concomitant disorders

A key component of the management of AF is the reduction of a patient's risk of stroke using antiplatelet or anticoagulation therapies where appropriate. The decision about which therapy, if any, to use is based on an assessment of the level of stroke risk, which is usually classified as low, moderate or high using internationally recognised scales such as the CHADS₂ score (see Section 2.2.1).

Controlling a patient's heart rate and/or rhythm may also be required as part of the overall patient management. Over recent years, electrophysiological management of heart rhythm (e.g. through ablation) has become more common. It is anticipated that, as such technologies develop, a greater percentage of AF management will involve ablation and related interventions.

Comprehensive management of a patient with AF also requires early identification and treatment of predisposing factors and concomitant disorders (e.g. hypertension and hypercholesterolaemia), which also increase a patient's risk of stroke and other cardiovascular conditions (Lip et al 2012b). Thus, the use of 'upstream therapies' (e.g. antihypertensives and cholesterol-lowering therapies) may be appropriate (Lip et al 2012b).

1.2.4 Many cases of atrial fibrillation are not diagnosed

The symptoms of AF can include palpitations, dizziness, chest pain and shortness of breath, often noticed as an inability to tolerate exercise. However, approximately 10–30% of people with AF have no symptoms; many of these people are not diagnosed and thus do not receive appropriate treatment for stroke risk.⁴ Such people are considered to be a major source of preventable strokes, indicating that there is a need for greater awareness of AF and appropriate investigations for the presence of AF, particularly in the elderly. A screening program has been piloted in Australian pharmacies to identify undiagnosed AF using a pulse palpation and hand-held single-lead electrocardiograph device (Lowres et al 2012). A recent consensus document from the Royal College of Physicians of Edinburgh recommended that a national screening program for AF be introduced in the United Kingdom (RCPE 2012). Similarly, the recent European Society of Cardiology (ESC) guidelines for the management of AF recommend opportunistic screening in patients 65 years of age or over using pulse-taking (Authors/Task Force et al 2012). The National Stroke Foundation could be approached to incorporate 'Know your pulse rate' into its 'Know your numbers' program.⁵

Recommendation 1 — atrial fibrillation awareness

Programs to increase the awareness of atrial fibrillation (AF) (including its prevention and detection) in patients and health professionals should be developed and implemented.

This recommendation should be facilitated by the development of an Australian clinical guideline for AF, and the implementation of a multifaceted educational program (see Chapter 2).

⁴ Submission from: Cardiac Society of Australia and New Zealand (2012)

⁵ <http://strokefoundation.com.au/health-professionals/nsf-programs/know-your-numbers/>

1.3 Further information

See Part A, Chapter 2 for Review findings and recommendations about the assessment of stroke risk.

See Part B, Chapter 5 for further information about AF.

2 Management of stroke risk in atrial fibrillation patients

2.1 Key issues

- A patient's stroke risk can be assessed using internationally recognised classifications.
- The decision to use antiplatelet or anticoagulation therapy depends on:
 - the patient's risk of ischaemic stroke
 - the patient's risk of bleeding
 - other patient factors or preferences.
- Warfarin is an effective oral anticoagulation therapy.
- Many people who are appropriate candidates for anticoagulant treatment do not receive warfarin.
- The management of AF may be complicated by the other comorbid medical conditions that are common in the elderly.
- There are no comprehensive Australian guidelines for the management of AF.

2.2 Review findings and recommendations

2.2.1 A patient's stroke risk can be assessed using internationally recognised classifications

The actual magnitude of the increased stroke risk in a particular patient with AF depends on the presence of other risk factors, which form the basis for internationally recognised scales for stratifying patients into categories of stroke risk. The two scales that are most commonly used are the CHADS₂ score (shown in Table 2.1 below) and the CHA₂DS₂-VASc score (see Section 6.2). In both of these scales, a score of 0 (no additional risk factors) is interpreted as low risk, a score of 1 as moderate risk and a score of 2 or above as high risk. Most AF patients (about 90%) have at least one additional risk factor for stroke (Nieuwlaat et al 2006), and hence fall into the moderate or high-risk categories.

Table 2.1 Calculation of CHADS₂ score

Risk factor	Score
Cardiac failure	1
Hypertension	1
Age ≥ 75 years	1
Diabetes mellitus	1
Prior stroke or transient ischaemic attack	2
Maximum	6

Source: Adapted from Gage et al 2001

The CHA₂DS₂-VASc score was developed more recently than CHADS₂ and incorporates several additional risk factors — vascular disease, age between 65 and 74 years, and sex (female). This score enables greater stratification at lower levels of risk, but means that a larger number of patients fall into the moderate and high-risk categories (Lip et al 2010b). The recent ESC guidelines recommend the use of CHA₂DS₂-VASc in preference to CHADS₂ in the calculation of stroke risk in patients with AF (Authors/Task Force et al 2012).

2.2.2 The decision to use oral anticoagulation or antiplatelet therapy depends on a patient's risk of stroke and bleeding and other patient factors

Risk of ischaemic stroke

Low risk (CHADS₂ = 0)

Major international guidelines recommend that patients at low risk of stroke receive either no therapy or antiplatelet therapy (usually low-dose aspirin).

Moderate or high risk (CHADS₂ ≥ 1)

Oral anticoagulation therapy is reserved for patients at moderate-to-high risk of stroke because, although such therapy is more effective than antiplatelet therapy (e.g. aspirin) at reducing the risk of stroke, it is generally associated with increased bleeding. However, submissions to the review clearly indicated that a proportion of patients who are at moderate-to-high risk of stroke, and who are therefore eligible for anticoagulation therapy under international guidelines, are not receiving such therapy.⁶ Instead, a clinical decision is often made to treat these patients with the less effective antiplatelet therapy.

Risk of haemorrhage

The use of anticoagulants in the prevention of stroke in patients with AF is a balance between reducing the risk of ischaemic stroke and minimising the risk of bleeding (particularly intracerebral haemorrhage).

An increased risk of bleeding has been shown to be associated with increasing age, hypertension, history of myocardial infarction (MI) or ischaemic heart disease, cerebrovascular disease, anaemia, abnormal renal or liver function, stroke, history of bleeding or concomitant use of medicines such as antiplatelet medicines and nonsteroidal anti-inflammatory drugs (NSAIDs). Therefore, patients who have a greater risk of ischaemic stroke (as determined by CHADS₂ or CHA₂DS₂-VASc score) also have a greater risk of bleeding (which can be classified using similar scoring systems to those used for ischaemic stroke — e.g. the HAS-BLED score, discussed in Section 6.5). Other factors that increase the risk of major haemorrhage for patients receiving anticoagulation therapy include international normalised ratio (INR) values greater than 4 (Hylek et al 2007), and the first 3 months of warfarin therapy (Hylek et al 2007, Mant et al 2007, Poli et al 2011, Torn et al 2005).

The most feared complication of antithrombotic therapy is intracerebral haemorrhage, which occurs more frequently in patients receiving anticoagulants than in those not receiving such medication, and has a mortality rate exceeding 50% (Hart et al 2012). However, this increased risk of intracerebral haemorrhage in patients receiving anticoagulants is generally outweighed by the benefit of anticoagulation treatment in reducing the more frequent ischaemic stroke (Lip et al 2011a).

A significant proportion of AF patients receiving warfarin also take concomitant aspirin. This is problematic because the combination of antithrombotic therapies may compound the risk of bleeding in these patients (see Chapter 7). A recent subanalysis of the ICH in the RE-LY trial showed that the independent risk factors for ICH were assignment to warfarin (relative risk [RR] 2.9), aspirin use (RR 1.6), age (RR 1.1), and previous stroke/TIA (RR 1.8) (Hart et al 2012). This analysis demonstrates the need for guidance regarding the appropriate use of combined aspirin-anticoagulant use, particularly in view of the recent recommendation that the combination should be avoided in many patients (You et al 2012).

⁶ Submissions from: Atrial Fibrillation Association; National Stroke Foundation; Blombery PA; Paceline Inc.; Krause M (2012)

Other factors or preferences

Some patients who may be eligible for anticoagulation therapy are unable to receive such therapy because of contraindications and these patients will often receive no therapy or be treated with antiplatelet therapy.

Absolute and relative contraindications to the use of warfarin, according to the New South Wales Therapeutic Advisory Group's Indicators for Quality Use of Medicines in Australian Hospitals (NSW TAG 2007), are outlined in Table 2.2.

Table 2.2 Absolute contraindications to warfarin

	Absolute contraindications	Relative contraindications
Medical	<ul style="list-style-type: none">• Bleeding disorder• Complicated liver disease• Active gastrointestinal ulceration or bleeding in past 3 months• Previous intracranial haemorrhage/surgery• Previous intracerebral aneurysm/tumour• Ophthalmic surgery in past 3 months• Diabetic proliferative retinopathy	<ul style="list-style-type: none">• Uncomplicated liver disease• Previous gastrointestinal bleeding or ulceration
Functional	<ul style="list-style-type: none">• Fall in past 6 months associated with major bleeding	<ul style="list-style-type: none">• High risk of falls• No medication supervision and either visual or colour blindness, deafness, or language barrier
Cognitive	<ul style="list-style-type: none">• Uncontrolled psychosis• Dementia	<ul style="list-style-type: none">• No medication supervision and mild cognitive impairment (Mini Mental State Examination score 15–24/30)
Social	<ul style="list-style-type: none">• Current alcoholism (male > 60 g alcohol/day; female >40 g alcohol/day)	<ul style="list-style-type: none">• Nursing home resident, socially isolated
Iatrogenic	<ul style="list-style-type: none">• No medication supervision and poor compliance likely• Unable to self-medicate• High-risk drug interactions• Previous adverse drug reaction to warfarin	<ul style="list-style-type: none">• Frequent use of nonsteroidal anti-inflammatory drugs

Relevance to new oral anticoagulants

Key factors relating to the assessment of patients and the decision to start oral anticoagulant therapy apply to both warfarin and other oral anticoagulants. However, there is uncertainty as to what extent these factors would be mitigated by the new oral anticoagulants (NOACs).

2.2.3 Warfarin is an effective oral anticoagulation therapy

Warfarin has been in clinical use since the 1950s and is the most commonly used oral anticoagulant in Australia. It is highly effective at preventing stroke (64% risk reduction), and very cost-effective when used optimally.

Warfarin has a narrow therapeutic index, and its effectiveness and safety is a tight balance between risk of stroke and risk of bleeding. A patient's response to warfarin is monitored by measuring the patient's INR, which is 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 2–3. There is an increased stroke risk when INR values are below this range, whereas INR values above 3–4 are associated with an increased bleeding rate. Thus, warfarin requires careful dose titration and monitoring. However, the ability to use a readily accessible, validated surrogate (i.e. INR) for anticoagulant response assists in the management of patients.

A measure of anticoagulant control for warfarin during a specified period of time is called the ‘time in therapeutic range’ (TTR) (Rosendaal et al 1993); TTR is the percentage of time that an AF patient is estimated to be within the INR range of 2–3. An improvement in TTR will improve the risk–benefit profile of warfarin and lead to better patient outcomes. However, the TTR varies significantly among individuals, with estimates in Australian community-based practice of 50–68% (DoHA 2011a).

In those patients with poor TTR (< 60%), the annual mortality rate, major bleeding rate, and stroke and systemic embolism rates are all higher than in patients with good control (TTR > 70%) (White et al 2007). Retrospective studies found that a 6.9% improvement in TTR significantly reduced the rate of major haemorrhage by one event per 100 patient-years of treatment (Wan et al 2008).

Relevance to new oral anticoagulants

The ‘net clinical benefit’ (composite outcome of reduction in stroke, systemic embolism, pulmonary embolism, MI, death or major bleeding) of dabigatran compared to warfarin has been shown to be significantly influenced by TTR (Wallentin et al 2010). Thus, the higher the TTR for warfarin, the less likely there is to be a difference between warfarin and dabigatran for some outcomes.

The average TTR in the warfarin arms of the three pivotal multinational trials of the NOACs (dabigatran, rivaroxaban and apixaban) were 64%, 55% and 62.2%, respectively (noting that the rivaroxaban trial recruited patients who were at higher risk of stroke).

However, no interaction between TTR and net clinical benefit was seen in the pivotal trial of apixaban, which may indicate that the dominant effect of apixaban may be related to intracerebral haemorrhage.

An improvement in TTR in Australian clinical practice would have a significant effect on the incidence of bleeding and stroke with warfarin therapy. Achieving such an improvement would require attention to both individual patient factors and the delivery of anticoagulation management programs.

Factors that influence TTR for an individual patient (causing inpatient variability) include patient compliance and adherence; changes in patient vitamin K intake (particularly when baseline vitamin K levels are low); medicine interactions; concurrent illness such as diarrhoea; and the availability of patient support, including participation in anticoagulant monitoring programs.

One factor that influences TTR across clinical settings is the anticoagulation program offered to patients. 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. These findings indicate that higher TTRs (and therefore better outcomes) can be achieved through structured anticoagulation control programs (Wan et al 2008). For example, Australian patients in the key clinical trials of the NOACs dabigatran and apixaban had an average centre TTR (cTTR) of around 74% (Wallentin et al 2010, Wallentin and Collet 2011), and in these two trials patients from countries with health systems similar to those of Australia had TTRs of at least 70%. These results indicate that it is possible to achieve better control in the context of the Australian (or similar) health system if appropriate support systems are in place (see Recommendation 8).

2.2.4 Many people who are appropriate candidates for anticoagulation therapy do not receive treatment

Many people who have been diagnosed with AF are not receiving pharmacotherapy that accords with existing treatment recommendations. Untreated and undertreated patients are considered to be a major source of preventable strokes.

It is estimated that only 40–60% of patients who are appropriate candidates for oral anticoagulation receive anticoagulant treatment. As noted above, some patients who are at moderate-to-high risk of stroke receive antiplatelet therapy (e.g. aspirin) rather than the more effective anticoagulant therapy. A range of factors contribute to underuse of warfarin, particularly:

- the need for regular monitoring of the anticoagulant response to warfarin (by measuring a patient's INR), which may be seen as an inconvenience to patients, carers and health professionals
- the difficulty in managing labile INRs in some patients
- the reluctance of or refusal by some patients to take warfarin
- fear of bleeding, which often influences a prescriber's decision making (with the fear of an anticoagulant-induced haemorrhagic stroke often cited as a significant barrier to warfarin uptake)
- medicine interactions, contraindications, risk of falls and dietary constraints.

Some of these barriers could be addressed by improving access to, and patient acceptance of, INR monitoring; providing guidelines to inform prescriber decision making; and providing education, particularly around patient reluctance and refusal to take anticoagulant therapies (especially in the context of risks and benefits).

The issues of reluctance or refusal to take warfarin, and fear of bleeding, may in part relate to whether patients (and prescribers) have an appropriate understanding that warfarin is significantly more effective at reducing the risk of stroke than antiplatelet therapy and offers a net benefit in patients at moderate-to-high risk of stroke — even when taking into account the increased bleeding risk (Hart et al 2007). Clinicians are likely to feel that they are causing less harm with aspirin than with warfarin in terms of bleeding risk; hence, the fear of bleeding may dominate prescriber decision making.

Facilitating increased consideration of warfarin therapy (where clinically appropriate) rather than aspirin or no therapy, through the removal or reduction of some of the barriers to prescribing of anticoagulant therapy, has the potential to result in a significant health gain by reducing a patient's risk of ischaemic stroke.

Relevance to new oral anticoagulants

Many factors relating to the use of oral anticoagulant therapy apply to both warfarin and the NOACs. However, there is uncertainty as to which factors would be addressed by NOACs, and to what extent. A recent survey of dabigatran use in the United States found that, in the period from October 2010 (when dabigatran became registered for stroke prevention in AF in the United States) until the end of 2011, the percentage of AF patients not receiving any antithrombotic therapy has remained constant at about 40% (Kirley et al 2012).

2.2.5 The management of atrial fibrillation may be complicated by the other comorbid medical conditions that are common in older people

The management of AF may be complicated by the other comorbid medical conditions that are common in older people — particularly heart disease, cognitive disorders, diabetes and musculoskeletal disorders. For example, these comorbidities may increase the absolute risk of stroke, increase the risk of bleeding, reduce the capacity of patients to manage warfarin therapy and increase the probability of medicine interactions. The current treatment algorithms do not provide detailed advice in regard to patients with comorbidities.

2.2.6 There are no Australian guidelines for management of atrial fibrillation

In view of the complexity of the issues that affect the decision to commence oral anticoagulation therapy, health care professionals and patients need clinical management guidelines to assist in the decision-making process and to optimise outcomes. An issue that was consistently raised by stakeholders throughout the Review process was the lack of a contemporary, comprehensive Australian guideline for the management of AF.

Recent years have seen the publication of a number of international guidelines on the management of AF, which include detailed discussions on the management of anticoagulation therapy. However, these guidelines reflect the particular regulatory, reimbursement and clinical practices of the region for which they were developed; thus, there is a need for guidelines that take account of the Australian health care system. There is also a need for a consumer version of the guideline to be developed.

In a submission to the Review, Boehringer Ingelheim stated that options such as the development of guidelines ‘should not delay the PBS availability of dabigatran’,⁷ and this sentiment was raised by a number of participants at the Stakeholder Forum.

Recommendation 2 — national guidelines

A national guideline for the detection and management of AF should be developed as part of a multifaceted program in order to bring about evidence-based changes in behaviour.

Recommendation 3 — scope of national guidelines

In regard to anticoagulation therapies in the management of AF, the national guideline will need to consider:

- a systematic approach to risk assessment (assessment of stroke risk through algorithms such as CHADS₂ and CHA₂DS₂-VASc, and bleeding risk through algorithms such as HAS-BLED); therapeutic options (including addressing barriers to the optimisation of anticoagulant use); and the cost-effectiveness of therapeutic options
- nationally endorsed dosing and management algorithms for all available anticoagulants; such algorithms would need to cover situations such as initiation, frequency of monitoring for efficacy and for toxicity, adjustment of dosage when required, cessation of therapy and switching between therapies. This should also include recommendations for the calculation and use of time in therapeutic range (TTR) for warfarin
- pre-operative and peri-operative management of bleeding risk
- management of bleeding or over anticoagulation taking into account different healthcare environments and resources available to mitigate or reverse this adverse effect
- consideration of concomitant medicines and comorbid conditions, including development of a resource for alternative treatment options to medicines shown to interact with warfarin or other

⁷ Submission from Boehringer Ingelheim in response to Issues and Options Paper (2012)

anticoagulants; and consideration of including this resource within prescribing and dispensing software and other information and communication systems

- the risk–benefit profile of combining anticoagulant and antiplatelet therapies
- guidelines on appropriate provision of patient education, including lifestyle issues (including recommendations regarding vitamin K intake in patients receiving warfarin, as outlined in Recommendation 14)
- overall management of patients on anticoagulants (for example how to monitor patients on NOACs in regard to renal function and signs of over anticoagulation).

The process of guideline development in Australia should be led by the National Health and Medical Research Council, and should involve multiple stakeholders to facilitate ownership, acceptance and implementation. Stakeholders include health professional colleges and societies, consumer and patient organisations, and relevant government agencies such as the Australian Commission on Safety and Quality in Healthcare, the National Lead Clinicians Group, Medicare Locals and NPS MedicineWise. The guideline should be part of a systematic, comprehensive and multifaceted program. For example, integration of the guideline into clinical practice could be promoted through linking it into existing programs, such as the *Medicare Health Assessment for Older Persons*. The guideline should be a dynamic document that is regularly reviewed and updated.

The cost of developing such a guideline is estimated to be around \$1 million.

Recommendation 4 — dissemination and implementation of guidelines

The national guideline should be widely disseminated. Modules should be developed from the guideline, which can then be integrated into clinical practice through decision-support systems, including prescribing software, and be available from multiple communication platforms, including applications (‘apps’) for mobile phones and tablets.

The multifaceted Australian guideline would form the basis of education programs for health professionals (including professional development programs), patients and carers. These could be developed by NPS MedicineWise, professional societies and colleges, and industry.

Improving consumer education could improve consumer adherence to anticoagulation therapies (e.g. through providing information around risks and benefits of anticoagulation, and providing accurate relevant and usable information around lifestyle), and aid consumers in making informed choices and playing active roles as partners in their health care.⁸

Educational materials could be rolled out in a ‘push model’ and, as discussed earlier, complemented by or integrated into existing public awareness campaigns, such as the National Stroke Foundation’s ‘Know your numbers’ program, which raises community awareness and detection of cardiovascular disease (and type 2 diabetes in New South Wales and Queensland, which is run in partnership with the Pharmacy Guild of Australia and Diabetes Australia), as outlined in Section 1.2.4.

Recommendation 5 — educational materials

To improve the health outcomes for patients with AF, appropriate resources should be developed from the national guideline and be available in a wide variety of formats. These should be readily accessible to consumers and carers and used in education, training and professional development programs for health professionals.

⁸ Submissions from: Australasian College for Emergency Medicine; Consumers Health Forum (2012)

2.3 Further information

See Part B, Chapter 6 for further information about stroke risk and prevention.

See Part B, Chapters 7 and 8 for further information about antiplatelet and warfarin therapy, respectively.

See Part B, Chapter 10 for further information about AF guidelines and education strategies.

3 Optimisation of current anticoagulant therapy

3.1 Key issues

- There is no consistent national approach to the initiation of warfarin therapy.
- Pharmacogenomic testing could assist with warfarin initiation in patients at high risk of bleeding.
- Warfarin therapy in Australia is managed using a number of health service models.
- Point-of-care testing could remove some of the barriers to warfarin use.
- Warfarin care programs are offered by some pathology laboratories in Queensland and Victoria.
- Improved multidisciplinary communication and access to patient records would improve the continuity of care between sectors.
- The high level of inpatient variability in warfarin response could be reduced by appropriate guidelines and education processes.

3.2 Review findings and recommendations

3.2.1 Initiation of warfarin therapy does not follow a nationally consistent approach

Some health facilities in Australia provide a comprehensive anticoagulation service, but there is no nationally consistent approach to the initiation of warfarin therapy. A significant proportion of adverse outcomes with warfarin occur in the first three months of therapy, particularly during the first two weeks of therapy (Hylek et al 2007, Palareti et al 2005). More intensive patient monitoring and support provided during this period has been shown to improve outcomes for patients, and could be specifically addressed as part of a national guideline. Since the cessation rate of anticoagulation therapy is higher during the early phase of therapy, improvement in the management of the initiation period is also likely to increase the number of patients who continue with warfarin on a chronic basis. The development of a range of models should be encouraged, and evaluation of the service should be undertaken as part of a quality assurance framework.

In particular, optimisation of the initiation phase and the continuity of care for patients started on warfarin in the hospital setting could be achieved through medicines reviews initiated in hospitals, hospital-in-the-home programs, or formal linkages with community-based initiatives for anticoagulant management. For patients started on warfarin in the community setting, comparable support could be provided through the Home Medicines Review or MedsCheck frameworks, or through existing community-based programs designed to optimise anticoagulant therapy.

When warfarin is commenced in the hospital setting, it is essential that there is timely communication between the hospital and GP regarding the patients' anticoagulation (refer to Recommendation 13 — access to patients' health records) and timely referral of the patient to their GP.

Recommendation 6 — warfarin initiation

During the initiation period, all patients commenced on warfarin should be included in one or more programs designed to optimise outcomes and minimise risks:

- For patients started on warfarin during a hospital admission, the proportion who participate in a structured initiation program should be considered by the Australian Commission on Safety and Quality in Healthcare as a key performance indicator in its standards for hospital accreditation.
- Medicare Locals should investigate the availability and coordination of community-based anticoagulation support services for patients started on warfarin in the community.

3.2.2 The place of pharmacogenomic testing in warfarin initiation

One of the difficulties in the management of warfarin therapy, particularly in the initiation phase, is the interpatient variability in dosing requirements. Up to 40% of such variability has been attributed to genetic polymorphisms in CYP2C9 and vitamin K epoxide reductase complex subunit 1 (VKORC1). Mutations in the genes encoding these enzymes will usually result in lower dosage requirements.

Knowledge of the pharmacogenomic status of a patient may be useful in the initiation of warfarin therapy. In patients with reduced activity of these enzymes, the commonly used starting doses (such as 5–10 mg) may result in an excessive risk of bleeding. However, a more conservative approach to dose titration (to avoid the risk of bleeding due to over anticoagulation) could lead to delays in achieving a therapeutic INR (and thus delays to the reduction in risk of stroke) during the initiation period. Stroke risk in patients during this period could be addressed with low molecular weight heparins (LMWHs), if clinically required. There may be a subgroup of patients (e.g. those with a combination of high CHADS₂ and HAS-BLED scores) in whom pharmacogenomic testing may be particularly beneficial and cost-effective in the initiation phase of warfarin therapy. Nevertheless, international guidelines have generally recommended against the routine use of pharmacogenetic testing for guiding doses of warfarin. Large clinical trials of this issue are currently ongoing, which will inform future consideration of pharmacogenomic testing.

Caution in the initiation phases of warfarin therapy, particularly for patients with high HAS-BLED scores, may have a similar benefit to pharmacogenetic testing.

Recommendation 7 — pharmacogenomic screening

Government funding of routine pharmacogenomic screening of patients commencing warfarin therapy is not recommended at this time.

However, a cost-effectiveness analysis of pharmacogenomic testing of CYP2C9 and vitamin K epoxide reductase complex subunit 1 (VKORC1) in AF patients with a high bleeding risk (e.g. HAS-BLED score ≥ 4) commencing warfarin should be undertaken to determine whether, in this subgroup of patients, such an intervention improves health outcomes and is cost-effective.

3.2.3 Warfarin therapy in Australia is managed using a number of health service models

In its evidence-based clinical practice guidelines for management of anticoagulant therapy, the American College of Chest Physicians states: ‘we suggest that health care providers who manage anticoagulation therapy should do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, followup, and good patient communication of results and dosing decisions’ (Holbrook et al 2012).

The need for regular INR monitoring is frequently stated to be a key barrier to the prescribing of warfarin in patients for whom such therapy is clinically indicated. INR monitoring has been managed within a range of practice settings, using a variety of processes. The list below shows examples of the models currently used for INR testing, both in Australia and internationally. Some of these processes involve point-of-care testing (PoCT) devices (otherwise known as coagulometers), which are hand held, provide immediate results and use blood obtained by a finger prick rather than by venipuncture.

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 pathology laboratory service centre (or is visited at the patient's place of residence) to have a blood sample taken by venipuncture. Some patient-relevant information may be collected at this time. The sample is then transported to an accredited laboratory for INR measurement. The results are then either communicated to the patient's medical practitioner (who responds to the result as appropriate) or directly to the patient or carer. If the patient has been referred to the pathology laboratory's anticoagulant service by the prescriber, the laboratory makes an assessment and, in accordance with defined protocols, contacts the patient or carer directly for further information, and/or makes recommendations about any required dosage adjustment or other actions. This information is also communicated to the patient's medical practitioner, but the day-to-day management of the patient's anticoagulant dosing and monitoring frequency is controlled by the pathology service.
3. The patient's primary medical practitioner or practice nurse conducts PoCT, and any required action can be undertaken quickly.⁹ A hybrid of options 2 and 3 also exists, whereby the INR values are measured using PoCT at a medical clinic, with the patient's results then being sent to the pathology laboratory's anticoagulant service for the management of the patient by that service. The pathology laboratory may provide the quality assurance framework for the PoCT.
4. PoCT 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 (Shaw et al 2011) and has been included in the recent New Zealand Community Pharmacy Services Agreement (refer to Appendix 2 for further information). Other examples of PoCT models include use in residential aged-care facilities,¹⁰ use by domiciliary nurses undertaking home visits and use in hospital-in-the-home programs.
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 throughout Europe and in the United States (CADTH 2011b).
6. Patients self-monitor their INR values using point-of-care devices. If the INR is outside an agreed or designated range, or patients are showing signs of bleeding, they either contact their health care practitioner for advice on any required action (self-monitoring) or manage any dosage adjustments themselves using an agreed management algorithm (self-management).

⁹ Submission from: Tideman P, St John A, Tirimacco R (2012)

¹⁰ Submission from: Edwards S (2012)

Models 1–3 are those most commonly practised in Australia at present.

Currently, to be eligible for a Medicare Benefits Schedule (MBS) subsidy, an INR test must be conducted by an accredited laboratory using blood obtained by venipuncture. The cost to the Australian Government for this service has been estimated to be \$22.52 per test, comprising \$13.80 for the blood test, about \$6 for a patient episode initiation fee, and the cost of one GP consultation per six blood tests. The net cost to the Australian Government for INR testing is estimated to be around \$100 million per year, with most of this cost being for patients with AF.

Issues that have been identified with the most common approaches include obtaining venous access (in some patients), the availability of laboratory facilities in rural areas, potential delays between the taking of a blood sample and any required subsequent change of management, patient time and travel costs, and effect on patient quality of life.

Recommendation 8 — Warfarin maintenance - optimisation of time in therapeutic range

Optimisation of the time in the therapeutic range (TTR) should be a goal for patients treated with warfarin, and identification of factors that influence TTR should be a key part of a warfarin management plan for each patient.

This recommendation should be facilitated by the development of the Australian clinical guideline for AF and the implementation of a multifaceted educational program (see Recommendation 5).

Advice regarding the measurement and application of a patient's TTR should be developed as part of the guidelines, and implementation of this could be facilitated through IT (such as Personally Controlled Electronic Health Records, prescribing software or pathology laboratory computer systems).

Recommendation 9 — government support of options for warfarin management

A wider range of options for the management of warfarin patients should be considered for government support. Options that should be considered are those that offer greater convenience and support to patients in a timely, systematic and coordinated fashion, and that incorporate patient education, systematic international normalised ratio (INR) testing, tracking, followup and effective communication of results and dosing decisions to patients.

3.2.4 Point-of-care testing could remove some of the barriers to warfarin use

The use of hand-held coagulometers (PoCT devices) for the measurement of INR is increasing in Australia and overseas. Research supports the accuracy and reproducibility of the results obtained, and the clinical suitability and acceptability of the INR results for use in warfarin management programs.

As noted above, PoCT of INR values with portable devices could occur in a number of settings, including:

- medical practices
- community pharmacies operating under a shared-care model with the patient's medical practitioner
- residential aged-care facilities by appropriate health practitioners under a shared-care model
- the patient's home by either the patient (self-monitoring or self-management) or by appropriately trained staff
- coagulation clinics or pathology laboratories.

PoCT has the potential to reduce the inconvenience of regular INR monitoring and to improve warfarin use. In rural and remote areas, it would significantly improve the timeliness of appropriate monitoring and patient management.

Advantages of PoCT include:

- improved patient convenience and satisfaction
- finger-prick blood sampling, which is a particular advantage for those patients with poor venous access (common in this older patient group with AF)
- an opportunity for immediate face-to-face communication between patients and health professionals; this enables immediate patient support and reinforcement, and the identification of issues that may have resulted in a change in INR control
- more timely access to appropriate interventions where necessary
- enabling those patients who are willing and able to self-monitor or self-manage warfarin treatment to have greater control over their disease management.

Disadvantages of PoCT include:

- the need for training and maintenance of equipment and for the implementation of quality assurance processes
- potential increased costs, given the economies of scale that can be achieved through pathology testing of venipuncture samples.

However, there is a lack of appropriate infrastructure and funding arrangements in Australia for PoCT of INR. The cost of PoCT is a barrier to its wider uptake because this service is currently not directly subsidised as a specific MBS item number.

Recommendation 10 — point-of-care testing

The use of point-of-care testing (PoCT) for the measurement of INR values should be considered as an option for warfarin management, particularly in the community setting. Such testing could be conducted at a medical practice or could involve a collaborative shared-care arrangement between a patient's medical practitioner and other health professionals with whom the patient has regular and convenient contact (e.g. domiciliary and residential care qualified staff, pharmacists). Uptake of PoCT in Australia, as a component of a warfarin management program, should be considered for government support.

Recommendation 11 — shared-care model

A nationally endorsed shared-care model for warfarin monitoring and management between health practitioners should be developed. This will require the development of standard protocols and quality assurance systems and consideration of relevant legislation. Such a model has the potential to significantly improve both health outcomes and patient satisfaction.

3.2.5 Some pathology services offer warfarin care programs

A number of pathology services in Queensland and Victoria offer 'warfarin care programs', in which the pathology provider manages the patient's warfarin therapy, including dosage adjustment and relevant patient education. In these two states it is estimated that most patients receiving warfarin are managed through such programs. Patients are referred by the medical practitioner to the service, and are required by some services to pay an out-of-pocket fee (e.g. a \$250 initiation fee incurred over the first five tests). Patients are contacted by the pathology service by phone or electronic means if the INR results indicate that a certain action is required. The laboratories use management algorithms developed for this purpose. Similar services do not appear to be available in other states and territories.

Warfarin care programs are somewhat similar to the anticoagulation clinics run in a number of other countries, except that in the latter there is usually face-to-face interaction with the health professional making the judgment as to whether action is required.

Warfarin care programs provide a consistent and structured approach to warfarin management, and provide the patient with rapid feedback in the event of further action being required. They also provide the patient's medical practitioner with a management option in cases where the practitioner does not feel confident in the management of warfarin in their patients, or where the time involved in management of patients receiving warfarin creates a difficulty. The data held by these services in regard to factors influencing inpatient INR variability represent a rich source of untapped information about the quality use of warfarin.

There are, however, potential disadvantages of a warfarin care program; these include:

- Lack of transparency regarding the management algorithms used.
- The warfarin care programs are not accredited and there are some differences as to the level of support provided. For example, some services only enrol patients who have been stabilised on warfarin, whereas others offer the service during the initiation phase.
- Lack of access to the current patient history. However, patients who participate in these services are asked at the time of sample collection about any recent change in medicines or medical history, and the operating procedures allow, when an INR value is outside the acceptance range, for contact with the patient, carer or medical practitioner to seek further information before management decisions are made.
- The additional out-of-pocket expenses charged by some services create a potential inequity.

Recommendation 12 — pathology laboratory warfarin programs

Consideration should be given to the development of a formalised structure of anticoagulation programs offered by pathology laboratories throughout Australia and to the funding of such a structure. This would need to involve accreditation of such programs as part of a model of shared responsibility, and the development and endorsement of standard operating procedures (including validation of decision algorithms, patient-management protocols and a quality assurance framework).

The Medical Services Advisory Committee should be asked to consider this matter. Introduction of a 'patient warfarin-management fee', or an incentive payment linked to the proportion of patients within a certain INR range, rather than an additional Medicare Benefits Schedule fee per INR test, would address concerns regarding potential overservicing of INR testing.

3.2.6 Improved multidisciplinary communication and access to patient records would improve handover between sectors

Irrespective of which warfarin management model is used, knowledge of a patient's current health status — including comorbidities, current medication and INR history — is required, and needs to be accessible to all personnel involved in INR monitoring and anticoagulant patient-management services. This can be a particular problem in situations such as patient transitions between health care setting (e.g. between hospital, community and residential aged-care settings), in emergency settings and in collaborative networks of therapy management.

The access to an up-to-date Personally Controlled Electronic Health Record of patients receiving anticoagulants would significantly address some of these issues.

Recommendation 13 — access to patients' health records

To improve the management of anticoagulation therapies through promoting access to a patients' current health record, patients on anticoagulation therapy and health practitioners involved in their care should be encouraged to register for e-health initiatives such as a Personally Controlled Electronic Health Record.

3.2.7 The high level of inpatient variability in warfarin response could be reduced by appropriate guidelines and education processes

A relatively common issue in warfarin management is the variability of INR values in some patients (inpatient variability). While there are a number of reasons for this variability, common factors include patient compliance, medicine and disease interactions, and vitamin K intake.

Many of the factors that contribute to inpatient variability in INR could, to some extent, be addressed by appropriate guidelines and education processes, as indicated in the following examples:

- Improved health professional and patient understanding of warfarin–medicine interactions. While warfarin has been reported to interact with many medicines, the evidence used to generate such reports is often not of high quality, and many interactions can be avoided or their impact minimised. The national guideline would need to include medicine interaction tables, as well as advice about alternative medicines of comparable efficacy that do not interact with warfarin and other anticoagulants. This information should be integrated within prescribing and decision-support systems, and patient education material.
- Strategies to address patient compliance. The requirement for INR monitoring of warfarin can be an aid to the evaluation of patient compliance, because compliance can be investigated as a possible cause for INR variability. In the absence of a simple monitoring test for the extent of anticoagulation, there is uncertainty regarding the variability of anticoagulation control.
- Variable intake of vitamin K has been shown to be a significant factor in the variability of INR results, particularly in patients with low blood concentrations and tissue stores of vitamin K. The current information provided to consumers in regard to diet is often variable and confusing. Simply providing a list of the vitamin K content of certain foods implies that those foods high in vitamin K should be avoided. The appropriate advice should recommend a consistent intake of such foods, and appropriate strategies as to how this can be achieved via a range of dietary options. The guidelines and education strategies around this would need to target patients and all health professionals involved in patient warfarin education (including pharmacists, dietitians and nurses) to ensure that patients receive consistent and accurate information.

Recommendation 14 — national vitamin K guideline

The Dietitians Association of Australia should be asked to develop appropriate material regarding dietary intake of vitamin K in patients receiving warfarin, as a component of the national AF clinical management guideline.

3.3 Further information

See Part B, Chapter 9 for further information on options to improve current anticoagulation therapy with warfarin.

4 Future use of new oral anticoagulants

4.1 Key issues

- In patients with AF, NOACs offer an alternative treatment to warfarin.
- There is considerable uncertainty about the extent of the effectiveness of NOACs (and therefore cost-effectiveness) compared to warfarin when used outside the clinical trial setting.

4.2 Review findings and recommendations

4.2.1 New oral anticoagulants offer an alternative treatment in patients with atrial fibrillation

A number of new anticoagulants have been developed and trialled during recent years. These agents have mechanisms of action that differ from that of warfarin, and inhibit selective steps in the coagulation pathway. Dabigatran was the first NOAC to be approved by the Therapeutic Goods Administration (TGA) in Australia for the AF indication (in 2011), followed by rivaroxaban (in 2012). A third NOAC — apixaban — is currently undergoing evaluation for stroke prevention in AF patients by both the TGA and the United States Food and Drug Administration (FDA). Because of the earlier registration of dabigatran, the amount of publicly available information is much greater for this medicine than the other two NOACs.

Dabigatran, rivaroxaban and apixaban have been compared to warfarin in patients with AF in three pivotal clinical trials (RE-LY, ROCKET-AF and ARISTOTLE, respectively¹¹). The data from these trials indicate that, generally, the NOACs are at least noninferior to warfarin in regard to the primary outcomes of stroke/systemic embolism and major bleeding, and are superior to warfarin with respect to the rate of intracranial bleeding and haemorrhagic stroke. The sponsors claim that these new agents do not require monitoring of anticoagulant response and that patients can be managed using fixed dose schedules.

There is no accepted, validated measure of anticoagulant effect for dabigatran (CADTH 2012a), although activated partial thromboplastin time (TGA 2011c), ecarin clotting time (Douxflis et al 2012) and diluted thrombin time with the HEMOCLOT thrombin inhibitor assay (Stangier and Feuring 2012) have been examined.

Some specific safety concerns from the trials have been noted regarding myocardial infarction (MI) and major gastrointestinal bleeding with the higher dose of dabigatran, and regarding major bleeding with rivaroxaban. Concerns have also been expressed in the literature about management of bleeding episodes in patients receiving NOACs.

There have been no direct comparison (head-to-head) randomised trials of these three NOACs, although indirect comparisons have been published that attempt to compare the three agents (Banerjee et al 2012, CADTH 2012b, Lip et al 2012a, Miller et al 2012, Schneeweiss et al 2012). These comparisons have identified some differences; however, in view of potential

¹¹ ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; 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

confounding, these comparisons are uncertain and are not considered to be sufficiently robust for clinical decision making (Cannon and Kohli 2012).

A consistent finding in all the pivotal studies of NOACs is a reduction in the incidence of intracranial haemorrhage (ICH) compared to patients on warfarin (Connolly et al 2009, Granger et al 2011, Patel et al 2011). A number of submissions identified that this was an important, clinically relevant difference between warfarin and the newer agents, due to the catastrophic outcomes of ICH.¹²

Data from the three pivotal trials show that:

- dabigatran 150 mg twice daily was the only regimen to demonstrate a statistically significant reduction in ischaemic stroke compared to warfarin
- dabigatran 110 mg twice daily and rivaroxaban were noninferior to warfarin in relation to total stroke and systemic embolism; while dabigatran 150mg twice daily and apixaban were superior to warfarin in preventing total stroke and systemic embolism
- NOACs were associated with a statistically significant reduction in haemorrhagic stroke, which was a major contributor to reduction in total stroke; this observation suggests that the incidence of haemorrhagic stroke is increased by warfarin possibly through a mechanism related to Factor VII, which is not influenced by the NOACs
- the number needed to treat (NNT) (based on a difference in event rates from the pivotal trials) to prevent a stroke or systemic embolism compared to warfarin treatment is large, as shown in Table 4.1 below
- the subject withdrawal rates from the trials were similar for warfarin and the NOACs
- dabigatran 110 mg twice daily and apixaban both caused less major bleeding than warfarin, but there was no significant difference between dabigatran 150 mg twice daily or rivaroxaban and warfarin in the rate of major bleeding episodes.

Table 4.1 Numbers needed to treat for one year based on event rates of the pivotal trials of the new oral anticoagulants compared to warfarin

Agent	Dabigatran 110 mg twice daily	Dabigatran 150 mg twice daily	Rivaroxaban	Apixaban
NNT to prevent one stroke/systemic embolism compared to warfarin	588	167	333	303
NNT to prevent one intracranial haemorrhage compared to warfarin	189	227	500	213
NNT to prevent one haemorrhagic stroke compared to warfarin	385	357	556	435

NNT = number needed to treat

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

Source: Connolly et al 2010, Patel et al 2011, Granger et al 2011.

Overall, NOACs all appear to be effective in reducing the incidence of total stroke in patients with AF, but the NNTs for stroke, intracranial bleeding and haemorrhagic stroke compared to the standard of warfarin care seen in the trials are high.

¹² Submissions from: Cardiac Society of Australia and New Zealand; National Stroke Foundation; Paceline Inc.; Royal Australasian College of Physicians; Blombery PA (2012)

4.2.2 New oral anticoagulants are new medicines and there is significant uncertainty about their safety, effectiveness and cost-effectiveness in wide clinical use

Extrapolation from outcomes in clinical trials to predicted outcomes in routine clinical practice is always problematic with new medicines, particularly when the comparator has been in use for many years and there is wide clinical knowledge and experience in its use. This uncertainty can be related to many factors, including:

- the applicability of the clinical characteristics of patients in the trial to those likely to receive the medicine in practice, because of patient selection requirements in clinical trials
- the clinical practice settings used in the trials
- the level of support provided during the trials
- the length of followup (i.e. the short duration of the trials).

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.¹³ Submissions raised concerns about whether the trial participants were representative of the Australian population likely to take the medicine in clinical practice.¹⁴ 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’.¹⁵

Predicted cost-effectiveness of medicines can be influenced both by these uncertainties and by assumptions made within the economic model, including patterns of use, switching patterns and toxicity considerations.

The extent to which management of these uncertainties will be required within health programs will be influenced by a range of factors, including the magnitude of the predicted expenditure and the extent of the uncertainty. This issue was noted by the Pharmaceutical Benefits Advisory Committee (PBAC), who informed the Minister for Health and Ageing in March 2011 that the ‘opportunity cost to the Australian Government of listing dabigatran would be significant’ (DoHA 2011a).

There is a much greater body of publicly available evidence for dabigatran than for rivaroxaban and apixaban and this makes comparison of the three agents problematic in regard to the magnitude of any uncertainty.

Areas of uncertainty identified by the Review

Duration of followup

The length of followup in the clinical trials was approximately two years. Anticoagulants in AF are generally a lifelong therapy, and will be used in a population of increasing age; thus, any change in effectiveness over time is uncertain (Furie et al 2012).

Quality of warfarin control, as measured by time in therapeutic range

In the pivotal trial of dabigatran (the RE-LY trial), for the outcome of net clinical benefit — defined as an unweighted composite of stroke, systemic embolism, pulmonary embolism, MI,

¹³ Submissions from: New South Wales Therapeutic Advisory Group; Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists; Royal Australasian College of Physicians; Council of Australian Therapeutic Advisory Groups; Royal Australian College of General Practitioners (2012)

¹⁴ Submissions from: Royal Australasian College of Physicians; Council of Australian Therapeutic Advisory Groups (2012)

¹⁵ Submission from: Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (2012)

death, or major haemorrhage — there was a significant interaction with cTTR (centre TTR — as measured by the mean TTR of the trial centre in which patients were enrolled). For this composite endpoint, dabigatran was only superior to warfarin in patients enrolled at trial centres with a cTTR of less than 57.1% (the lowest quartile of warfarin control) (Wallentin et al 2010). No interaction with TTR was seen for the two endpoints of stroke and haemorrhagic stroke; nevertheless, interaction between TTR and the composite endpoint indicates changes in certain components of that endpoint with TTR. A similar analysis of the impact of TTR on outcomes from the ARISTOTLE trial (apixaban), showed a TTR-outcome interaction for major and clinically relevant bleeding (Wallentin and Collet 2011).

The Australian patients in the RE-LY and ARISTOTLE trials had a TTR of approximately 74%, and patients from countries with similar health systems had a TTR of at least 70% (Wallentin et al 2010, Wallentin and Collet 2011). The average cTTR across all centres was approximately 63%. This indicates that it is possible to achieve better INR control in the context of the Australian (or similar) health system if appropriate support systems are in place such as in a clinical trial. It should also be recognised that 50 and 57% of patients in the RE-LY and ARISTOTLE trials, respectively, had received prior long-term vitamin K antagonist therapy (Connolly et al 2009, Granger et al 2011).

TTR is a post-randomisation variable, where the subjects with higher TTR are inherently different from those with lower TTR both within and across sites. There were several significant differences in the baseline patient characteristics within the different cTTR quartiles. For example, in the RE-LY trial, patients enrolled in centres with better INR control were older (average age of 72.5 years in the highest quartile, compared to 70.0 years in the lowest quartile), heavier (84.9 kg compared to 77.3 kg); had more permanent AF and less persistent AF; were more likely to have a CHADS₂ score of 0–1 (35% compared to 28%); had lower baseline rates of use of aspirin (36% compared to 43%) and amiodarone (15% compared to 8%), and higher baseline rates of use of statins, beta blockers and angiotensin converting enzyme inhibitors/angiotensin receptor antagonists (Wallentin et al 2010). In general, centres in the higher quartiles of cTTR appeared to have better overall health management.

Patient age

The average patient age in the NOAC trials ranged from 71 to 73 years, which is lower than the average age of patients with AF in Australia. [REDACTED]

[REDACTED] Further, it has been recently stated that the average age of patients with AF is increasing and it now averages between 75 and 85 years (Authors/Task Force et al 2012). This contrasts with the age of patients in the pivotal trial. A subgroup analysis for age in the RE-LY trial showed a significant interaction between age (< 75 years or ≥ 75 years) and major bleeding for both dosage regimens (110 mg twice daily or 150 mg twice daily), although no interaction term was seen with the outcome of stroke/systemic embolism or for intracranial haemorrhage (Eikelboom et al 2011).

Information from the New Zealand national dispensing data for dabigatran in the period July to December 2011 shows that 31% of patients receiving dabigatran were aged 80 years and over (Metcalf and Moodie 2012). This contrasts to 17% of such patients in the RE-LY trial. Further 51% of New Zealand patients receiving dabigatran were aged 75 years and over (in the ARISTOTLE trial for apixaban, 31% of patients were aged 75 years and over). The age of patients using dabigatran in New Zealand clinical practice is similar to that recently reported in the United States (Kirley et al 2012).

[REDACTED]

As mentioned earlier, there is no accepted, validated measure of the anticoagulant effect of dabigatran, although the TGA's Australian Public Assessment Report (AUSPAR) for dabigatran advised that an activated partial thromboplastin time of more than 80 seconds (corresponding to a pre-dose plasma concentration of approximately 200 ng/mL) is correlated with an increased risk of bleeding (TGA 2011b).

Since many AF patients who will receive anticoagulant therapy are over the age of 75, the influence of age on the magnitude of total benefit of dabigatran over warfarin in clinical use is likely to be uncertain. As shown in Table 4.2, the advantage with respect to major bleeding seen in the RE-LY trial with dabigatran 110 mg twice daily is not seen in patients aged 75 years and over (number needed to harm [NNH] =1667). In fact, based on data from the RE-LY trial there is an increase in the rate of major bleeding with the NNH to cause a major bleed with dabigatran 150 mg twice daily compared to warfarin being 137. However, it is noted that the Australian product information for dabigatran recommends that the 110 mg twice daily dose should be used in patients aged 75 and over (Boehringer Ingelheim 2012).

Table 4.2 Numbers needed to treat (or harm) based on results of subgroup analyses of the pivotal trials of the new oral anticoagulants^a

Agent	Dabigatran 110 mg twice daily	Dabigatran 150 mg twice daily	Rivaroxaban	Apixaban
Stroke and systemic embolism				
NNT to prevent one stroke/systemic embolism compared to warfarin in patients aged < 75	909	189	1000	416
NNT to prevent one stroke/systemic embolism compared to warfarin in patients aged ≥ 75	400	141	179	167
<i>P</i> -value for interaction between age and efficacy (stroke/systemic embolism)	0.81	0.81	0.313	0.12
Major bleeding				
NNT to prevent one major bleed compared to warfarin in patients aged < 75	87	109	1000	164
NNT to prevent one major bleed compared to warfarin in patients aged ≥ 75	-1667 (NNH)	-137 (NNH)	-217 (NNH)	53
<i>P</i> -value for interaction between age and major bleeding	< 0.001	< 0.001	0.34	0.64

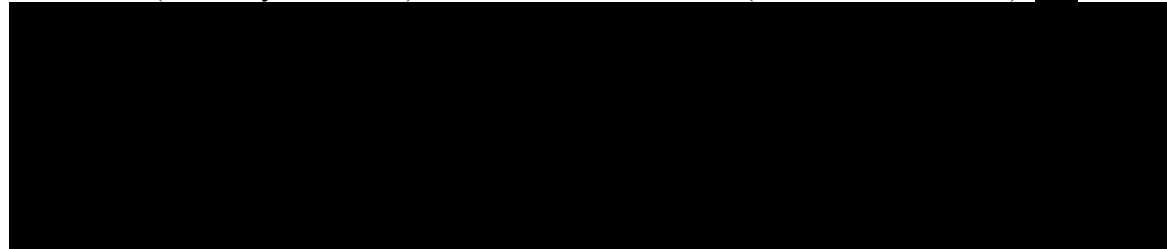
NNH = number needed to harm; NNT = number needed to treat

^a These numbers need to be treated with caution as they are based on post-hoc analyses

Sources: Eikelboom et al 2011, Halperin et al 2012, Granger et al 2011

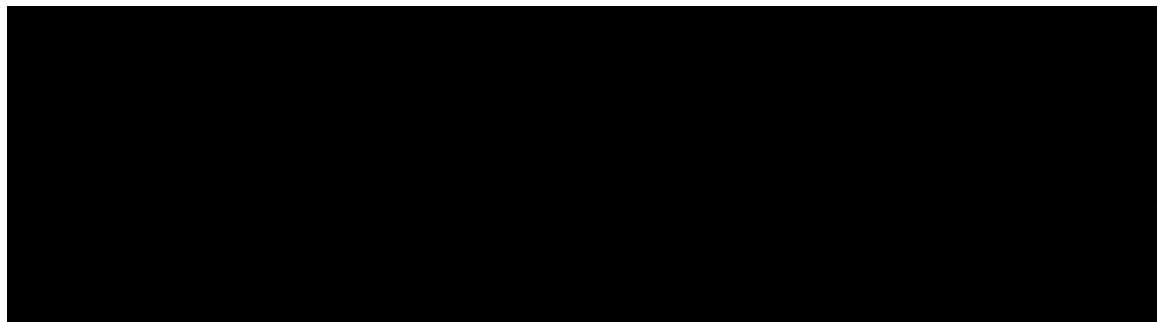
Impact of renal function

Major bleeding risk increases with age and declining renal function. This was confirmed in both the RE-LY (Connolly et al 2009) and ARISTOTLE studies (Hohnloser et al 2012).





It is noted that the approved product information for dabigatran suggests that for patients with a CrCL of 30–50 mL/min a reduction in dose to 110 mg twice daily may be considered.¹⁶

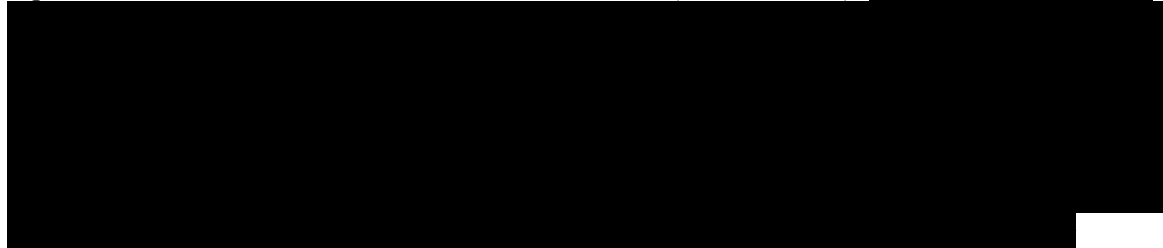


The balance between stroke reduction and bleeding risk is more complex in patients with renal impairment and the impact may differ between anticoagulants depending on which physiological factors influence their pharmacokinetics and pharmacodynamics.

Switching patterns

In view of the interaction between age and major bleeding, clinicians may consider retaining patients on aspirin and/or clopidogrel rather than commencing an anticoagulant. Alternatively, if the decision is made to commence a NOAC, there may be a tendency to start at lower doses, which has the potential to impact on cost-effectiveness, at least on the basis of currently available data. A recent nationally representative audit of office-based providers in the United States on national trends in anticoagulant use showed that since the introduction of dabigatran in 2010, there has been a reduction in warfarin use but antiplatelet use as monotherapy remained constant at roughly 4.6% of AF treatment visits (Kirley et al 2012).

Another issue with dabigatran is that, because of the significant incidence of dyspepsia, lower doses may be used to minimise this common side effect. The sponsor of dabigatran has used a 50:50 split of 110 mg and 150 mg dosage schedules, and a 50:50 split of patients switching from aspirin and warfarin in their cost-effectiveness model (DoHA 2011a),



Information from New Zealand suggests that, in the first 12 months after the public funding of dabigatran, the lower strength was used more frequently in older patients (Metcalf and Moodie

¹⁶ Submission from: Boehringer Ingelheim (2012)

2012). Of the patients prescribed the 110 mg product, 89% were over the age of 70, compared with only 44% of the patients using dabigatran 150 mg. Further, the data from New Zealand indicates that 63% of patients receiving dabigatran had been previously receiving warfarin (with or without aspirin).

Measurement of anticoagulant response

There is no validated surrogate for the extent of anticoagulant control and bleeding risk with NOACs. The lack of surrogate is a disadvantage in routine clinical practice, because it poses a potential risk of undertreating or overtreating individuals. 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) and in cases of bleeding, overdose, emergency surgery or switching between agents.¹⁷

Several recent reports [REDACTED] have recommended the development of a monitoring tool (e.g. dilute thrombin time or activated partial thromboplastin time) for the monitoring of dabigatran (Duffull et al 2012, Ten Cate 2012). There are nonspecific coagulation tests that could be used to determine the presence of an anticoagulant response to NOACs but not to measure anticoagulation intensity. It has been stated that these tests should not be used for dosage adjustment (Authors/Task Force et al 2012). If a validated monitoring test becomes available for NOACs, and is used in clinical practice, this may have a significant influence on their cost-effectiveness, because the cost of this has not been considered in published economic models for dabigatran (Kamel et al 2012, Shah and Gage 2011).

While significant information regarding medicine interactions is available for warfarin, their impact on NOACs is uncertain, and there is no way of detecting whether the interaction has the potential to be clinically significant before an adverse event occurs.

Recently a genetic variant that reduces exposure to active dabigatran with a subsequent reduction in bleeding risk has been reported (Paré et al 2012) (see Chapter 12).

Management of bleeding

There is no widely available, clinically proven antidote for the NOACs, and the management of patients receiving NOACs with bleeding episodes or those requiring emergency surgery has been reported to be problematic. The cost of management of bleeding episodes that occur with NOACs compared to those that occur with warfarin is uncertain. The lack of an antidote for the NOACs was stressed in many submissions to the Review as a major factor to consider in the introduction of NOACs into clinical practice.¹⁸

In the case of warfarin, there are antidotes that can be used if a patient requires emergency surgery (where a patient's level of anticoagulation becomes an issue), or to attempt to reverse a bleeding episode (see Section 6.4.2).

Adherence and transition between anticoagulants

Factors relevant to long-term, real-world adherence are not known, especially if NOACs are used outside of a care structure designed to assess adherence, such as occurs through the INR-

¹⁷ Submissions from: Australasian Society of Thrombosis and Haemostasis, Haematology Society of Australia and New Zealand, and Australian and New Zealand Society of Blood Transfusions; Tideman P, St John A, Tirimacco R; Royal Australasian College of Physicians; Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists; Pillans P; Council of Australian Therapeutic Advisory Groups; Australian Association of Consultant Pharmacy (2012)

¹⁸ Submissions from: National Stroke Foundation; Society of Hospital Pharmacists of Australia; Royal Australasian College of Physicians; Australasian Society of Thrombosis and Haemostasis, Haematology Society of Australia and New Zealand, and Australian and New Zealand Society of Blood Transfusions; New South Wales Therapeutic Advisory Group; Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists; Council of Australian Therapeutic Advisory Groups (2012)

monitoring framework around warfarin. This is particularly relevant given that the discontinuation rates of NOACs in the clinical trials were similar to those for warfarin, and that poor compliance will not be able to be identified through a readily available test such as INR. It has been stated that the inconvenience of the requirement for INR testing is an impediment to warfarin uptake and continuance. However, in the RE-LY trial the discontinuation rate in the warfarin arm was less than with dabigatran, even though those patients receiving warfarin had to undergo regular INR monitoring as part of the open-label trial design (while those on dabigatran did not).

Because of their shorter half-lives and the twice daily schedule for dabigatran and apixaban, patients who are noncompliant and who regularly miss medication doses might be at risk for thromboembolism.

The transition between NOACs, or between NOACs and warfarin, must be managed carefully and may constitute a period of increased risk.

It is not known whether patients receiving NOACs but otherwise eligible for thrombolysis can be safely treated with a thrombolytic agent for an acute ischaemic stroke (Furie et al 2012).¹⁹

4.2.3 Summary

In extrapolating from the clinical trial scenario to clinical practice, there are considerable areas of potential uncertainty in regard to the relative benefits of NOACs versus best care with warfarin.

The reduction in the incidence of ICH by NOACs compared to warfarin is a consistent finding, and is the most clinically relevant outcome in view of the high morbidity and mortality of these events. The overall net benefit in actual clinical use is subject to considerable uncertainty, which extrapolates to uncertainty in cost-effectiveness. These issues of uncertainty have also recently been raised by the Health Council of the Netherlands in a document regarding NOACs, in which the council recommended initiating a comparative study upon the launch of the NOACs (Health Council of the Netherlands 2012).

Extrapolation of cost-effectiveness from clinical trial data to clinical practice

The importance of having a greater degree of confidence in the extrapolation from cost-effectiveness derived from trial data to cost-effectiveness in clinical practice is heightened when the total cost of the intervention is large and where toxicity issues are of potential concern. The issue can only be addressed by an effective postmarketing program, through which specific data to address the areas of uncertainty can be obtained. This approach has been recognised in the Memorandum of Understanding between the Australian Government and Medicines Australia, by the provision of managed entry scheme arrangements. Such an arrangement is relevant when there is seen to be a clinical need but where considerable uncertainty in effectiveness and cost-effectiveness exists.

The literature contains many statements indicating that patients who are well controlled on warfarin should not be switched to NOACs and that these new agents should be reserved for patients who are unable to tolerate warfarin or to maintain a satisfactory TTR. This is the approach recommended by the Canadian Drug Expert Committee and the Royal College of Physicians of Edinburgh (CADTH 2012c, RCPE 2012). The 'second-line' approach acknowledges the uncertainty in the magnitude of benefit of NOACs over well-controlled warfarin therapy. Such an approach would certainly address the immediate need for alternative agents in those patients with AF whose stroke risk cannot be reduced because of issues with the

¹⁹ Comments on Issues and Options Paper from the Australasian College for Emergency Medicine (2012)

currently available anticoagulant therapy. The proportion of patients who are unable to tolerate warfarin (that is, patients in whom warfarin is contraindicated) is estimated to be around 20% (Go et al 1999). If PBAC were to recommend such an approach, a price–volume arrangement would need to be developed that acknowledges the likelihood of use outside the restriction of second-line therapy. However, with all NOACs, there is a high degree of certainty of a small but clinically significant reduction in haemorrhagic strokes, even in patients in whom warfarin therapy is well controlled.

Multi-variant sensitivity analyses, which take into account factors that contribute to the uncertainty, would be informative.

Recommendation 15 — new oral anticoagulants

While warfarin will retain a place in the management of stroke risk in patients with atrial fibrillation, new oral anticoagulants (NOACs) offer an important clinical benefit in reducing the incidence of intracranial haemorrhages in AF patients who receive anticoagulants and offer patients who are unable to take warfarin an effective alternative. However, the net overall benefit of NOACs in clinical practice and the subsequent impact on cost-effectiveness is uncertain at this stage, given the further information about dabigatran use that has become available since the Pharmaceutical Benefits Advisory Committee (PBAC) decision regarding this NOAC in 2011.

In view of the uncertainties identified in the Review regarding the magnitude of any incremental clinical and cost-effectiveness benefit of NOACs over other therapies when introduced into widespread clinical practice, and the high total predicted cost, it is recommended that the Minister for Health asks PBAC to review its previous recommendations of NOACs, including consideration of the following options:

- a) The establishment of a managed entry scheme for the PBS availability of NOACs. This would take into account the identified uncertainties while acknowledging the clinical need for effective alternatives to warfarin. In considering a managed entry scheme, PBAC should evaluate the entry price that addresses the uncertainties and what ‘fit for purpose’ evidence would be required to address these to ensure that acceptable cost-effectiveness is achieved in the clinical practice setting once the medicines are subsidised.
- b) The PBS listing of NOACs as a restricted benefit for patients unable to tolerate warfarin therapy and/or who are unable to obtain satisfactory INR control despite specific measures. There would need to be a definition of ‘satisfactory INR control’ together with a price–volume arrangement which addresses the risk to the Australian Government of use beyond any restriction.

The Review notes that PBAC is the statutory committee with the legal responsibility of making recommendations (including advice regarding any restrictions) to the Minister for Health regarding the listing of medicines on the Pharmaceutical Benefits Scheme (PBS), and may make recommendations different to the two options presented above.

4.3 Further information

See Part B, Chapters 11 and 12 for further information about NOACs.

PART B
SUPPORTING DETAILS AND EVIDENCE

5 Atrial fibrillation

This chapter provides further details on atrial fibrillation (AF), and how it is diagnosed and managed to reduce the risk of stroke. This Review focuses on stroke prevention with anticoagulation therapy; however, the other management options described here are also important.

5.1 Definition

AF is a common form of irregular heart rhythm. It can be categorised as paroxysmal (recurrent episodes that self-terminate, usually within 48 hours), persistent (recurrent episodes that last more than one week) or permanent (ongoing AF). The condition progresses from short, rare episodes to longer, more frequent attacks and, over time, many patients develop sustained forms of AF.

Nonvalvular versus valvular atrial fibrillation

Some cases (10%) of AF occur in the presence of rheumatic mitral valve disease, a prosthetic heart valve or mitral valve repair. These cases are called *valvular AF*. The other 90% of AF is described as *nonvalvular AF* (Ang et al 1998).

Differentiating between valvular and nonvalvular AF can be difficult in clinical practice because many older patients with AF also have a degree of heart valve disease but do not routinely undergo the echocardiography required for differential diagnosis. Thus, the distinction between valvular and nonvalvular AF is not always made in clinical practice.

AF increases the risk of stroke by about five-fold (Wolf et al 1991). It has been estimated that AF is implicated in 15–25% of all ischaemic strokes (those that arise from an occlusion of blood flow to part of the brain) and in as many as 35% of strokes in patients over the age of 80 (Gattellari et al 2011). Strokes in patients with AF are more severe than other types of ischaemic stroke, resulting in greater morbidity and mortality (Béjot et al 2009, Gattellari et al 2011). Types of stroke and risk factors are discussed in Chapter 6.

5.2 Prevalence of atrial fibrillation

AF affects 1–2% of Australians (the equivalent of 240,000–400,000 people) (Go et al 2001, Miyasaka et al 2006, Sturm et al 2002).²⁰ This percentage increases sharply in older people, as shown in Table 5.1. The median age of patients with nonvalvular AF is 75 years and 84% of patients with nonvalvular AF are over the age of 65 (Feinberg et al 1995). It has been recently suggested that the average age of patients with AF is now between 75 and 85 years (Authors/Task Force et al 2012).

²⁰ Submission from the National Stroke Foundation (2012)

Table 5.1 Prevalence of nonvalvular atrial fibrillation by age group (including both diagnosed and undiagnosed cases)

Age group (years)	Prevalence (%) of NVAFA	Estimated total number of people in Australia with NVAFA (at June 2010)
50–59	1.3	36,353
60–69	3.8	80,638
70–79	9.8	123,682
≥ 80	13.3	111,392

NVAFA = nonvalvular atrial fibrillation

^a Adapted from: Deloitte Access Economics 2011

Note: The total number of people with AF in each age group was calculated using Australian Bureau of Statistics data series A3201 (release of June 2010).

Based on projections from the United States (Miyasaka et al 2006), it is estimated that by 2030 there will be 750,000 people in Australia with AF. The number of people with stroke is also expected to increase significantly as the population ages (Go et al 2001, Rothwell et al 2004, Stewart et al 2001). Thus, AF will have an increasing impact on health care services and costs in the coming years. The increasing prevalence of AF was raised as a major issue in a number of submissions to the Review.²¹

5.3 Diagnosis and management of atrial fibrillation

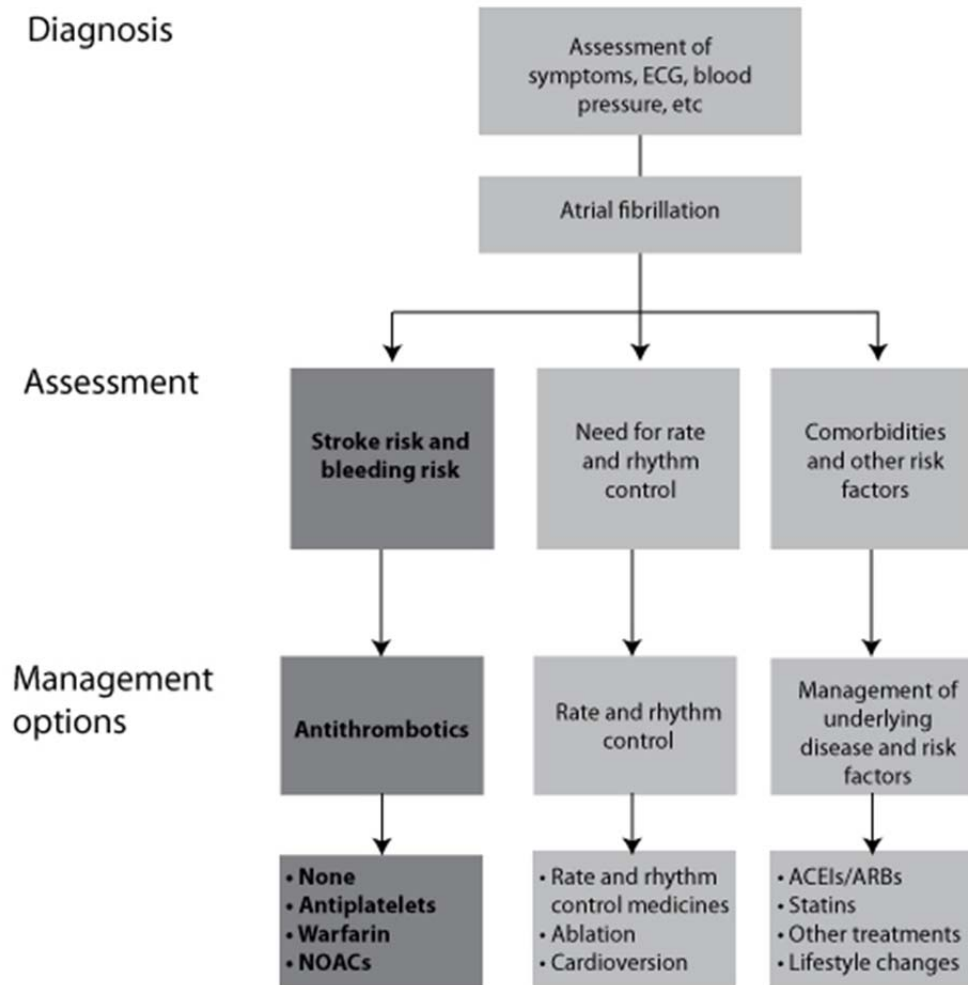
Figure 5.1 shows a typical management algorithm for people with AF. The cascade shows that overall management of AF may involve consideration of three components, depending on the subtype of a patient's AF and the severity of their AF-related symptoms (Lip et al 2012b):

- decreasing the stroke risk (see Chapter 6)
- managing underlying diseases or comorbidities, which may include altering lifestyle
- controlling the heart rate and rhythm.

After diagnosis and initial assessment, the next step is to determine the person's stroke risk and need for anticoagulation (ESC Task Force 2010). In addition, other comorbidities need to be considered, along with whether a person has symptoms that warrant a strategy directed at restoration and maintenance of sinus rhythm and/or control of heart rate. Each step is described in sections 5.3.1–5.3.3.

Patients with paroxysmal AF should be treated in the same manner as those with persistent and permanent AF since the trial data suggests that paroxysmal AF confers a relative risk of stroke similar to persistent or permanent AF (You et al 2012).

²¹ Submissions from: Cardiac Society of Australia and New Zealand; Stroke Society of Australasia; National Stroke Foundation; Australian Association of Consultant Pharmacy; Paceline Inc. (2012)



ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin-receptor blocker; ECG = electrocardiogram; NOAC = new oral anticoagulant

Bold text indicates main focus of the Review.

Figure 5.1 Management cascade for patients with atrial fibrillation

5.3.1 Initial assessment and diagnosis

Diagnosis of AF usually involves a cardiac examination including electrocardiogram (ECG), pulse and blood pressure readings, and a lung examination.

However, approximately 10–30% of people with AF have no symptoms,²² and many of these people are not diagnosed.²³ In some asymptomatic cases, AF may be detected as the result of investigations for other purposes. A person with undiagnosed AF will not be assessed and treated to reduce their risk of stroke. Reducing the incidence of AF-related strokes will therefore need a greater awareness of AF and improved processes to detect the condition. Unfortunately, many people with previously undiagnosed AF are identified as having AF following hospital presentation for stroke.

²² Submission from: Cardiac Society of Australia and New Zealand (2012)

²³ Submission from: Stroke Society of Australasia; National Stroke Foundation (2012)

5.3.2 Assessment of comorbidities and risk factors for atrial fibrillation

Although the causes of AF are poorly understood, it is known to be associated with a range of other conditions, including many that are common in older people. For example, a recent study found that 56.5% of new-onset AF could be attributed to common modifiable cardiovascular risk factors, including hypertension, obesity, diabetes and smoking (Huxley et al 2011). Other factors that predispose people to AF include advanced age, coronary heart disease, sleep apnoea, chronic obstructive pulmonary disease, renal disease and thyroid disease (ESC Task Force 2010). In other cases, AF may be related to acute, temporary causes, including alcohol intake ('holiday heart syndrome'), surgery, electrocution, myocardial infarction, pericarditis, myocarditis, pulmonary embolism or other pulmonary diseases and metabolic disorders. In such cases, successful treatment of the underlying condition often eliminates AF (Fuster et al 2006).

Thus, an essential part of overall management of AF is the identification and treatment of any predisposing factors and concomitant disorders that further increase a patient's risk of stroke and other cardiovascular conditions. The use of 'upstream therapies' (antihypertensives and cholesterol-lowering therapies) may be appropriate (Lip et al 2012b).

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). An audit of patients aged 65 years and older with AF found that 68% were taking at least eight medicines.²⁴ Similarly, a survey by the Australian Government Department of Veterans' Affairs indicated that many patients with AF also take anti-inflammatory agents, proton-pump inhibitors (PPI) and antiplatelet therapy. These comorbid conditions, risk factors, and medicines may lead to drug interactions and disease state interactions with medicines used for stroke prevention. This poses a challenge for the management of stroke prevention in AF (see Chapters 8 and 11).

Lifestyle changes, such as maintaining a healthy body weight, eating a healthy diet, refraining from smoking or excessive consumption of alcohol and coffee, and doing regular exercise, could also prevent and help manage AF.

Table 5.2 shows the risk factors for AF. Assessment of stroke risk is described in detail in Chapter 6.

²⁴ Submission: from Royal Australian College of General Practitioners (2012)

Table 5.2 Risk factors for atrial fibrillation

Category	Risk factor
Demographics	Increasing age (see Table 5.1) Males generally suffer greater incidence and prevalence of AF Race may be a risk factor, because recorded prevalence tends to be higher among Caucasians (but there are few large studies of non-Caucasian cohorts)
Cardiac conditions	Congestive heart failure (CHF) Valvular disease Myocardial infarction Hypertension
Cardiovascular risk factors	Diabetes mellitus Obesity Cigarette smoking
Dietary and lifestyle factors (may also be cardiovascular risk factors)	Excessive alcohol consumption Excessive caffeine consumption Emotional or physical stress Excessive sports practice Sleep apnoea
Other factors (emerging evidence)	A wide pulse pressure Inflammation (e.g. post-cardiac surgery)

AF = atrial fibrillation
Source: PWC 2010

5.3.3 Rhythm or rate control therapies

In patients with newly diagnosed AF, the short-term treatment goal is generally to control symptoms through rhythm or rate control therapies (Lip et al 2012b). With rhythm control, the aim is to maintain the patient in sinus rhythm; with rate control, the aim is to control the ventricular rate with medication (Samardhi et al 2011).

Rhythm control

Severe symptoms usually drive the decision to pursue a rhythm control strategy. In symptomatic patients, it may be reasonable to attempt to restore normal heart rhythm (Samardhi et al 2011). It may also be necessary to restore sinus rhythm on an emergency basis in particular groups of at-risk patients. However, up to 50% of patients with recent onset AF convert back to sinus rhythm spontaneously. For the remaining 50% of patients who do not convert spontaneously, electrical stimulation or pharmacological therapy can be used to achieve sinus rhythm. These strategies are mainly pursued in those who remain symptomatic despite rate control. In patients with minimal symptoms, aggressive attempts to maintain sinus rhythm have not been shown to reduce mortality, improve quality of life, or prevent heart failure or thromboembolic complications (Samardhi et al 2011). Once reset, the heart's rhythm may be controlled using medications including flecainide, disopyramide, sotalol and amiodarone.

Sinus rhythm may also be achieved through ablation, which is a surgical intervention usually only undertaken in AF patients who do not successfully respond to rhythm or rate control modalities (Authors/Task Force et al 2012).

Recent guidelines state that 'for patients with AF being managed with a rhythm control strategy (pharmacologic or catheter ablation), we suggest that antithrombotic therapy decisions follow

the general risk-based recommendations for patients with AF regardless of the apparent persistence of normal sinus rhythm' (You et al 2012).

Rate control

Patients with AF may also be managed by controlling the ventricular rate. This can be achieved using beta blockers, non-dihydropyridine calcium channel blockers (e.g. verapamil) or digoxin (Samardhi et al 2011).

While rhythm and rate control can offer important benefits (including in quality of life and ventricular function or heart structure), such control has not been shown to decrease the risk of stroke. One possible explanation for this finding is that those patients thought to have been successfully converted to sinus rhythm have asymptomatic episodes of AF. All patients with AF who are at moderate/high risk of stroke should be continued on long-term anticoagulation, even if they appear to have been successfully restored to sinus rhythm (Sherman 2007).

Interactions

Pharmacological control of rhythm and/or rate may lead to interactions with medicines used for stroke prevention, and this may pose a challenge for the management of stroke prevention in AF. For example, amiodarone interacts with both warfarin (a reduction of warfarin dose by one-quarter is usually recommended when taking amiodarone) and the new oral anticoagulants (NOACs). In addition, verapamil interacts with the NOACs. This is discussed further in Chapter 11.

6 Stroke risk assessment and management options

This chapter provides details about the different types of stroke that are relevant to AF and anticoagulation therapy, how stroke risk is assessed, and the antithrombotic therapies that are used to prevent strokes in people with AF.

6.1 Definition

The term ‘stroke’ refers to a collection of diseases or events that result in a loss of brain function. The most common form is *ischaemic stroke* (a stroke that arises from an occlusion of blood flow to part of the brain). Ischaemic stroke causes a loss of vision, or weakness or loss of sensation in one or on both sides of the body. In some cases, these symptoms only last a few minutes or hours and then resolve themselves; these are known as transient ischaemic attacks (TIAs). Ischaemic strokes can be further classified as:

- **small vessel disease** (lacunar infarcts, occlusion of a small artery in the brain) — which is probably best prevented by lowering blood pressure and ceasing smoking
- **large vessel disease** (artery to artery embolism) — which is best prevented by lowering cholesterol and blood pressure, antiplatelet therapy and ceasing smoking
- **cardioembolic stroke** (heart to artery embolism) — which is best prevented by anticoagulation therapy (Harrison's online 2012).

A less common, but generally more catastrophic, form of stroke is *haemorrhagic stroke*, which occurs when a blood vessel is damaged, resulting in intracerebral (i.e. intraparenchymal and intraventricular) bleeding. Haemorrhagic stroke is best prevented by intensive lowering of blood pressure and ceasing smoking. Haemorrhagic stroke is a type of intracranial haemorrhage. Intracranial haemorrhage is a broader term which generally also includes subdural, subarachnoid and epidural haemorrhages, which occur outside the brain matter.

6.1.1 AF-related strokes

The two types of stroke that are relevant to this Review are cardioembolic stroke and haemorrhagic stroke. Cardioembolic stroke is more common, and can be caused by AF. Haemorrhagic stroke can be caused by the use of anticoagulants; oral anticoagulants have been implicated in 5–12% of intracerebral haemorrhages (Cervera et al 2012).

6.1.2 Changing proportion of atrial fibrillation-related strokes

While AF has commonly been reported to be implicated in 15–25% of all ischaemic strokes, recent data from an Australian population-based epidemiological study found that AF was implicated in about 35% of ischaemic strokes. This is based on approximately 42% of strokes being cardioembolic and 84% of cardioembolic strokes being due to AF (Leyden 2011) and represents a significantly higher proportion than in other populations (Béjot et al 2009, Gattellari et al 2011). The increasing proportion of cardioembolic stroke in Australia is probably due to a number of factors, including lower incidence rates of other subtypes of stroke due to better risk-factor control, and longer survival of patients with ischaemic heart disease.²⁵

²⁵ Submission from: Stroke Society of Australasia (2012)

6.2 Stroke risk assessment in patients with atrial fibrillation

Additional risk factors affect the magnitude of increased stroke risk in people with AF. These factors can be used to stratify patients into categories of stroke risk, using risk scales such as the CHADS₂ score (Table 6.1). The higher a patient's CHADS₂ score, the greater the patient's risk of stroke, as shown in Table 6.2. Most AF patients (about 90%) have at least one additional risk factor for stroke (Nieuwlaat et al 2006). Stroke-risk stratifications can be useful in determining which patients to target for anticoagulation therapy although the decision must also take into account the risk of bleeding, which is a feature of all anticoagulant therapies.

Table 6.1 Calculation of CHADS₂ score

Risk factor	Score
Cardiac failure	1
Hypertension	1
Age ≥ 75 years	1
Diabetes mellitus	1
Prior stroke or transient ischaemic attack	2
Maximum	6

Source: Adapted from Gage et al 2001

Table 6.2 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 ESC Task Force 2010, Gage et al 2001, Lip et al 2010a

A more recent stroke risk classification, CHA₂DS₂-VASc, incorporates several additional risk factors — vascular disease, age between 65 and 74 years, and sex (female) — enabling greater stratification at lower levels of risk (Lip et al 2010b). The use of the CHA₂DS₂-VASc score has recently been recommended in international guidelines (Authors/Task Force et al 2012). Table 6.3 shows how the CHA₂DS₂-VASc score is calculated; and Table 6.4 shows the associated stroke risk.

Table 6.3 Calculation of CHA₂DS₂-VASc score

Risk factor	Score
Cardiac failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Prior stroke or transient ischaemic attack	2
Vascular disease	1
Age 65–74 years	1
Female	1
Maximum	9

Source: Adapted from Lip et al 2010b

Table 6.4 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 ESC Task Force 2010, Lip et al 2010a

6.3 Changing stroke risk over time

6.3.1 Improved control of stroke risk factors

Data from several large epidemiological studies suggest that improved control of some stroke risk factors over the past 30–50 years has lowered the overall incidence of stroke, in spite of a rapidly ageing population and the increasing prevalence of AF (Carandang et al 2006, Rothwell et al 2004).

Data from the Framingham study in the United States shows that, over the past 50 years, rates of high blood pressure have decreased (with increasing use of blood pressure lowering medicines), rates of smoking have decreased and average total cholesterol has decreased (Table 6.5). However, the incidence of AF in men at age 65 increased from 2% in 1950–1977 to 5% in 1990–2004; the incidence of diabetes and average body mass index also increased in this period.

Table 6.5 Framingham risk factors (%) among men at age 65

Risk	1950–1977	1978–1989	1990–2004	P-value
BP > 140/90	48	43	34	< 0.001
BP treatment	11	33	37	< 0.001
AF	2	4	5	0.01
Diabetes	7	8	12	0.04
Smoking	38	24	13	< 0.001
Body mass index	26	28	29	< 0.001
Total cholesterol (mmol/L)	6.0	5.70	5.2	< 0.001

AF = atrial fibrillation; BP = blood pressure
Source: Carandang et al 2006

From 1950 to 2004, the study observed a reduction in stroke from:

- 7.6 to 5.3 per 1000 person years ($P = 0.02$) for men
- 6.2 to 5.1 per 1000 person years ($P = 0.01$) for women.

Similar results were seen in another study in Oxfordshire in the United Kingdom (Rothwell et al 2004). The study found that the age-specific incidence of major stroke has fallen by 40% over the past 20 years, in association with increased use of preventive treatments and major reductions in premorbid risk factors.

The Oxfordshire study looked at the characteristics of patients who had a first-ever stroke in 1981–1984, compared to those of patients who had a first-ever stroke in 2002–2004. Table 6.6 compares the premorbid risk factors in the two populations, and shows clearly that AF is the one risk factor for stroke that has increased dramatically. This increase mirrors the substantial reductions in the proportion of smokers, mean total cholesterol and mean blood pressure, and the major increases in premorbid treatment with lipid-lowering and blood pressure lowering medicines.

Table 6.6 Premorbid risk factors and medication in patients with incident stroke in the Oxfordshire study

Risk	1981–1984	2002–2004	P-value
Mean BP	156/88	148/82	< 0.0001
BP treatment (%)	20%	47%	< 0.0001
Known previous AF	9.6%	16.8%	0.005
Diabetes	10.5%	9.5%	0.69
Smoking	33%	18%	< 0.0001
Total cholesterol	6.2 mmol/L	5.4 mmol/L	< 0.0001
Cholesterol-lowering treatment	0%	11%	< 0.0001

AF = atrial fibrillation; BP = blood pressure
Source: Rothwell et al 2004

Although 28% more strokes were expected due to demographic change in the Oxfordshire study (i.e. a 33% rise in the population 75 years of age or over), the absolute number of incident strokes fell (286 in 1981–1984 versus 262 in 2002–2004).

6.4 Stroke prevention in patients with atrial fibrillation

6.4.1 Decision to use anticoagulation therapy

Anticoagulation therapy offers the greatest protection against stroke in people with AF. Management of stroke prevention is a balance between reducing the risk of stroke and minimising the risk of bleeding caused by the therapy. In AF patients for whom the risk of stroke is low (CHADS₂ or CHA₂DS₂-VASc of 0), the risk of bleeding with anticoagulant therapy outweighs the risk of stroke. However, where the risk of stroke increases (CHADS₂ or CHA₂DS₂-VASc of 1 or more) the benefits of anticoagulation therapy generally outweigh their risks.

Recent major international AF-management guidelines all recommend that patients at low risk of stroke (i.e. CHADS₂ or CHA₂DS₂-VASc of 0) receive either no therapy or aspirin (Wasmer and Eckardt 2011), and that those with a CHADS₂ or CHA₂DS₂-VASc of 1 or more are recommended for anticoagulation therapy. Antiplatelet therapy (usually aspirin or clopidogrel) may instead be used for those who unable or unwilling to take warfarin. Table 6.7 compares the recommendations of four major international guidelines for patients at different risks of stroke.

Because of the greater stratification at lower levels of risk, the CHA₂DS₂-VASc score identifies a greater proportion of the population who are at risk of stroke and for whom anticoagulation therapy can be recommended, compared to the CHADS₂ score alone (Kaier et al 2011).

Table 6.7 Comparison of recommendations for stroke prophylaxis across four international guidelines

Score	American College of Cardiology Foundation, American Heart Association and Heart Rhythm Society ^a	Canadian Cardiovascular Society ^b	European Society of Cardiology ^c	CHEST (American College of Chest Physicians Evidence-Based Clinical Practice Guidelines) ^d
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	No therapy (aspirin if patient chooses antithrombotic therapy)
CHADS ₂ score = 1	Aspirin or warfarin/ NOAC (based on patient preference, bleeding risk, and access to high-quality anticoagulation monitoring)	Dabigatran, warfarin or aspirin (with dabigatran preferred in most patients)	Evaluate further with CHA ₂ DS ₂ -VASc score	Anticoagulation — dabigatran preferred to warfarin (or aspirin–clopidogrel or aspirin monotherapy if patient is unsuitable for, or refuses, anticoagulation)
CHADS ₂ score ≥ 2	Warfarin or NOAC	Dabigatran or warfarin (with dabigatran preferred in most patients)	Anticoagulation	Anticoagulation—dabigatran preferred to warfarin (or aspirin–clopidogrel or aspirin monotherapy if patient is unsuitable for, or refuses, anticoagulation)
CHA ₂ DS ₂ -VASc score	Not used	Not used	0 — no therapy ≥1 — anticoagulation (or aspirin–clopidogrel — or, less effectively, aspirin monotherapy — if patient refuses anticoagulation)	Not used

NOAC = new oral anticoagulant

a American College of Cardiology, American Heart Association, Heart Rhythm Society (Furie et al 2012, Wann et al 2011)

b Skanes et al 2012

c European Society of Cardiology (Authors/Task Force et al 2012)

d American College of Chest Physicians (You et al 2012)

Source: Adapted from Wasmer and Eckardt 2011

6.4.2 Anticoagulant therapy

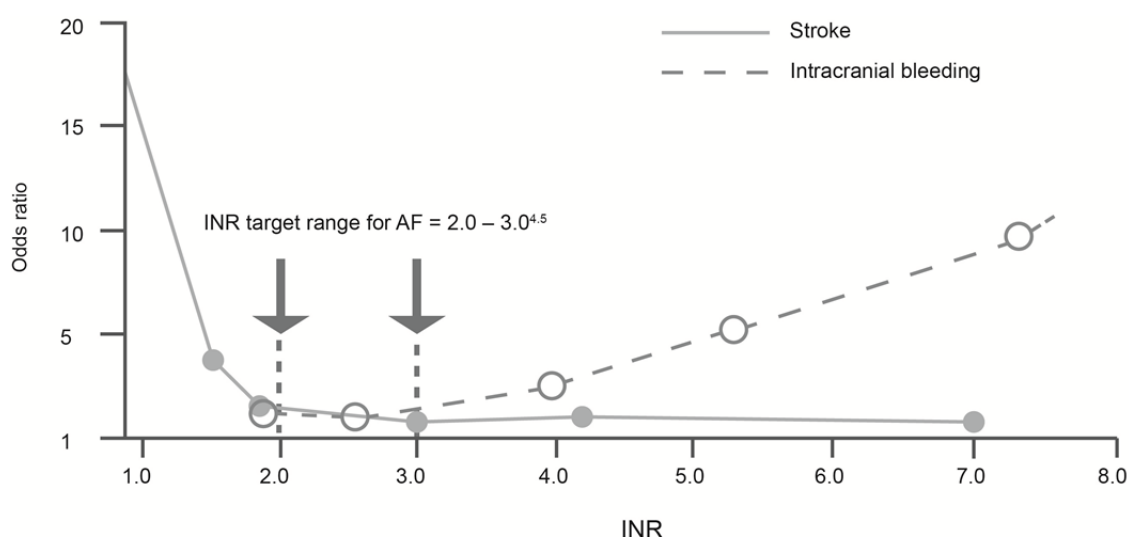
Warfarin

The most common anticoagulant used in Australia is warfarin, which has been in clinical use for more than 50 years. Warfarin is highly effective in reducing the incidence of stroke in patients with AF, regardless of the patient's stroke risk level, and is very cost-effective when used properly. A meta-analysis demonstrated that, when compared to placebo, adjusted-dose warfarin reduced stroke risk by 64%, compared to 22% with antiplatelet agents (Hart et al 2007). Although more effective than antiplatelet therapy at reducing the risk of stroke, adjusted-dose warfarin doubles the risk of major extracranial bleeding and ICH (Hart et al 2007).

Warfarin has a narrow therapeutic index and its effectiveness and safety is a tight balance between the risk of stroke and the risk of bleeding — too little warfarin and the stroke risk is not sufficiently controlled, too much and the bleeding risk is increased. The key is, therefore, to give the correct dosage of warfarin to reduce the risk of stroke without significantly increasing the risk of major extracranial bleeding and ICH. Thus, warfarin requires careful dose titration and monitoring.

Monitoring a patient's response to warfarin is performed by measurement of their international normalised ratio (INR), which is a measure of the extent of anticoagulation. In AF patients, the net clinical benefit of warfarin is highly dependent on maintaining the INR within the therapeutic range of 2–3 (Hylek et al 1996, Oake et al 2008, Odén et al 2006). As shown in Figure 6.1, INR values below this range increase the risk of stroke, while those above 3–4 are associated with an increased rate of bleeding (Fuster et al 2006). At an INR of more than 4.5, warfarin doubles a patient's risk of major extracranial bleeding and ICH (Hart et al 2007).

Vitamin K, fresh frozen plasma and prothrombin complex concentrate are antidotes to warfarin that can be used if a patient receiving warfarin therapy requires emergency surgery (where a patient's level of coagulation becomes an issue), in the event of a haemorrhage, or when INR is elevated above a particular level. However, while prothrombin complex concentrate can rapidly correct an elevated INR in patients with intracranial haemorrhage, associated mortality and morbidity rates remain high (Dowlatshahi et al 2012).



AF = atrial fibrillation; INR = international normalised ratio
Source: Fuster et al 2006

Figure 6.1 Maintaining international normalised ratio in the therapeutic range is crucial to prevent strokes and avoid bleeding

New oral anticoagulants

A number of new oral anticoagulants (NOACs), with mechanisms of action different from that of warfarin, have been developed and trialled in recent years: dabigatran, rivaroxaban and apixaban. The new agents appear to have at least a similar efficacy (i.e. are noninferior) to warfarin for reduction in stroke in people with AF, with a consistent finding in all the pivotal clinical trials of NOACs of a reduction in the incidence of ICH compared to patients on warfarin (Connolly et al 2009, Granger et al 2011, Patel et al 2011).

Internationally, other NOACs (e.g. edoxaban) are still under development, and major clinical trials of these agents are ongoing.

NOACs are discussed in more detail in chapters 11 and 12.

6.5 Bleeding risk and anticoagulant therapy

As discussed in Section 6.4, any anticoagulation therapy involves balancing the risk of stroke and the risk of bleeding. Hence, management approaches to stroke prevention in patients with AF should take into account a patient's risk of both stroke (e.g. through CHADS₂ and CHA₂DS₂-VASc) and bleeding (Garcia et al 2010, Hughes and Lip 2007). One algorithm for calculating bleeding risk is the HAS-BLED score, which is shown in Table 6.8 (Lip et al 2011a, Lip et al 2011b, Pisters et al 2010). A HAS-BLED score of 3 or more indicates a high risk of bleeding.

Factors not included in the HAS-BLED scale but which increase the risk of bleeding include history of myocardial infarction (MI) or ischaemic heart disease, cerebrovascular disease and anaemia. For patients receiving warfarin, the cumulative incidence of major haemorrhage has been reported to be increased three-fold (from 4.7% per year to 13.1% per year) for patients over the age of 80 compared to those under the age of 80; the rate was highest in patients with a CHADS₂ score greater than 2 (Hylek et al 2007). INR values greater than 4 have also been associated with increased risk of bleeding (Hylek et al 2007). There is also a higher incidence of major bleeds in the first three months of warfarin therapy (Hylek et al 2007, Mant et al 2007, Poli et al 2011, Torn et al 2005).

AF management should include systematic assessment of bleeding risk; for example, using bleeding risk algorithms such as HAS-BLED (Authors/Task Force et al 2012).

Table 6.8 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 international normalised ratios (INRs)	1
Elderly (e.g. > 65 years)	1
Medicines or alcohol (1 point each)	1 or 2
Maximum	9 points

Source: Adapted from Lip et al 2011a, Lip et al 2011b, Pisters et al 2010

The recent focused update of the European Society of Cardiology (ESC) 'Guidelines for the management of atrial fibrillation' recommends the use of HAS-BLED to assess bleeding risk when prescribing antithrombotic therapy (Authors/Task Force et al 2012). The ESC Working Group on Thrombosis has published a position document on assessment and management of bleeding risk in AF patients, which 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’ (Lip et al 2011a). Hence, in patients receiving anticoagulants, the increased risk of bleeding is generally outweighed by the reduced risk of stroke. The 2012 ESC guidelines recommend ‘the HAS-BLED score per se should not be used to exclude patients from oral anticoagulation therapy but allows clinicians to make an informed assessment of bleeding risk (rather than relying on guesswork) and, importantly, makes them think of the correctable risk factors for bleeding: for example, uncontrolled blood pressure, concomitant use of aspirin/non-steroidal anti-inflammatory drugs (NSAIDs), labile INRs, etc.’ (Authors/Task Force et al 2012).

In its submission to the Review, the Cardiac Society of Australia and New Zealand (CSANZ) noted that assessment of bleeding risk in clinical practice is usually a subjective assessment, and that risk scores for bleeding (e.g. HAS-BLED) ‘are not widely used in clinical practice’.²⁶

The difficult balance between reducing stroke and minimising the risk of bleeding is exemplified by the fact that the HAS-BLED algorithm contains elements that are also used in the CHADS₂ and CHA₂DS₂-VASc stroke risk prediction scores (i.e. hypertension, prior stroke and age).

6.5.1 Intracranial and intracerebral haemorrhages

Rates of intracranial and intracerebral haemorrhages

The most feared complication of antithrombotic therapy is intracerebral haemorrhage, which occurs 8–10 times more frequently in anticoagulated patients than in those not taking anticoagulants and is associated with a mortality rate exceeding 50% (Hart et al 2012). While intracerebral haemorrhages represent only 20% of all strokes (Leyden 2011), they have been estimated to cause more than 50% of the overall stroke mortality (Nilsson et al 2000). The higher mortality risk compared with ischaemic stroke (hazard ratio [HR] 1.56) is maintained after adjustment for age gender, stroke severity and cardiovascular risk (Cervera et al 2012). It has been estimated that 3000 of the 60,000 intracerebral haemorrhages occurring each year in the United States are caused by warfarin use (Hart et al 2005).

Recent estimates of the absolute rates of intracerebral haemorrhage in patients taking anticoagulants range from 0.3% to 0.6% per year (Huhtakangas et al 2011). This is consistent with rates of haemorrhagic stroke observed with warfarin in the recent major clinical trials of NOACs (see Chapter 12), shown in Table 6.9. The rates recently reported represent a decline from 1% per year (as observed in the late 1990s and early 2000s [Hart et al 2005], presumably due to better warfarin control and management of hypertension (Huhtakangas et al 2011).

Table 6.9 Rates (per 100 person-years) of intracranial haemorrhage and haemorrhagic stroke in the warfarin arms of the major clinical trials of the new oral anticoagulants

	RE-LY ^a	ROCKET-AF ^b	ARISTOTLE ^c
Rate of ICH in warfarin arm	0.76	0.7	0.80
Rate of haemorrhagic stroke in warfarin arm	0.38	0.44	0.47

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ICH = intracranial haemorrhage; 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

^a Connolly et al 2010

^b Patel et al 2011

^c Granger et al 2011

²⁶ Submission from: Cardiac Society of Australia and New Zealand (2012)

Risks for intracerebral haemorrhage

The incidence of intracerebral haemorrhage is reduced by maintaining the INR below 3, controlling hypertension and avoiding concomitant aspirin (Hart et al 2005). Reductions in systolic blood pressure of 9 mmHg and 12 mmHg led to a reduction in haemorrhagic stroke of 50% and 76%, respectively (Chapman et al 2004). However, two studies showed that 62% and 68% of all warfarin-related haemorrhages occurred at an INR of 3.0 or less (Fang et al 2004, Rosand et al 2004). These data suggest that most intracerebral haemorrhages occur when the INR is in the reference range, although the risk increases as the INR exceeds 4.

The use of oral anticoagulants may unmask intracerebral bleeding that would otherwise remain asymptomatic (Hart 2000). However, since the risk is greater at elevated INR values, oral anticoagulation may also directly cause intracerebral haemorrhage. It has been postulated that adequate levels and functionality of vitamin K clotting factors VII, IX and X are essential to counteract the stress placed on blood vessels and to prevent bleeding (Weitz 2012). The risk of intracerebral haemorrhage at INR values below 2 did not differ from the risk at INR values 2–3 (Fang et al 2004). Thus, management should focus on maintaining the INR within the therapeutic range, since reducing anticoagulation to prevent intracerebral haemorrhage is not supported.

Data on the increased incidence of intracerebral haemorrhage in patients taking a combination of warfarin and aspirin are inconsistent; nevertheless, increased risk is probable, particularly given the results of a sub-analysis of the RE-LY trial (Hart et al 2012), and the combination should be used with caution in elderly patients and those with cerebrovascular disease (Hart 2000). In practice, use of a combination of aspirin and warfarin is common. Recent guidelines recommend against the combination in patients with stable coronary artery disease, the most common indication for co-administration (Holbrook et al 2012).

The risk for intracerebral haemorrhage increases with age (especially in those over the age of 75). Increased endothelial fragility may be responsible, which would make older patients more susceptible to anticoagulant-induced bleeding (Beyth 2001).

Factors contributing to an increased risk of cerebral haemorrhage in patients receiving anticoagulants are shown in Table 6.10.

Table 6.10 Proven and possible risk factors for cerebral haemorrhage in patients receiving anticoagulants

Proven risk factors	Possible risk factors
Advancing age (i.e. > 75 years)	Increased variation in INR
Hypertension (especially SBP > 160 mmHg)	Concomitant use of aspirin
History of cerebrovascular diseases	Cerebral amyloid angiopathy
Intensity of anticoagulation (mainly if INR > 4.0)	Tobacco smoking
	Heavy alcohol consumption
	Diabetes
	Serious heart disease
	Liver disease
	Malignancy

INR = international normalised ratio; SBP = systolic blood pressure
Source: Cervera et al 2012

6.5.2 Intracranial haemorrhages and falls

The risk of traumatic intracranial haemorrhage may influence the selection of antithrombotic therapy (Gage et al 2005). Also, surveys have shown that antithrombotic therapy is often avoided in elderly patients with AF who are prone to falls (Monette et al 1997). Although such patients are at high risk of traumatic intracranial bleeds, the net benefit of anticoagulation therapy may still be positive if the CHADS₂ score is at least 2, because of the high risk of stroke (Gage et al 2005). The incidence of ICH in patients who are at risk of falling has been investigated (Gage et al 2005):

- Rates of ICH were 2.8 in patients at high risk for falls and 1.1 in other patients per 100 patient-years.
- Rates of traumatic ICH were 2.0 for those at high risk of falls and 0.34 in others per 100 patient-years.
- The ischaemic stroke risk was 13.7 for those at high risk of falls and 6.9 in others per 100 patient-years.

AF has recently been shown to be an independent risk factor for non-accidental falls (i.e. falls that are not precipitated by slipping or tripping on an object or surface) and it has been recommended that patients presenting with these falls be investigated for AF (Sanders et al 2012).

7 Antiplatelet therapy

This chapter provides further details about the efficacy and safety of antiplatelet therapy compared to warfarin for prevention of stroke in people with AF.

7.1 Mechanisms of action

Both aspirin and clopidogrel inhibit platelet aggregation. Aspirin inhibits cyclooxygenase, a key enzyme in thromboxane A₂ generation, while clopidogrel blocks the P2Y₁₂ receptor, thereby inhibiting the adenosine diphosphate (ADP)-dependent pathway of platelet activation (Savi et al 2006).

7.2 Dosage

The trials of aspirin for stroke prevention in patients with AF have used dosages ranging from 50 mg/day to 1200 mg/day (Hart et al 2007). In Australian clinical practice, dosages ranging from 100 mg/day to 300 mg/day are commonly used.²⁷ There are no data supporting a particular strength of aspirin for stroke prevention; however, lower dosages (e.g. 100 mg/day) are likely to be associated with a lower risk of bleeding.

The usual dosage of clopidogrel is 75 mg/day.

7.3 Efficacy and safety

International guidelines recommend that AF patients with low risk of stroke (CHADS₂ of 0, or CHA₂DS₂-VASc of 0 in the ESC Guidelines) should receive either no therapy, or aspirin (75–325 mg daily) if an antithrombotic is selected. The use of anticoagulation or combination antiplatelet therapy is not recommended in this patient group. For AF patients with a moderate-to-high risk of stroke (CHADS₂ of ≥ 1, CHA₂DS₂-VASc of ≥ 1 in the ESC Guidelines), anticoagulation therapy is recommended. In patients unsuitable for, or who chose not to take, an anticoagulant, combined clopidogrel and aspirin is recommended in some guidelines (Authors/Task Force et al 2012, Wann et al 2011, You et al 2012).

For AF patients with stable coronary artery disease who choose anticoagulation therapy, anticoagulant monotherapy is recommended in preference to combination antiplatelet–anticoagulant therapy. Triple therapy (anticoagulant plus aspirin plus clopidogrel) is recommended for AF patients at high risk of stroke requiring a coronary artery stent, while dual antiplatelet therapy is recommended for those with low to moderate risk (You et al 2012).

7.3.1 Efficacy compared to placebo

A meta-analysis of the effectiveness of antiplatelet agents (predominately aspirin) on stroke prevention in patients with AF identified seven trials that compared aspirin therapy to placebo (Hart et al 2007). The data demonstrated a 19% (–1% to 35%) reduction in the incidence of stroke. Aspirin was associated with a 13% reduction in disabling strokes and a 29% reduction in non-disabling strokes. When only ischaemic strokes were considered, a 21% (–1% to 38%) reduction was observed (Hart et al 2007). The largest trial involving a majority of primary prevention patients was the SPAF 1 trial, which gave a relative risk reduction of 42% in the rate of stroke and systemic embolism (Cairns 1991).

²⁷ See the NPS MedicineWise website at:

http://www.nps.org.au/health_professionals/publications/prescribing_practice_review/current/nps_prescribing_practice_review_44

For primary prevention in AF patients with an average stroke rate of 4% per year, about 10 strokes are likely to be prevented each year for every 1000 AF patients given aspirin (Aguilar and Hart 2005). However, it has been argued that this result is driven by the SPAF 1 trial (Kalra and Lip 2007). A recent consensus statement from the Royal College of Physicians of Edinburgh recommended that aspirin should not be used for stroke prevention in AF due to a lack of efficacy (RCPE 2012).

7.3.2 Efficacy and safety compared to warfarin

A 40% relative risk reduction in stroke was reported in a direct comparison between aspirin and warfarin (Hart et al 2007). A meta-analysis demonstrated that, compared to placebo, adjusted-dose warfarin reduces stroke risk by 64% and antiplatelet agents reduce it by 21% (Hart et al 2007). Thus, adjusted-dose warfarin appears to be more effective than antiplatelet therapy; however, it doubles the risk of major extracranial and intracranial haemorrhage (Hart et al 2007). The analysis also showed that warfarin was associated with a 37% reduction in the risk of stroke compared to antiplatelet therapy (but this meta-analysis did not include the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study described below). It also reported a doubling of the risk of intracranial haemorrhage with warfarin compared to aspirin, although the absolute risk difference was only 0.2% per year (Hart et al 2007). It has been reported that ‘treating 1000 patients with AF for one year with warfarin rather than aspirin would prevent 23 ischaemic strokes and cause 9 additional major bleeds’ (van Walraven et al 2002).

One study suggested that, in patients aged 75 and over, warfarin and aspirin gave similar rates of total stroke (ischaemic and haemorrhagic) (4.6% and 4.3% per year, respectively) (Stroke Prevention in Atrial Fibrillation Investigators 1994). The aspirin dosage in this study was 325 mg per day, and the INR target was 2.0–4.5. What impact this dose or the wider range of INR (i.e. compared to the accepted therapeutic index for this indication of 2–3) may have on these results is uncertain.

The BAFTA study was a randomised controlled trial in which patients aged 75 and over with AF were assigned to warfarin (INR target 2–3) or aspirin (75 mg/day), with a followup period of 2.7 years (Mant et al 2007). The primary outcome measure was fatal or disabling stroke (ischaemic or haemorrhagic), ICH or arterial embolism. Warfarin was associated with a lower risk of primary endpoints than aspirin for all age groups, with an absolute rate difference of 2% (1.8% for warfarin versus 3.8% for aspirin) and relative risk [RR] = 0.48 (0.28–0.80). The incidence of extracranial bleeds was similar between the two medicines — 1.4% for warfarin and 1.6% for aspirin (RR = 0.87 [not significant]). In this trial, the event rate was less than predicted — only 3.3% for patients on aspirin with a CHADS₂ score of 3–6, compared to an anticipated rate of 9%. The observed rate in both arms of the ACTIVE W study was also less than predicted from earlier studies (ACTIVE W 2006). It has been suggested that this lower incidence of stroke rate may be due to better management of risk factors such as hypertension and hypercholesterolaemia compared to earlier studies.

The magnitude of the benefit of warfarin over antiplatelet therapy has been reported to depend on the quality of anticoagulant therapy, as measured by the time in the therapeutic range (TTR), with a value above 58% being needed to demonstrate a benefit of warfarin over antiplatelet therapy (Connolly et al 2008).

7.3.3 Combined aspirin and clopidogrel co-therapy

A trial comparing the combination of clopidogrel and aspirin to warfarin monotherapy in patients with AF and at least one other risk factor for stroke found clear evidence of superiority of warfarin for prevention of vascular events (ACTIVE W 2006). The trial was stopped on the recommendation of the Drug Safety and Monitoring Board before planned followup was completed, because the combination of clopidogrel and aspirin proved inferior to warfarin

(ACTIVE W 2006). The bleeding risk was higher with a combination of aspirin and clopidogrel (total haemorrhage rate of 15.4% per year) than with warfarin monotherapy (13.2% per year) (ACTIVE W 2006).

A followup trial was conducted in patients with AF who were at increased risk for stroke and for whom therapy with a vitamin K antagonist was considered unsuitable. It found that a combination of clopidogrel and aspirin reduced the rate of ischaemic stroke by 28% compared to aspirin alone (ACTIVE Investigators 2009). An analysis of the two ACTIVE trials demonstrated that adding clopidogrel to aspirin (compared to aspirin monotherapy) resulted in a small non-significant benefit, defined as ischaemic stroke equivalents prevented (Connolly et al 2011a).

The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and, especially in the elderly, also with aspirin monotherapy) has recently been considered as being similar to oral anticoagulants (Authors/Task Force et al 2012).

7.3.4 Combination anticoagulant–antiplatelet therapy

A significant proportion of AF patients receiving warfarin also take concomitant aspirin (Boehringer Ingelheim 2010). This is problematic because the combination of antithrombotic therapies may compound the risk of bleeding in these patients.

A review of randomised controlled trials reported that there was ‘no evidence for improved effectiveness of combination therapy compared to antiplatelet therapy alone for the prevention of recurrent cardiovascular events in patients with noncardioembolic stroke or peripheral artery disease, or compared with anticoagulant therapy alone for the prevention of stroke in patients with atrial fibrillation’ (Paikin et al 2011). A nationwide cohort study in Denmark involving 132,372 patients with AF also reported that the combination of a vitamin K antagonist and aspirin did not yield any additional benefit compared to anticoagulant alone, but gave an increased risk of bleeding (Olesen et al 2011). Similarly, other studies have reported a 1.5–2.0-fold increase in bleeding compared to warfarin alone (Dentali et al 2007, Flaker et al 2006, You et al 2012). This increased bleeding risk due to the combination has also been reported in Australia (Ghiculescu 2008). Similarly, in the ARISTOTLE and RE-LY trials, the bleeding rate in patients receiving concomitant aspirin was higher than in those patients not receiving concomitant aspirin (Boehringer Ingelheim 2010, Connolly et al 2009, Granger et al 2011).

Vitry et al (2011) reported that in Australian veterans receiving warfarin, bleeding associated hospitalisation rates were significantly increased when warfarin was co-prescribed with low dose aspirin, clopidogrel and aspirin–clopidogrel combination (Vitry et al 2011).

The 2012 American College of Chest Physicians clinical practice guidelines on antithrombotic therapy in AF (You et al 2012) include the following recommendation:

For patients with AF and stable coronary artery disease (e.g. no acute coronary syndrome within the previous year) and who choose oral anticoagulation, we suggest adjusted-dose VKA²⁸ therapy alone (target INR 2.0–3.0) rather than a combination of adjusted-dose VKA and aspirin.

This advice is relevant because approximately one-third of patients with AF also have coronary artery disease (Kralev et al 2011).

These guidelines suggest a combination of warfarin and/or dual antiplatelet therapy in particular patients after coronary artery stenting (You et al 2012):

²⁸ Vitamin K antagonist (coumarins; i.e. warfarin in Australia, but internationally, phenprocoumon and acenocoumarol are used)

For patients with AF at high risk of stroke (e.g., CHADS2 score of 2 or greater) during the first month after placement of a bare-metal stent or the first 3 to 6 months after placement of a drug-eluting stent, we suggest triple therapy (e.g., VKA therapy, aspirin, and clopidogrel) rather than dual antiplatelet therapy (e.g., aspirin and clopidogrel) (Grade 2C). After this initial period of triple therapy, we suggest a VKA (INR 2.0–3.0) plus a single antiplatelet drug rather than VKA alone (Grade 2C). At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease.

For patients with AF at low to intermediate risk of stroke (e.g., CHADS2 score of 0 or 1) during the first 12 months after placement of an intracoronary stent (bare metal or drug eluting), we suggest dual antiplatelet therapy rather than triple therapy (Grade 2C). At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease.

Table 7.1 shows the recommendations of four major international guidelines for the use of antiplatelet therapy.

Table 7.1 Current international recommendations for using antiplatelet therapy

	ESC^a	ACC/AHA/HRS^b	Canadian^c	CHEST guidelines^d
Place of aspirin in therapy	<p>Should be limited to the few patients who refuse any form of OAC and cannot tolerate aspirin–clopidogrel combination therapy (e.g. due to excessive bleeding risk)</p> <p>The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and — especially in the elderly — also with aspirin monotherapy) should be considered as being similar to OAC</p>	<p>Aspirin is recommended as an alternative to OAC in low-risk patients or in those with contraindications to OAC</p> <p><i>CHADS</i> = 1 — aspirin or OAC, depending on the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences.</p>	<p><i>CHADS</i>₂ = 0 — should receive aspirin or none (no prophylaxis may be appropriate in selected young patients with no stroke risk factors)</p> <p><i>CHADS</i> = 1 — NOAC or warfarin or aspirin (with NOAC preferred in most patients)</p>	<p><i>CHADS</i>₂ = 0 — no therapy (aspirin if patient chooses antithrombotic therapy) (Grade 2B)</p> <p><i>CHADS</i>₂ = 1 — OAC; for patients who are unsuitable for or choose not to take an OAC (for reasons other than concerns about major bleeding), combination therapy with aspirin and clopidogrel is suggested rather than aspirin alone</p>
Combination warfarin-antiplatelet (e.g. vascular disease/ACS)	<p>Stable vascular disease (e.g. > 1 year, with no acute events), OAC monotherapy may be considered, and concomitant antiplatelet therapy should not be prescribed in the absence of a subsequent cardiovascular event</p> <p>When OAC is given in combination with clopidogrel or low-dose aspirin, careful regulation of the anticoagulation dose intensity may be considered, with an INR range of 2.0–2.5 (ESC Task Force 2010)</p> <p>ACS or stenting/PCI</p> <p>A period of triple therapy is needed (OAC plus aspirin plus clopidogrel), followed by the combination OAC plus single antiplatelet drug and, after one year, management can be with OAC alone in stable patients</p>		<p>Patients with AF or atrial flutter who have experienced ACS or who have undergone percutaneous coronary intervention should receive antithrombotic therapy selected on the basis of a balanced assessment of their risks of stroke, of recurrent coronary artery events, and of haemorrhage associated with the use of combinations of antithrombotic therapies, which in patients at higher risk of stroke may include aspirin plus clopidogrel, plus OAC</p>	<p>For patients taking VKAs, avoid concomitant treatment with antiplatelet agents except where benefit is known or is highly likely to be greater than harm from bleeding; for example, patients with mechanical heart valves, ACS or recent coronary stents or bypass surgery (Holbrook et al 2012)</p> <p>For patients with AF and stable coronary artery disease (e.g. no ACS within the previous year) and who choose OAC, use OAC alone rather than in combination with aspirin</p> <p><i>CHADS</i>₂ score ≥ 1 and ACS (no intracoronary stent) for the first 12 months — adjusted-dose VKA therapy plus single antiplatelet therapy rather than dual antiplatelet therapy or triple therapy</p> <p>After 12 months, see stable coronary artery disease</p> <p><i>CHADS</i>₂ = 0 — suggest dual antiplatelet therapy (e.g. aspirin and clopidogrel); after 12 months, see stable coronary artery disease</p>
Combination aspirin and clopidogrel	<p>Dual antiplatelet therapy — aspirin and clopidogrel should be considered for stroke prevention in patients who refuse to take OAC therapy</p>	<p>The addition of clopidogrel to aspirin to reduce the risk of major vascular events, including stroke, might be considered in patients with AF in whom OAC is considered unsuitable due to patient preference or the clinician's assessment of the patient's ability to safely sustain anticoagulation</p>		<p>For patients with <i>CHADS</i>₂ ≥ 1, who are unsuitable for or choose not to take an OAC (for reasons other than concerns about major bleeding), combination therapy with aspirin and clopidogrel is suggested rather than aspirin alone</p>

ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulant; VKA = vitamin K antagonist (coumarins; i.e. warfarin in Australia, but internationally, phenprocoumon and acenocoumarol are used)

^a European Society of Cardiology (Authors/Task Force et al 2012)

^b American College of Cardiology, American Heart Association, Heart Rhythm Society (Wann et al 2011)

^c Cairns et al 2011

^d American College of Chest Physicians (You et al 2012)

8 Warfarin therapy

This chapter provides details of the mechanism of action, efficacy, safety and monitoring of warfarin therapy.

Warfarin, a derivative of coumarin, has been used clinically since the 1950s, and is among the most widely studied medicines currently in clinical use (Link 1959). Thousands of papers have been published relating to warfarin's use and ways of optimising therapy.

Warfarin was the 17th most frequently dispensed PBS-subsidised medicine, with 2.5 million prescriptions for concessional patients dispensed in 2010–11 (DoHA 2011b). It is highly effective in reducing the incidence of stroke in patients with AF (generally 64% reduction in stroke), regardless of the patient's stroke risk level, and is more effective than antiplatelet medications in preventing stroke (see Chapter 6).

Warfarin is currently available in Australia as the products Coumadin[®] and Marevan[®] (both brands supplied in Australia by Aspen Pharmacare).

8.1 Mechanism of action

Warfarin is a mixture of two compounds, R and S-warfarin (called a racemic mixture), which are mirror-image forms of one another. 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 into inactive, or largely inactive, substances by liver enzymes from the cytochrome P450 family. As shown in Figure 8.1, particular enzymes are responsible for the metabolism of the S and R-enantiomers.

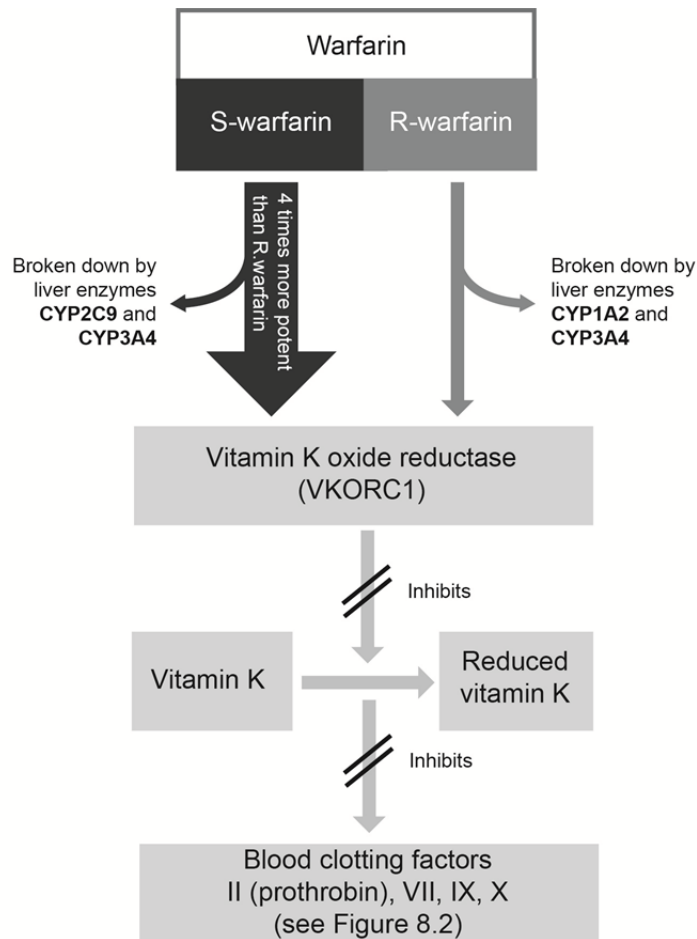
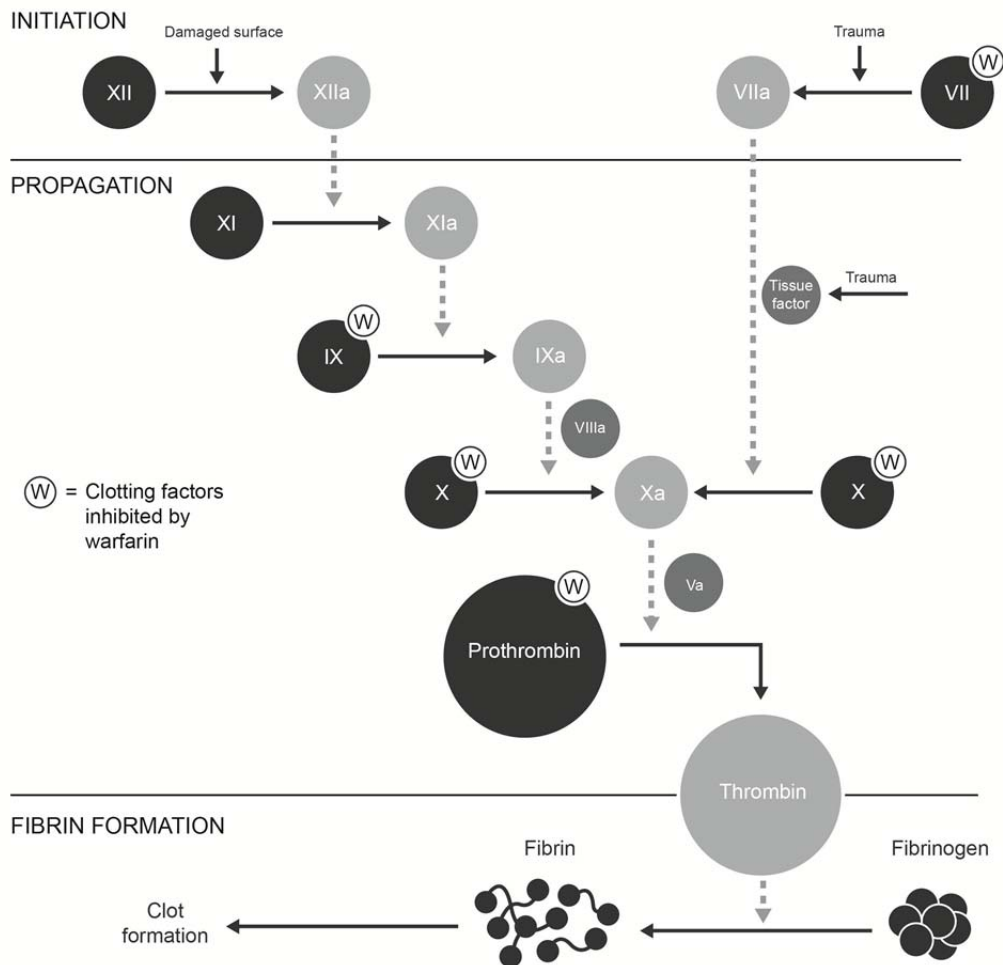


Figure 8.1 Metabolism of warfarin

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 (Friedman et al 1977, Malhotra et al 1985). As shown in Figure 8.2, 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

Figure 8.2 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 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 that:

- 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.

The liver enzymes that metabolise warfarin (see Figure 8.1) 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.

8.2 Time in therapeutic range

As described in Chapter 6, the clinical benefits of warfarin in preventing stroke in AF patients are highly dependent on maintaining the INR within the therapeutic range of 2–3 (Hylek et al 1996, Oake et al 2008, Odén et al 2006); maintaining an INR of < 3 reduces the incidence of intracranial haemorrhage (ICH) (Rosand et al 2004).

A measure of anticoagulant control during a specified period of time is the TTR (Rosendaal et al 1993). In patients taking warfarin who have poor control (i.e. TTR < 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%) than in patients with good control (i.e. > 70% TTR) (White et al 2007). Retrospective studies have shown that a 6.9% improvement in TTR significantly reduced major haemorrhage by one event per 100 patient-years of treatment (Wan et al 2008).

The TTR varies significantly among individuals, with estimates in Australian community-based practice ranging from 50% to 68% (DoHA 2011a). 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 (Wan et al 2008).

Australians who participated in the RE-LY and ARISTOTLE trials had TTRs of approximately 74% (Wallentin et al 2010, Wallentin and Collet 2011). Further advice from one of the pathology laboratories providing an anticoagulant service indicated that the average of INR values from their database was over 70%. This suggests that TTRs of at least 70% are possible in the presence of a dedicated anticoagulant management program.

8.3 Warfarin initiation

The initiation phase of warfarin therapy is a critical period for patients, because adverse outcomes occur more frequently early in therapy. It takes time for warfarin to reach the therapeutic range — during which time the patient is exposed to increased stroke risk unless a loading dose is used; hence, some clinicians may use shorter acting injectable anticoagulants during this time. The risk of bleeding is higher during this stage and a higher frequency of INR testing is required. It has been suggested that the common starting dosage of 5 mg daily would lead to over-anticoagulation in 82% of women and 65% of men over the age of 70 (Garcia et al 2005).

Warfarin therapy can be especially problematic when patients are commenced in hospital. Patients may be discharged before a stable INR has been achieved, and management of the patient is then transferred to the local general practitioner (GP). The continuity of care can be fragmented unless formal and timely postdischarge processes are in place.

8.4 Monitoring

Warfarin is one of the few medicines in wide clinical use for which there is a readily available validated surrogate for therapeutic response (i.e. INR). The therapeutic INR range of 2–3 is internationally accepted as the target for warfarin therapy in AF patients. However, it is acknowledged that intracerebral haemorrhage can occur with INR values that are within the therapeutic range (Fang et al 2004, Rosand et al 2004).

8.4.1 Frequency of monitoring

Patients taking warfarin need to have their INR checked frequently: daily to weekly during the initiation stage and once or twice a month (or, if stable, every 2–3 months) during the maintenance stage.

In Australia, one factor that increases the inconvenience of frequent testing is that the only Medicare-subsidised method of blood sampling for INR measurement is by venipuncture, usually taken at a pathology collection centre, a medical practice, the patient's home or residential aged care facility. The blood sample is then transported to a pathology laboratory for analysis, and the results communicated to the referring GP or specialist. About 75% of warfarin testing is estimated to be performed in this way in Australia. This can be a major disadvantage to patients in rural areas,²⁹ those who have poor venous access³⁰ and patients who are travelling³¹. The testing can affect patients' quality of life, and their job and employment opportunities, and may impose an additional financial burden.³²

There is a period of time between the blood sampling, the measurement of the INR, receipt of results by the medical practitioner and any necessary action. This time can sometimes be protracted³³ and, in the case of a highly elevated INR, can potentially place the patient at risk.

During maintenance therapy, the frequency of INR testing depends on the stability of INR values. In patients with stable INR values, testing is generally recommended every 4–8 weeks (Ageno et al 2012). A survey of 596 GPs found that, for a scenario of a patient aged 78 diagnosed with nonvalvular atrial fibrillation (NVAf) after a stroke (equivalent to a CHADS₂ score of at least 2), 78% of respondents indicated they would monitor INR monthly, whereas 14% would monitor fortnightly (Gattellari et al 2008a). In particularly stable patients, three-monthly monitoring has recently been shown to have the same outcome as more regular (4-weekly) monitoring (Schulman et al 2011). Note that this was in patients whose maintenance dose had not been changed for 6 months. In patients with a labile INR response, or in situations where dosage needs to be adjusted, more frequent monitoring is required (Franke et al 2008).

An audit of INR monitoring from the General Practice Research Network (GPRN) database suggests that, in Australia, patients on warfarin for AF have an average of 1.7 INR tests per month, or around 20 tests per patient per year.³⁴ This is greater than the figure reported in the ARISTOTLE trial of apixaban (Granger et al 2011); an Australian trial that found an average of 9.3 INR tests per patient per year (DoHA 2009); and in a United Kingdom study, which reported 8–12 INR tests per person per year (Jowett et al 2008). It is uncertain whether the rate of testing seen in the GPRN database is necessary, particularly in relatively stable patients, and what percentage of these tests result in a change in dosing.

On the other hand, some people find the regular INR monitoring, as part of a regular review by their medical practitioner, reassuring. For example, the trial of 4-weekly versus 12-weekly monitoring mentioned above (Schulman et al 2011) was designed so that 4-weekly true INR values were recorded, even though sham results were forwarded to the treating clinician for two of the three 4-weekly periods for patients in the 12-weekly group. Where an INR result was out

²⁹ Submissions from: National Stroke Foundation; Cardiac Society of Australia and New Zealand; Royal Australasian College of Physicians; Baker Heart & Diabetes Institute; Tideman P, St John A and Tirimacco R. (2012)

³⁰ Submissions from: Edwards, S; Colquhoun, D; the Australasian Society of Thrombosis and Haemostasis, The Haematology Society of Australia and New Zealand, The Australian and New Zealand Society of Blood Transfusion's; Blombery, P. Submission to Review. (2012)

³¹ Submission from Flecknoe-Brown, S. (2012)

³² Submissions from: Atrial Fibrillation Association, National Stroke Foundation; Colquhoun, D; Scott M; Levendel, A; Cardiac Society of Australia and New Zealand. (2012)

³³ Submissions from: Edwards, S; Baker Heart & Diabetes Institute. (2012)

³⁴ Submission from: Boehringer Ingelheim (2012)

of range (i.e. < 1.5 or > 4.5) for a patient in this group, the true value was sent to the treating physician for action. Therefore, although the study showed that the 12-weekly monitoring regime was noninferior to assessment every 4 weeks, there was nonetheless a safety net for these patients. This support would not be present if 12-weekly monitoring (i.e. monitoring once every 12 weeks) became standard practice.

There is evidence in the literature that with point-of-care testing (PoCT) by patients or in general practice the number of INR test per year is increased. In a cost analysis submitted to the Review, Boehringer Ingelheim assumed that, with PoCT, patients would use 32.4 tests per year in patient-managed testing, while PoCT in general practice would use 26.3 tests per year. This is compared to 20.4 tests per year from GPRN data for usual care (see Section 9.3.2).³⁵

8.5 Reversing warfarin-related intracranial haemorrhages

Guidelines for the reversal of warfarin-related ICH are available (Cervera et al 2012). These guidelines all include 5–10 mg of vitamin K given intravenously with prothrombin complex concentrate (PCC). The Australasian guidelines recommend administering fresh frozen plasma in addition to PCC (Baker et al 2004), although PCCs achieve a faster reduction in INR than fresh frozen plasma. In patients who present with ICH, rapid reversal of coagulopathy is recommended to an INR of 1.2 or less (Appelboom and Thomas 2009). However, there is only a small window in which to minimise the size of the haematoma that has been associated with poorer outcomes (Zubkov 2008). Vitamin K administration takes 2–24 hours to bring INR values to within the normal range (Steiner et al 2006).

8.6 Perioperative management

Health care professionals face a major clinical issue when a patient taking warfarin requires surgery. The half-life of warfarin is approximately 40 hours, and its anticoagulant effects last 2–5 days. Withholding warfarin places the patient at risk of a thromboembolic event, which may be exacerbated by the surgery itself. However, perioperative anticoagulation increases the risk of bleeding.

Management algorithms for perioperative management have been published; for example, (Douketis et al 2012, Dunn and Turpie 2003, Merriman and Tran 2011, Sridhar and Grigg 2000). The American College of Chest Physicians has issued the following guideline (Douketis et al 2012):

- In patients who require an interruption to warfarin treatment before surgery, cease warfarin 5 days before surgery and resume 12–24 hours after surgery.
- In patients with AF and high risk for thromboembolism, begin bridging anticoagulation during interruption of warfarin treatment.
- For patients requiring minor dental procedures, co-administer warfarin with an oral prohaemostatic agent, or stop warfarin administration 2–3 days before procedure.
- For cataract surgery and minor dermatological procedures, it is recommended to continue taking warfarin.

This is consistent with other reports that have recommended that most patients undergoing dental procedures, joint and soft tissue injections, arthrocentesis, cataract surgery and upper endoscopy or colonoscopy can undergo the procedures without any change in the anticoagulant regime (Dunn and Turpie 2003). For other procedures, it is suggested to withhold oral anticoagulation and decide whether to commence heparin or low molecular weight heparin

³⁵ Submission from: Boehringer Ingelheim (2012)

(LMWH) on the basis of risk associated with the surgery and the risk of thromboembolism (see Table 8.1). Recommendations have been published for perioperative anticoagulation of patients undergoing major elective surgery, which take into account the patient's risk of thromboembolism (CHADS₂) and the type of surgery (see Table 8.1, and also Merriman and Tran 2011, Sridhar and Grigg 2000).

The Australian guideline for the management of AF should include recommendations on the perioperative management of patients receiving anticoagulants.

Table 8.1 Guidelines for the perioperative management of anticoagulation for procedures that require anticoagulation therapies to be ceased

Indication for anticoagulation	Examples	Recommendation
Indication with low annual risk of thromboembolic stroke (< 4%) without anticoagulation	AF without history of thromboembolic stroke; cardiomyopathy without AF; Guidelines from the American College of Chest Physicians (2012) recommend CHADS ₂ 0–2 (Douketis et al 2012)	Withhold oral anticoagulation
Indication with moderate annual risk of thromboembolic stroke (4–7%) without anticoagulation	Mechanical aortic valve; Guidelines from the American College of Chest Physicians (2012) recommend CHADS ₂ 3–4 (Douketis et al 2012)	Withhold oral anticoagulation Optional administration of either treatment-dose intravenous heparin or subcutaneous LMWH while INR subtherapeutic dependent on an assessment of individual patient- and surgery-related factors
Indication with high annual risk of thromboembolic stroke (> 7%) without anticoagulation	Mechanical mitral valve; AF with history of thromboembolic stroke; Guidelines from the American College of Chest Physicians (2012) recommend CHADS ₂ 5–6 (Douketis et al 2012)	Withhold oral anticoagulation and administration of either treatment-dose intravenous heparin or subcutaneous LMWH while INR subtherapeutic

AF = atrial fibrillation; INR = international normalised ratio; LMWH = low molecular weight heparin
Source: Dunn and Turpie 2003, Douketis et al 2012

8.7 Inpatient variability

The variability in INR values seen within a patient makes patient management problematic, and labile INR values increase the risk of bleeding.

A number of submissions to the Review from consumers raised the issue of labile INR blood test results³⁶, and prescribers outlined particular patients for whom maintaining an INR within an acceptable range was difficult to achieve³⁷ or whose usually stable INR changed markedly for no apparent reason.³⁸

This inpatient variability is problematic, with patients having periods of under- and over-anticoagulation, or needing multiple dosage adjustments — a situation that can lead to patient confusion and a ‘chasing the dose’ phenomenon (i.e. frequent dosage adjustments). In addition, there is no nationally endorsed, readily available Australian algorithm to help clinicians adjust warfarin doses in response to INR values.

³⁶ Submissions from: consumers (submissions numbered 8 and 9) (2012)

³⁷ Submission: from Rao S (2012)

³⁸ Submission from: Colquhoun D (2012)

Further, fear of erratic INRs leading to increased bleeding risk can potentially lead clinicians to adopt a conservative underdosing approach to warfarin management, thus reducing the efficacy of warfarin in stroke prevention.

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/tissue vitamin K levels
- concurrent illness.

8.7.1 Medicine interactions

Pharmacokinetic interactions with warfarin are unlikely to involve issues with bioavailability because the medicine is well absorbed and does not undergo gut or hepatic first-pass extraction. Although warfarin is extensively bound to plasma proteins, it has a low intrinsic metabolic clearance; thus, it is unlikely that changes in protein binding will have any significant clinical effect on chronic dosing.

The literature often reports that warfarin has multiple medicine interactions, and publications often list many medicines reported to interact with warfarin (Holbrook et al 2005, Jonsson et al 2007). However, many of the examples of warfarin medicine interactions given within the literature are not well supported by robust clinical evidence; in fact, a significant proportion of these examples rely on single case reports (Ageno et al 2012). In addition, for many of these case reports, the reported medicine interactions have no obvious or plausible biological mechanism. In these cases a possible explanation is a reduction in vitamin K intake due to dietary changes as a result of the acute illness, particularly in patients with low vitamin K plasma/tissue levels.

Where a medicine interaction has been shown in controlled trials, there is often a suitable alternative from within the same therapeutic class of the interacting medicine. One submission noted that medicine interactions with warfarin are ‘often poorly understood by GPs and patients’.³⁹

For those medicine-interactions that have been validated, some of the interacting medicines (e.g. rifampicin) have a limited use in clinical practice and are often used only in specialised units. This means that the number of patients potentially exposed to such interactions is likely to be small and appropriate dosage adjustments can be made. There are several ways in which medicine interactions with warfarin can be avoided or their impact minimised. For example:

- appropriate monitoring of a patient’s medication record (including use of decision-support tools) and prescribing alternative medicines of comparable efficacy that are known not to interact with warfarin (where an alternative exists)
- predicting dosage requirements before starting interacting agents such as amiodarone (dosage reduction is likely to be 25%)
- active patient counselling about over-the-counter products and their interaction with warfarin (e.g. paracetamol and complementary medicines) (PSA 2012).

Further discussion of drug interactions with oral anticoagulants is provided in Section 11.5. Other reported interactions are discussed below.

³⁹ Submission from: Australian Association of Consultant Pharmacy (2012)

Metabolic medicine interactions

As shown in Figure 8.1, several liver enzymes are involved in the metabolism of warfarin. The most important enzyme is CYP2C9 because it is principally responsible for the metabolism of the more potent S-enantiomer. Medicines that inhibit these enzymes, particularly CYP2C9, can reduce the clearance of warfarin, resulting in an increased steady state concentration, which results in an increased anticoagulant response. Inducers of the enzymes can increase the clearance of warfarin and thus reduce the anticoagulant response. Interactions involving CYP3A4 and CYP1A2 may have a smaller impact because of their involvement in the metabolism of the less potent R-enantiomer. (Refer to Section 11.5 for a list of medicines that induce or inhibit CYP2C9, CYP3A4 and CYP1A2.)

Combination of warfarin and inhibitors of platelet aggregation

The combination of warfarin with antiplatelet agents has been shown to increase the bleeding risk. Antiplatelet medicines such as aspirin and clopidogrel are discussed in Chapter 7.

Another group of agents reported to influence platelet aggregation are the selective serotonin reuptake inhibitors (SSRIs) (Juurlink 2011, Schalekamp et al 2008). They have been reported to cause epistaxis, bruising, and gastrointestinal (GI) and vaginal bleeding due to the inhibition of serotonin in platelets. Increased bleeding with a combination of an SSRI and warfarin has been reported (Schalekamp et al 2008). The combination of an anticoagulant with an SSRI is likely to be relatively common, and the possibility of an interaction cannot be excluded. This may also apply to the NOACs as bleeding rates in the pivotal trials were higher in those patients receiving aspirin.

Combination of warfarin and nonsteroidal anti-inflammatory or analgesic medicines

Musculoskeletal disorders are common in the elderly. The Australian Government Department of Veterans' Affairs database indicates that almost 30% of AF patients on aspirin, clopidogrel or warfarin monotherapy were co-prescribed NSAIDs or COX-2 inhibitors (12%, 10% and 7%, respectively) (unpublished data, Veterans' Medicines Advice and Therapeutics Education Services, University of South Australia, Adelaide, 2012). All NSAIDs have been reported to cause bleeding, particularly in the GI tract.

In the pain management of osteoarthritis, the use of regular paracetamol is recommended as first-line therapy. An interaction resulting in an increase in INR has been reported between paracetamol at dosages of more than 2 g/day and warfarin. The mechanism is unknown, but various hypotheses involving the coagulation pathway have been proposed (Lopes et al 2011); however, the patient-specific factors for this interaction are not clear (Hughes et al 2011). The regular intake of paracetamol may be managed via INR measurement and warfarin dosage adjustment. Periodic intake or varying compliance with chronic paracetamol therapy may manifest as variable INR and the possibility of enhanced bleeding. Until the exact mechanism is known, the possibility of an interaction with the NOACs cannot be excluded, particularly if the interaction is via the coagulation pathway, as has been suggested.

8.7.2 Patient compliance and adherence

Warfarin has a long half-life (40 hours) and is administered once per day. As with other chronic medications, patient compliance can be a significant factor in achieving optimal outcomes.

Many factors can affect patient compliance. The CSANZ identified a range of such factors, including dose frequency, patient perception of treatment benefits, patient–clinician

communication, patient motivation, socioeconomic background, family and social support, and age.⁴⁰

It has been suggested that the requirement for regular INR monitoring, and the routine around this, may improve patient compliance with warfarin therapy (DoHA 2009). 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 mainly used in an elderly population 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 mg, 2 mg, and 5 mg, and Marevan[®] 1 mg, 3 mg 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 because they have not been shown to be bioequivalent (Stafford et al 2011a). 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. Warfarin is 100% bioavailable (Aspen Pharmacare Australia 2009) (this contrasts with dabigatran, which is only 6% bioavailable) and it is unlikely that the brands of warfarin tablets would not be bioequivalent, provided the dissolution rates are appropriate. The fact that the medicine has a narrow therapeutic index should 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 (Granger et al 2011). This presumably required broken 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.

It has been reported that, in some patients, dosage changes of 2% per week (e.g. from 28 mg to 28.5 mg per week, dosed as 4 mg per day for days 1–6 and 4.5 mg on day 7, compared to 4 mg daily) can significantly influence INR values (QML Pathology 2011). This reported sensitivity of INR to such small changes is remarkable because the change in a dose of this magnitude is likely to be no greater than the week-to-week variability that will arise through content variability in the tablets.

8.7.3 Warfarin and vitamin K intake

Since warfarin exerts its action via inhibition of VKORC1 (which is responsible for the recycling of vitamin K), a vitamin K deficiency at the site of action in the liver will decrease the production of activated carboxylated coagulation factors, and thus reduce their plasma concentrations (Holmes et al 2012). The degree of anticoagulation is a balance between vitamin K intake and VKORC1 inhibition.

Most (90%) of vitamin K is obtained from the diet, particularly from green leafy vegetables (Holmes et al 2012). Less than 10% is obtained from nondietary sources in the form of menaquinones, which are largely synthesised by colonic bacteria (Holmes et al 2012). Therefore, changes in diet are likely to have a greater impact on plasma or tissue 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 advice given to

⁴⁰ Submission from: Cardiac Society of Australia and New Zealand (2012).

patients is sometimes inconsistent with best practice, particularly in relation to the omission of vitamin K from the diets of patients on warfarin.⁴¹

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. This is particularly the case in patients with low vitamin K plasma/tissue levels. Patients with higher dietary vitamin K intake (and thus higher baseline plasma or tissue levels of vitamin K), have significantly more stable INR values than patients with lower intakes of vitamin K (Cushman et al 2001, de Assis et al 2009, Franco et al 2004, Khan et al 2004, Kim et al 2010, Lurie et al 2010, Rombouts et al 2010, Schurgers et al 2004, Sconce et al 2005). The tissue stores of vitamin K are limited and can readily be depleted (Holmes et al 2012). Some studies have achieved stable INRs through regular daily administration of low-dose vitamin K, which is thought to maintain relatively constant plasma or tissue levels (Ford et al 2007, Khan et al 2004, Sconce et al 2007).

8.7.4 Concurrent illness

Concurrent illnesses such as diarrhoea have been reported to result in a four-fold increase in the risk of having an INR of more than 6 (Hylek et al 1998). This has been suggested to be due to the malabsorption of vitamin K (i.e. the body may not absorb vitamin K optimally when a patient has diarrhoea). Because decreasing vitamin K levels can increase a patient's INR, a greater anticoagulation effect can be seen with the same dose of warfarin. However, high-quality evidence to support this hypothesis is lacking (Black 1994). An alternative explanation may be that dietary vitamin K intake changes during periods of illness such as diarrhoea, and thus the magnitude of the impact is influenced by baseline vitamin K levels. Notwithstanding the uncertainty of the reasons for the elevation in INR in these circumstances, it is a commonly reported phenomenon that requires further investigation.

8.8 Interpatient variability

A number of submissions raised the issue of significant interpatient variability in warfarin dosage requirements.⁴² Such differences 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.

Patients with severe renal impairment (i.e. a creatinine clearance [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 (Limdi et al 2009).

8.8.1 Pharmacogenomic testing

Up to 40% of the interpatient variability seen in warfarin-dose requirements is attributable to genetic differences between patients with respect to two particular enzymes (Sanderson et al 2005):

- *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 (Meckley et al 2008). It is estimated that this genetic variation, which results in a reduced clearance rate of warfarin, affects 2–14% of patients (Cavallari et al 2011).

⁴¹ Submission from: Flecknoe-Brown S (2012)

⁴² Submissions from: Krause, M; Colquhoun, D; Amerena, J; Rouhead, D (2012)

- *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 (Schwarz et al 2008).

A number of studies have found that a significant proportion (60%) of the interpatient variability in warfarin dosage requirements could be explained by a combination of age, weight and height, and *CYP2C9* and *VKORC1* genotype (Sconce et al 2005, Vecsler et al 2006). 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 (Anderson et al 2007, Caraco et al 2007, Epstein et al 2010, International Warfarin Pharmacogenetics et al 2009, Meckley et al 2008, Wadelius et al 2009). In August 2007, the United States Food and Drug Administration (FDA) approved a change in warfarin labels, which now state that ‘lower initiation doses should be considered in patients with certain genetic variations in *CYP2C9* and *VKORC1* enzymes’.

Pharmacogenomic testing for mutations in the *CYP2C9* and *VKORC1* genes could be used to improve health outcomes for patients by increasing the TTR and decreasing the time it takes to reach an INR of 2–3. This may be helpful during the initiation stages and in patients with a high bleeding risk.

9 Optimising warfarin therapy — costs and benefits

This chapter addresses the issue of underuse of warfarin therapy, barriers that are preventing the use of warfarin therapy and options for improving its use.

9.1 Underuse of anticoagulation therapy

Although warfarin has been shown to be highly effective in reducing stroke risk in patients with AF, it is still underused. A number of submissions raised the issue that undertreatment of AF patients is a ‘significant’ cause of preventable stroke.⁴³ 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 at participating audited hospitals (NSF 2011). 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 (Bajorek and Ren 2012).

This is supported by recent data from the United States that shows that almost 40% of medical visits about AF are for patients who are not prescribed an anticoagulant, and the percentage of visits in which neither an anticoagulant nor an antiplatelet medicine was reported was approximately 35%. These proportions have not changed since the introduction of dabigatran (Kirley et al 2012).

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 international guidelines (outlined in Section 6.4), are not being given anticoagulants, but are instead being treated with less effective antiplatelet therapy (e.g. 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 (Hart et al 2007).

It has been estimated that 10,700 strokes would occur due to AF in Australia in 2011, representing 23% of all strokes (DAE 2011). The direct cost of treating a stroke has been estimated to be around \$30,000 in the first year after diagnosis, and around \$50,000 over five years. Thus, the direct cost of strokes due to AF in Australia was estimated to be \$314.4 million in 2011, and \$562.7 million over five years. These data only included the direct costs of a patient’s ‘first-ever’ stroke due to AF that occurred in 2011, and the cost increases if further costs are included (e.g. lost productive output and heart failure).

It has also been estimated that, during the 2008–09 financial year, AF cost the Australian economy \$1.25 billion as a result of lost productive output, medical costs and the cost of the long-term care required for those with an AF-related disability (PWC 2010). This reflects a cost of \$5200 per year for every person with AF. Of these costs, 64% are due to stroke and heart failure, or premature mortality associated with AF.

⁴³ Submissions from: Stroke Society of Australasia; Paceline Inc.; Atrial Fibrillation Association; Krause M (2012)

9.2 Barriers to warfarin therapy

A range of factors contribute to the underuse of anticoagulation therapy, including the following barriers:

- The fear of increased bleeding risk, particularly intracranial haemorrhages (ICHs), although the risk of cardioembolic strokes is greater.
- The need for frequent monitoring and possible dosage adjustments due to the narrow therapeutic index of warfarin. People on warfarin may need INR testing once or twice per month, resulting in increased patient travel time and cost (Jowett et al 2008). Patients may need to be tested even more frequently when initiated on warfarin therapy; and this may be particularly difficult for people in remote or rural locations unless PoCT is used.
- Currently, the most commonly used process for warfarin monitoring in Australia is blood sampling by venipuncture, transfer of the sample to a pathology laboratory for INR analysis, then communication of the results to the referring GP or specialist. There can be a delay in taking any required actions, and this may be important to patient outcomes.
- Venipuncture, the most commonly used method for obtaining the blood sample for INR monitoring in Australia, may be difficult for people who have poor venous access.
- There may be issues of continuity of care when warfarin therapy is started while a person is in hospital and is discharged before warfarin therapy has been stabilised. Difficulties in this initiation period can have a significant effect on patients continuing chronic warfarin therapy.
- Many factors influence variability of warfarin-dose requirements, including medicine interactions, vitamin K status, renal function and concurrent illnesses. These may result in variable INR results, with resultant issues for patient management by both patients and prescribers.
- Interpatient variability, via mutations in the CYP2C9 and VKORC1 genes, can make warfarin therapy difficult to initiate.

Some submissions pointed to the results of a survey in which Australian GPs were asked about factors that they consider when deciding whether or not to prescribe warfarin.⁴⁴ The results are summarised in Table 9.1.

Table 9.1 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 followup	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 2008b

⁴⁴ Submissions from: National Stroke Foundation; Blombery PA (2012)

It is interesting to note that several of the barriers outlined in Table 9.1 may equally apply to all anticoagulants, regardless of whether regular monitoring is required.

Overall, the fear of an ICH is one of the largest barriers to a wider warfarin uptake. This fear, combined with the other difficulties, means that people may be reluctant or even unable to take warfarin. However, while there is an increase in risk of bleeding in patients receiving anticoagulants, this is generally outweighed by the benefit of anticoagulation treatment in reducing overall stroke incidence.

9.3 Options to improve warfarin therapy

Several models can be used to manage warfarin therapy in patients; these models are described in sections 9.3.1–9.3.3. Providing patients with a range of options and allowing them to select one that best fits their circumstances is likely to result in greater patient acceptance.

9.3.1 Programs to improve warfarin initiation

Programs to improve warfarin initiation focus on maintaining the continuity of care, especially in cases where the initiation occurs in hospital and the patient is discharged before being stabilised in the therapeutic INR range.

Hospital discharge programs

A pilot study, conducted in Hobart, compared a postdischarge program involving a home visit (which included point-of-care INR testing and education) by a pharmacist every two days over a period of eight days to a program where patients received usual care. At discharge, the percentage of patients who were in the therapeutic range were 45% and 42% of patients in the usual care and intervention arms respectively. On day 8, a greater percentage of patients in the pharmacist-intervention group had a therapeutic INR compared to those receiving usual care (67% versus 42%). Furthermore, 26% of usual care patients had a high INR, compared to only 4% of the pharmacist-intervention group. Bleeding events assessed at three months postdischarge occurred in 15% of the intervention group compared to 36% of the usual care group (Jackson et al 2004b).

A subsequent study using similar methodology was conducted for patients discharged from eight hospitals in three states across five metropolitan, rural and remote regions of Australia (Stafford et al 2011b). The study excluded patients with dementia, residents in aged-care facilities and non-English speakers. The patients recruited into the pharmacist intervention arm received either two home visits (the first visit on day 2 or 3, and the second on day 7 or 8 post discharge) (65% of the group), or three home visits (an additional visit between days 4 to 6) (35%) by a trained, home medicines review–accredited pharmacist, depending on the patients bleeding risk classification (using the Outpatient Bleeding Risk Index). Rates of combined minor and major haemorrhagic events were significantly reduced in the pharmacist intervention group compared to the usual care group after 8 days (0.9% versus 7.2%) and after 90 days (5.3% versus 14.7%). The combined haemorrhagic and thrombotic events after 90 days was also lower in the pharmacist intervention group (6.4% versus 19.0%), and persistence with warfarin therapy improved (95.4% versus 83.6%). No significant difference was observed in readmission or death rates between the two groups, although a reduction was noted in the warfarin-related readmissions in the pharmacist intervention group. Unlike the pilot program, no statistical difference in INR control was noted, although a trend suggested improved INR control.

Continuity of care

To optimise warfarin initiation and management, it is critically important to optimise the continuity of care between hospitals and the community. It is estimated that a large proportion 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 often becomes the responsibility of the patient's GP, who may not have received a comprehensive discharge summary prior to the patient presenting for evaluation. Further, it may not be possible for the patient to obtain an appointment with their GP in an appropriate timeframe. If the GP does not have PoCT, a critical delay in obtaining INR results can occur in this high-risk period.

9.3.2 Programs to improve warfarin maintenance

Point-of-care international normalised ratio testing

The ability to measure an INR at the time a patient is reviewed offers a potential advantage to both patients and health professionals. This system is used in some medical practices, anticoagulant clinics, domiciliary services and community pharmacist-led services, and has been trialled as part of home medicines reviews. Self-monitoring or self-management may also be an option for some patients using this type of testing.

Point-of-care management strategies use portable coagulometers. These are small, hand-held devices that use a finger prick instead of venipuncture to obtain a blood sample for INR testing. For these machines to be suitable for clinical decision making, they need to provide the same degree of accuracy and precision as the current standard of care (i.e. venipuncture, followed by pathology laboratory analysis).

Accuracy is a measure of how far a result is from the 'true value', and precision is the degree of reproducibility. It has been recommended that the accuracy should be no more than ± 0.2 INR within the therapeutic range of 2–3 (Christensen and Larsen 2012). The same authors reported that portable coagulometers generally tended to overestimate the INR at values greater than 4, and underestimate values within or below the therapeutic range. However, the precision and accuracy of the devices was considered to be acceptable for clinical use.

An Australian study found a greater consistency between portable coagulator results and laboratory values at INR values in the therapeutic range (Jackson et al 2004a). At INR values above 3.5, a greater difference between CoaguChek S and laboratory values was seen, with only 39% of results within $\pm 10\%$ of each other, compared to 58% of values in the range 2.0–3.5. Furthermore, the mean difference between the two values was -0.08 ± 0.34 in the range 2.0–3.5, but -0.27 ± 0.82 when the values were greater than 3.5.

The CoaguChek S machine, provided by Roche Diagnostics, was used for INR testing in the Australian Government Point of Care Testing in General Practice study (DoHA 2009). PoCT was found to be noninferior to pathology laboratory testing, with clinical agreement occurring 91% of the time against published expanded criteria (Yelland et al 2010). Overall, 86% of the dual INR measurements were within 0.5 INR units of each other. This percentage was higher for values below 3, but at values greater than 3 the agreement fell to 69%. A trial of a more recent device, the CoaguChek XS Plus, found that INRs greater than 4.5 and less than 8.0 were comparable to laboratory INRs when measured with this device (Lawrie et al 2012).

There are many settings where portable coagulometers could be used. As discussed in Section 3.2.4, advantages are the absence of a need for venipuncture, convenience (for patient and health care provider) especially in rural settings, and immediate INR result. Disadvantages are concerns regarding accuracy (although for clinical decision making this seems acceptable), and, potentially, an increase in the number of INR tests performed, as discussed in Section

8.4.1.⁴⁵ International experience suggests that PoCT programs can be successfully implemented to improve TTR, allowing TTRs of greater than 75% to be achieved (Wieloch et al 2011).

Point-of-care testing in general practice

A number of medical practices in Australia use PoCT in the management of patients receiving warfarin — up to 10–20% of INR results for patients with AF might be measured in this way. In most such practices, it is likely that the testing would be undertaken by the practice nurse. PoCT may be a more convenient option for patients, because the measurements can often be incorporated with usual medical visits. More importantly, it allows an immediate response regarding any dosage amendments and other advice to be provided at the time of INR measurement, and allows face-to-face interactions that will reinforce the quality use of medicine issues for warfarin therapy.

PoCT of INR is not reimbursed by Medicare as a specific MBS item number, but it is likely that a Level A or B consultation may be charged to evaluate an INR result.

The Point-of-Care Testing in General Practice Trial

A large PoCT project has been undertaken in Australia, comparing PoCT with conventional management, using the primary outcome of the proportion of patients within the therapeutic range at the end of the trial (DoHA 2009). The purpose of the study was to determine whether the Australian Government should implement PoCT in general practice. This project considered a number of conditions and associated measurements (e.g. HbA1c, total cholesterol and triglyceride, urine albumin, albumin–creatinine ratio, high-density lipoprotein [HDL] and INR). INR values were taken with a portable coagulometer. The intervention arm involved the test being taken on-site at the time of consultation, by or on behalf of the treating doctor, allowing the result to be used to make immediate decisions about patient treatment. Some clinical outcomes (e.g. hospitalisation rates) were measured in the trial, but because of the design of the trial with randomisation based on practices and not patients, these results may have been confounded and the resultant incremental cost-effectiveness ratio (ICER) is highly uncertain.

The study was conducted between September 2005 and February 2007 in 58 practices (26 randomised to the control group and 32 randomised to the intervention point-of-care group) over a range of urban, rural and remote settings. Of the 5234 patients recruited, 944 were receiving anticoagulant treatment. The testing was conducted by practice staff (only 5/80 were GPs), pathology providers or laboratories (DoHA 2009).

The study found that the median of the last INR test result was not different between the two groups, with both recording a median INR of 2.5 (DoHA 2009). Patient surveys from the Point of Care Testing in General Practice Trial indicated satisfaction with the PoCT program, and indicated that patients would be more motivated in better managing their condition as a result of regular PoCT (DoHA 2009).

Anticoagulant clinics

In a number of countries and regions, including Canada, Europe and the United States, specialised anticoagulant clinics manage anticoagulant services, including monitoring and dosage adjustment.

Several randomised controlled trials and cohort studies have been published comparing outcomes in anticoagulant clinics compared to usual care (Chiquette et al 1998, Lalonde et al 2008, Matchar et al 2002, Nichol et al 2008, Wilson et al 2003). These studies indicate that, while there may be an improvement in the mean TTR (3.6% in the RCTs and 10% in cohort studies), there is insufficient evidence to conclude that this improvement leads to better health

⁴⁵ Submission from: Boehringer Ingelheim (2012)

outcomes for patients with respect to thromboembolic strokes or major bleeding. However, patient satisfaction was greater with the anticoagulant clinics, particularly in regard to convenience and the improved education services (Bloomfield et al 2011b). In its evidence-based management of anticoagulant therapy Clinical Practice Guidelines, the American College of Chest Physicians state ‘we suggest that health care providers who manage anti-coagulation therapy should do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow up, and good patient communication of results and dosing decisions’ (Holbrook et al 2012). All these activities are more likely to be achieved in a service dedicated to anticoagulant management (e.g. anticoagulant clinic) and to a significant degree by pathology laboratories providing an anticoagulant management service. A protocol for the establishment of an optimised warfarin management service has been developed (Garcia et al 2008).

The Canadian Agency for Drugs and Technologies in Health (CADTH) published *Optimum Warfarin Management for the Prevention of Thromboembolic Events in Patients with Atrial Fibrillation: A Systematic Review of the Clinical Evidence* (CADTH 2011b). None of the studies included in the literature review were conducted in Australia, but it is likely that the results can be generalised so that they are applicable to the Australian health care system. The review found that specialised anticoagulant clinics result in a higher TTR compared to usual care, but ‘do not tend to result in significant differences in bleeding events, thromboembolism or mortality’. They also concluded that ‘based on a review of existing systematic reviews and additional primary studies, specialised anticoagulation services improve TTR compared to usual care. However depending on the study design, this improvement in TTR may not translate into a reduction in haemorrhage, thromboembolism, or in need for additional medical care’.

A number of other studies and reviews have reported an improvement in warfarin management (measured by TTR or patient-relevant outcomes such as bleeding rates) when patients are managed through specialised anticoagulant services or clinics compared to usual care (Baker et al 2009, Dolan et al 2008, Nichol et al 2008, Wilson et al 2003).

Warfarin management by pathology services

In addition to their regular role in INR measurement, some pathology services in Queensland and Victoria provide an anticoagulant program whereby the laboratory is generally responsible for the day-to-day warfarin management of the patients, including dosage adjustment and other relevant advice (e.g. regarding diet). It is estimated that over 80% of patients taking warfarin in these states are managed by pathology services. Patients are referred to the anticoagulant service by their medical practitioner, and may be required to pay an out-of-pocket fee to some services. The pathology services offering this program, including those that charge a management fee, indicated that they incurred a significant cost in providing the warfarin management program, but continued to do so as a service to clients of their pathology services.

The pathology service generally informs patients or their carers of the INR results by mail or telephone. If the patient’s INR and dose are stable, then results are usually mailed to them. However, if the INR result is out of range or if the patient is initiating warfarin therapy, then the results and any advice regarding any action required (e.g. urgent medical attention or dosage adjustment) are communicated via telephone. SMS messaging to mobile phones may also be available through some services. The INR results and any action are communicated to the referring doctor for their records.

The pathology services providing this program use local software systems, including warfarin dosing algorithms, generally developed in-house. The algorithms underpinning these systems are considered to be commercial-in-confidence, and it is not possible to determine whether the decision-support systems are consistent between laboratories or what quality assurance programs are being used.

The pathology services' lack of access to up-to-date, comprehensive patient details (including patient social history) is a potential issue. However, the laboratories that offer this program generally require patients to complete a form at each blood test to inform the service of any changes to their medical history, and these are viewed by medical staff if the patient's INR is out of range. In view of the importance of relevant patient information to the quality of decision making, it is essential that this component of the program be optimised. The role of personally controlled electronic health records for this purpose needs to be considered (see Section 9.5).

Interviews with 40 patients being managed by a large metropolitan pathology service in Melbourne, and with their treating doctors, revealed multiple issues (Lowthian et al 2009). In 75% of the patients, cognitive dysfunction, possible depression and medication nonadherence were revealed. Of the 36 doctors interviewed, 12 were unaware of these difficulties in their patients. Only 5 of the doctors considered that they had sole responsibility for their patients' anticoagulation, while 15 confirmed a mutual relationship with the pathology service, and 16 (almost 50%) deferred total responsibility to the pathology provider. Less than half of the doctors (14/36) reported providing patient education at warfarin therapy initiation, with the other 22 stating that this was the responsibility of the initiating specialist, pathology service or dispensing pharmacist. The authors stated that, where the specialist initiates therapy, that person may not be aware of social factors affecting the patient, and that this information may not be transferred to the pathology laboratory by the GP.

Another issue that has been raised with this option for management is that GPs may become reliant on these services, and lose specific skills in warfarin management.

Pharmacist-led anticoagulation services

A warfarin management system through accredited community pharmacies using PoCT and a shared-care model has recently been trialled in New Zealand using the web-based INR Online system.⁴⁶ The final report of the study demonstrated a significant increase in the TTR and a high degree of patient satisfaction (Shaw et al 2011). As discussed in Appendix 2, the success of this trial resulted in the inclusion of *Community Pharmacy Anticoagulation Management Services* as part of the New Zealand Community Pharmacy Services Agreement.

The trial involved 693 patients at 15 pharmacy sites. For the 154 patients for whom prestudy TTR values were calculated, there was an increase in TTR from 60.4% for standard care to 77.5% for the point-of-care service. The pharmacist received a standing order from the GP, and patients gave informed consent. Following a standard protocol, the INR was measured using a CoaguChek XS Plus device. Dose management was achieved using a web-based algorithm. If the INR result was in the range 1.5–4.0, the dose and date of the next test as recommended by the algorithm was accepted by the pharmacist, and the results and dosing information were sent electronically to the GP's patient-management system. INR results of less than 1.5 or greater than 4.0 were automatically referred to the GP for review. The pharmacist generated an email for the GP that included the latest INR result, recommended dose, date of next test and a graph showing recent INR results. If the INR was less than 1.5 or greater than 4.0 (but below 4.5) the pharmacist was able to accept the recommended dose and test date, but was required to inform the patient that the result was being sent to the GP for review. If the INR value was greater than 4.5 (but 5.0 or less) the patient was advised to miss the day's dose and return for a repeat test the following day. If the value was greater than 5.0, the pharmacist was required to discuss the result with the supervising GP. The percentage of INR test results greater than 5.0 was 0.9% in the intervention group compared to 1.4% in the standard care arm. This suggests that only in a relatively few cases is a discussion with the GP required before taking action. All pharmacy sites achieved a mean TTR in excess of 70% (range 71.4–84.1%).

⁴⁶ <http://www.inronline.net/>

PoCT (using a CoaguChek S device) was piloted by pharmacists in 16 Australian rural pharmacies, in a feasibility study to determine whether the rural pharmacist involvement of patients receiving warfarin improved patient care (Jackson et al 2005). The pharmacist took one sample (N = 120), then a pathology laboratory took another sample within four hours. The results showed significant correlation. An additional 398 pharmacy-based tests were conducted. Of these pharmacy-based tests, the study found that 8.5% of the INR measurements resulted in a dosage amendment. The authors concluded that monitoring was well received by pharmacists, GPs and patients. Difficulties in rural areas in relation to the lack of availability of funded INR point-of-care testing was identified as an issue in one submission.⁴⁷

An Australian hospital-in-the-home program, conducted by a clinical pharmacist-led anticoagulation service in partnership with GPs, used standard local management guidelines to manage warfarin. The study demonstrated that the difference in the mean time required to achieve two consecutive therapeutic INR values following warfarin initiation in hospital was reduced by three days in the pharmacist intervention arm (Dooley et al 2011).

A number of studies conducted overseas have also demonstrated the benefits from pharmacist-led anticoagulation services, for example, Saokaew et al (2012).

Several studies have examined the outcomes in nurse or pharmacist-managed clinics compared to usual care (Aziz et al 2011, Garton and Crosby 2011, Garwood et al 2008, Hall et al 2011, Rudd and Dier 2010). These studies all demonstrated an improvement in TTR and a reduction in hospitalisation rates. Overall, many studies have indicated that involvement of pharmacists in warfarin management can improve health outcomes. In a number of studies, bleeding rates were significantly decreased using pharmacist-based warfarin care (CADTH 2011b).

Home medicines reviews

A recent study reported on the impact of a GP–pharmacist collaborative home medication review in Australian war veterans (average age 81.5 years, and 6–7 comorbidities) on the rate of hospitalisation for bleeding (Roughead et al 2011). The study demonstrated a 79% reduction in likelihood of hospitalisation for bleeding between two and six months after the review compared to unexposed patients. The impact was not seen in the 6–12 month period after the review and six-monthly reviews were recommended for patients on warfarin at a high risk of bleeding. However, under the current arrangements for home medication reviews, only one review per year is allowed, except where there has been a significant change in the patient’s condition or medication regimen that necessitates a new review.

It has been stated that one of the barriers to the use of home medicines reviews to improve warfarin use is the low uptake of this program based on data to 2007–08.⁴⁸ It should be noted that uptake of medicines review programs has increased steadily since this time, for example the number of GP claims for Home Medicines Review (MBS item 900) has increased from 36,020 in 2007–08 to 77,932 in 2011–12.⁴⁹ The Australian Government Department of Health and Ageing is in the process of establishing a hospital-referred pathway for home medicines reviews.

Self-monitoring and self-management

Using PoCT, some patients are able to monitor their own INR (self-monitoring), while some patients are able to use these results to manage dosage adjustments based on a treatment algorithm (self-management). This is similar to the situation with people with insulin-dependent diabetes who monitor blood glucose levels and adjust insulin doses as appropriate. This type of self-management offers patients a more convenient method of INR monitoring.

⁴⁷ Submission from: Tideman P, St John A and Tirimacco R (2012)

⁴⁸ Submission from: Boehringer Ingelheim (2012)

⁴⁹ <http://www.medicareaustralia.gov.au/provider/medicare/mbs.jsp>

A Cochrane Review found 18 randomised trials that compared self-monitoring or management with standard monitoring (the review was not restricted to patients with AF, who may be older and have more comorbidities than other non-AF patients on warfarin) (Garcia-Alamino et al 2010). The review concluded that self-monitoring and self-management can improve patient outcomes by increasing the TTR, thereby reducing thromboembolic events by 50% and major haemorrhage by 13%. The authors stated that, overall, the reduction in thromboembolic events was probably due to the raised INR values (that is, fewer INR levels < 2). The review indicated that self-monitoring and self-management by suitable patients can improve the quality of anticoagulation therapy compared to standard monitoring. CADTH reports that ‘systematic reviews comparing self-testing or self-management with other models of anticoagulation care showed that self-testing or self-management resulted in lower mortality rates and lower incidence of thromboembolic events. However, no significant difference was shown in the rates of bleeding’ (CADTH 2011b). A meta-analysis found that patient self-testing or self-management with a point-of-care device reduced the risk of major thromboembolic events (odds ratio [OR] = 0.49, confidence interval [CI] = 0.30 to 0.79), was associated with fewer deaths (OR = 0.48, CI = 0.24 to 0.944) and resulted in better INR control than laboratory INR testing. No significant difference in major haemorrhages was observed (Wells et al 2007). These findings are consistent with the Cochrane Review (Garcia-Alamino et al 2010) and the CADTH review (CADTH 2011b). However, Fitzmaurice et al (2005) suggested that only 25% of patients are good candidates for self-testing and self-management. Furthermore, they noted that the frequency of testing and education on anticoagulant therapy was greater for patients who were involved in self-testing and self-management. A 2007 report found that self-management was more effective than poor-quality community-based care, and as effective as specialised services in maintaining the quality of anticoagulation (Cannock et al 2007). The report also found that self-monitoring resulted in fewer thromboembolic events.

A meta-analysis of randomised trials compared the patient outcomes from warfarin self-monitoring or self-management to outcomes in patients managed by a personal clinician, anticoagulation clinics or managed services (Heneghan et al 2012). Overall, there was a 49% risk reduction of thromboembolic events (HR = 0.51) in the self-management group, but no risk reduction for major haemorrhage or death. The benefit was mainly seen in younger patients (aged < 55 years) with mechanical heart valves. In the NVAf subgroup, the thromboembolic risk was reduced by 33% (HR = 0.67), but this was not statistically significant. The conclusions align with the recommendation that younger patients with mechanical heart valves should be offered self-management, but for other groups it should only be offered to patients unable to access routine care (Kyrle and Eichinger 2012).

A sample of 2922 patients receiving warfarin for mechanical valves and AF (77% with NVAf) who were competent in the use of PoCT (including competency evaluation) were randomly allocated to weekly at-home testing or monthly high-quality testing in a clinic (Matchar et al 2010). There was no difference in the time to a first stroke, major bleeding episode or death. However, the self-testing group had a small but significant increase in TTR (3.8%), as well as improvement in patient satisfaction and quality of life. The authors recommended that PoCT be limited to those patients with poor access to high-quality anticoagulation care if the alternative would be to withhold the use of warfarin.

In a randomised controlled trial, patients who participated in an education program associated with self-management had higher TTRs than patients who were managed by usual out-patient care (Sawicki 1999). The patients in the intervention arm also had higher quality-of-life measures.

One systematic review (of 22 randomised controlled trials that investigated patient self-testing alone or in combination with patient self-monitoring, compared to care delivered in specialised or nonspecialised clinics) found that patients in the self-testing and self-monitoring groups generally expressed greater treatment satisfaction and quality of life (Bloomfield et al 2011a).

Three studies in the review reported significantly higher self-efficacy and less distress, fewer daily difficulties and less strain on social networks.

Overall, these reviews and studies on self-monitoring and self-management show:

- a significant reduction in thromboembolic events
- no change in major bleeding rates
- an improvement in TTR by approximately 5% over standard care
- an improvement in the quality of life of patients
- a greater frequency of INR testing
- a benefit to those capable of self-management, particularly where access to high-quality anticoagulation services is limited.

However, the magnitude of benefit may be moderated by a selection bias for those patients deemed to be capable of self-monitoring or self-management — that is, it is likely that only those patients with reasonably stable INR will be selected to participate in these programs. These patients are likely to have a higher than average TTR, and thus to have less capacity for improvements in clinical outcomes by improving warfarin use.

Not all patients will be suitable for point-of-care testing (approximately 25% of patients may be suitable for self-management (Fitzmaurice et al 2005), and any program will require patient education and training, and a consideration of affordability and cost-effectiveness.

9.3.3 Cost of programs for INR monitoring

Cost components for INR testing

Current situation

The cost of INR monitoring can be divided into three components:

- collection of the blood sample
- analysis of the sample
- management of the patient where required.

Under the model wherein GPs manage warfarin patients by using a pathology laboratory for INR testing through the Medicare Benefits Schedule (MBS), Boehringer Ingelheim estimated that the overall cost to the Government per test would be \$22.52,⁵⁰ as outlined in Table 9.2 below.

Table 9.2 Costs for INR monitoring under MBS venipuncture model

Costs for INR monitoring under MBS venipuncture model	Estimated cost per INR test
Collection of the blood sample	\$6
Analysis of the sample	\$13.80
Management of the patient	\$2.72 ^a
Total	\$22.52

INR = international normalised ratio; MBS = Medicare Benefits Schedule

^a Boehringer Ingelheim estimated that warfarinised patients with AF require a short GP consultation every six tests and the consultation is charged as an Item 3 at \$16.30 per INR test (MBS Item 3 — Level A consultation). This results in a \$2.72 cost to the Government per test.

Source: Boehringer Ingelheim submission to Review (2012)

⁵⁰ Submission from Boehringer Ingelheim (2012)

INR monitoring approaches to improve warfarin management

As outlined above, there are a range of different ways in which INR monitoring could be provided, including via: PoCT in GP surgeries, in pharmacies or in residential aged care facilities; pathology service warfarin management programs; and patient self-management and self-monitoring. These models will have varying cost impacts on each of the three components of INR testing, as each model will involve different components of service. The same outcomes could be achieved at the same total cost through establishing cost-neutral fee structures against the MBS claimable fees for INR testing.

For example, under PoCT in general practice, the costs could be estimated to remain at \$22.52 as outlined in Table 9.3. This is because no venipuncture is needed; analysis of the sample would be simplified but more resource intensive management of the patient would be required. Note that this table outlines one potential scenario only.

In addition, INR testing via PoCT would need to be underpinned by a training and competency framework for the health professionals performing the test, and rigorous quality assurance of the device. Such a framework would need to be agreed by appropriate bodies such as the National Pathology Accreditation Advisory Council and the Royal Australian College of General Practitioners.

Table 9.3 Example estimate of cost to government for INR monitoring by PoCT in general practice

A potential estimate of INR monitoring by PoCT in General Practice	Estimated cost per INR test (indicative only)	Notes
Collection of the blood sample	Not Applicable	Sample is finger-prick rather than venipuncture
Analysis of the sample	\$8.80 for capital and consumable costs associated with PoCT (i.e. one testing strip plus amortised cost of PoCT device)	Test could be conducted by Practice Nurse, under Practice Nurse Incentive Payment Program
Management of the patient	\$13.72	Potentially, a greater level of GP involvement may be required under this model as the analysis is being conducted outside an accredited laboratory.
Total	\$22.52	

INR = international normalised ratio; PoCT = point-of-care testing

Another example is pathology service warfarin management programs, and in the model the costs could be estimated to remain at \$22.52 as outlined in Table 9.4. Note that this table outlines one scenario only.

Table 9.4 Example estimate of cost to government for INR monitoring by 'Pathology laboratory warfarin management' under a new model

A potential estimate of INR monitoring by PoCT 'Pathology laboratory warfarin management'	Estimated cost per INR test (indicative only)
Collection of the blood sample	\$6
Analysis of the sample	\$13.80
Management of the patient	\$2.72 ^a
Total	\$22.52

INR = international normalised ratio; PoCT = point-of-care testing

^a While this is represented on a per test basis in this example, a 'patient warfarin-management fee', or an incentive payment linked to the proportion of patients within a certain INR range, rather than an additional MBS fee per test could be developed.

The above tables demonstrate that a range of different scenarios for INR monitoring to improve warfarin maintenance could be implemented within a cost neutral framework. Notwithstanding the above, studies have indicated that particular models of INR monitoring are associated with an increase in the number of INR tests performed. For example, if GP PoCT were to result in a 10% increase in the number of tests performed, and 50% of all MBS items 65120 to 65129 (the MBS items that include INR monitoring, although it is believed that the majority of this is related to INR testing) were to be conducted by PoCT, the cost to the Government could be around \$5.5 million per year (based on an extra 240,000 tests being performed at \$22.52 per test). However, note that this increase in the frequency of testing may potentially lead to improved health outcomes with warfarin therapy.

Medicines reviews

Medicines reviews could form part of a patient's anticoagulant initiation program. Patients on chronic oral anticoagulation therapy would also benefit from having a medicine review every six months, particularly for patients at a high risk of bleeding (Roughead et al 2011).

Under the Fifth Community Pharmacy Agreement, four medicine review programs are funded, and these are outlined in Table 9.5. It is noted that some changes to current rules for some of the programs would be required to facilitate routine six-monthly medicine reviews for patients on oral anticoagulants for chronic conditions. Further, anticoagulation management could be developed as an area of advanced pharmacy practice, with certified anticoagulation care pharmacists being able to provide specific anticoagulation medicines reviews.

Table 9.5 Outline of medicines review programs

Program	Domiciliary Medication Management Reviews	Residential Medication Management Reviews	Medicines Use Review (MedsCheck)	Diabetes Medication Management (Diabetes MedsCheck)
Payment	Pharmacist — \$200.92 GP under MBS — \$148.90	Pharmacist — \$101.60 GP under MBS — \$101.95	Pharmacist — \$60	Pharmacist — \$90
Initiation	GP	GP (generally)	Consumer/pharmacist	Consumer/pharmacist
Location	Patients home (generally)	Aged care facility	In-pharmacy	In-pharmacy
Eligibility criteria (in addition to Medicare eligibility requirements etc)	Patients for whom a review is clinically necessary to ensure the quality use of medicines or to address a patient's needs. Examples of risk factors include patients taking a medicine with a narrow therapeutic index or that requires therapeutic monitoring, or those currently taking five or more regular medicines	Permanent resident of an Australian Government funded aged care facility	Community-based patients. To be eligible for the service a patient must be taking five or more prescription medicines, or have had a recent significant medical event	Community-based patients: • with recently diagnosed type 2 diabetes (in the last 12 months); <i>or</i> • with less than ideally controlled type 2 diabetes; <i>and</i> • unable to gain timely access to existing diabetes education /health services in their community
Limits to service provision	Once in each 12 month period, except where there has been a significant change in the patient's condition or medication regimen requiring a new review	Once in each 12 month period, except where there has been a significant change in the patient's condition or medication regimen requiring a new review	Patients who have not received a MedsCheck, Diabetes MedsCheck, Home Medicines Review or Residential Medication Management Review in the preceding 12 months	Patients who: • have not received a MedsCheck, Diabetes MedsCheck, • have not received a Home Medicines Review <i>or</i> Residential Medication Management Review in the preceding 12 months
Pharmacist qualifications	Accredited pharmacist	Accredited pharmacist	Registered pharmacist	Registered pharmacist
Process	Pharmacist conducts the review and prepares a report which is discussed with the patients GP and community pharmacist. A medication management plan is then agreed between the patient and their GP		Pharmacists educate patients about their medicines, identify any problems they may be experiencing with their medicines; and help patients improve the effective use of their medicines.	Focus on type 2 diabetes medicines management, monitoring devices, education and self-management.
Number of services provided	~78,000 in 2011–12 (Based on associated MBS item)	~65,000 in 2011–12 (Based on associated MBS item)	Data unavailable (program commenced on 1 July 2012)	Data unavailable (program commenced on 1 July 2012)

GP = general practitioner; MBS = Medicare Benefits Schedule

It is estimated that around 52,000 concessional patients commenced warfarin therapy in 2011–12 (unpublished PBS data). The proportion of these patients on warfarin for long-term conditions (as opposed to prevention and treatment of venous thromboembolism) is likely to be around 70–75% (Access Economics Pty Ltd 2008), or approximately 38,000 concessional patients — noting that availability of NOACs for AF may further increase the number of patients on oral anticoagulation who would benefit from a six-monthly medicines review. It is noted that patients on oral anticoagulants are likely to already be high users of medicine review programs.

If an additional 50,000 medicine review services were required, the additional cost to government would be around \$11 million per annum. This assumes a mix of additional Domiciliary Medication Management Reviews, Residential Medication Management Reviews and MedsCheck services, depending on the appropriate service for a particular patient's circumstances.

9.3.4 Cost-effectiveness and management options

The Point of Care Testing in General Practice Trial (DoHA 2009) estimated that point-of-care INR testing was associated with significantly higher costs per patient for GP consultations and pharmaceuticals, and that the point estimates of the ICER for PoCT were dominated by its comparator (i.e. standard care). However, this estimation is highly uncertain and a full cost-effectiveness analysis would need to be undertaken. For example, the following limitations were identified by Laurence et al (2010):

- the costs associated with introducing PoCT within a quality framework were high and involved accreditation, a quality assurance program and training. Laurence et al (2010) state 'while a quality framework is essential for the introduction of PoCT in General Practice, it may be possible to achieve the same quality outcomes at a reduced cost by adding these to existing organisations or programs or by using alternatives such as online training.' Such facilities have since been developed such as those available through the Australian Government-funded Australian Point of Care Practitioner's Network.
- the establishment costs included the cost of the device, training, and quality assurance and this element of the cost per patient would decrease if patient volume increases (noting that there was an average of 21 patients per general practice enrolled in the PoCT intervention arm of the trial).
- the trial used the proportion of patients whose last INR in the study was within the therapeutic range as the primary outcome. This indicator is specific to this trial and not generalisable, unlike TTR, life-years gained or QALYs, thus making the interpretation of the acceptability of the trade-offs difficult.

The Point of Care Testing in General Practice Trial proceeded a 2005 Medical Services Advisory Committee conclusion that, overall, there was no significant difference in diagnostic performance between PoCT and standard laboratory-based testing; but that there was insufficient evidence to support the use of INR PoCT in general practice at that stage (MSAC 2005).

A CADTH review of cost-effectiveness studies examined three costing studies of hospital-based specialised anticoagulation clinics and one cost-utility study of patient self-management (CADTH 2011a). The CADTH report considered that the costing studies were limited, and concluded that 'the costs of specialized anticoagulation services in Canada are uncertain' (CADTH 2011a). The cost-utility study examined the cost-effectiveness of patient self-management compared to community-clinician managed care in Canada using a Markov model with the probability of transiting between five health states (i.e. no events, minor and major haemorrhagic event, major thromboembolic event or death) determined by the time spent in the therapeutic INR range (Regier et al 2006). With a 5-year time frame as the base case, an ICER

of C\$14,129 per quality-adjusted life-year (QALY) was calculated; with a 10-year time frame, this dropped to C\$2995 per QALY. The report notes that the analysis was based on a single randomised controlled trial (mixed population) and the correlation between the TTR and thromboembolic events was extrapolated from a single cohort study. Taken together with other factors, this means that generalising these results to the larger population of patients receiving anticoagulants may not be reasonable (CADTH 2011a).

An economic analysis undertaken by the Ontario Medical Advisory Secretariat (Canada) in 2009 found that point-of-care strategies are cost effective compared to traditional laboratory testing, with patient self-management being the most cost effective.

A cost-effectiveness analysis of an anticoagulation management service in the United States compared to usual care in patients with AF demonstrated that the service appears to cost less and provide greater effectiveness than usual care (Sullivan et al 2006).

Overall, there seem to be conflicting statements about the cost effectiveness of self-management and specialised anticoagulation management services between various reports.

9.4 Pharmacogenomic testing

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 (Sconce et al 2005, Vecsler et al 2006). 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 (Anderson et al 2007, Caraco et al 2007, Epstein et al 2010, International Warfarin Pharmacogenetics et al 2009, Meckley et al 2008, Wadelius et al 2009).

Knowing the pharmacogenomic status of a patient may be useful at the initiation stage of therapy, since adverse outcomes are more likely for the patient at this initiation phase. If the treating physicians do not know a patient's pharmacogenomic status, they may take a more conservative dose titration, but this could lead to delays in achieving a therapeutic INR, and may lead to some patients being put at risk of thrombus formation and subsequent stroke. Furthermore, the increased time to stable INR may be a particular issue when warfarin is started in hospital and discharge is likely to occur before the dosage is stabilised. Thus, there may be subgroups of patients (e.g. those with a combination of high CHADS₂ and HAS-BLED scores, and/or at a high risk of bleeding with a HAS-BLED score ≥ 4) for whom pharmacogenomic testing may be of benefit in the initiation phase of warfarin therapy. However, caution in the initiation phases of warfarin therapy, particularly for patients with high HAS-BLED scores, may have a similar benefit.

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 (Epstein et al 2010). However, the cost-effectiveness of such an approach may depend on a range of variables and has not consistently been shown to be favourable in overseas trials (Eckman et al 2009, Meckley et al 2010).

In August 2007, FDA approved a change on warfarin labels, which now state that 'lower initiation doses should be considered in patients with certain genetic variations in CYP2C9 and VKORC1 enzymes'.

Since the maintenance dose of warfarin at steady state is best managed by regular INR testing, the most likely impact of pharmacogenomic testing for variations in the CYP2C9 and VKORC1 enzymes is on the selection of a starting dose, and during the initiation period (when over-anticoagulation may occur because of an inappropriate dose due to genetic polymorphism). Patients with CYP2C9 variants, compared to those without, achieved stable INR value later, spent a higher proportion of time above the therapeutic range during the first month of therapy and had a higher risk of an INR greater than 5.0 (OR = 4.15, $P = 0.03$) (Meckley et al 2008). During the initiation of therapy, homozygosity for CYP2C9 and VKORC1 variant alleles increased the risk of over-anticoagulation, with HRs of 21.8 and 4.6 for each variant, respectively (Wadelius et al 2009). During the first month of therapy, 12.5% of patients with CYP2C9*3/*3 experienced severe bleeding compared to 0.3% of other patients.

9.4.1 Cost effectiveness of pharmacogenomic testing

The marginal cost-effectiveness of pharmacogenomic-based dosing of warfarin has been estimated to be more than US\$170,000 per QALY (Eckman et al 2009). It has been suggested that if screening occurred only in those patients with a high haemorrhagic risk (e.g. HAS-BLED ≥ 3), the ICER may become acceptable (Eckman et al 2009). Genotyping before warfarin initiation was considered to be cost-effective by the authors (ICER < \$50,000 per QALY) only if it reduced the out-of-range INR values by more than 5–9% compared to usual care (anticoagulant clinics) (Patrick et al 2009).

Tests for two common genetic variants in the CYP2C9 gene (CYP2C9*2 and CYP2C9*3) and variants in the VKORC1 gene are available in Australia. However, it must be noted that in order for the pharmacogenetic testing to be clinically useful it must be available in a timely manner (Eckman et al 2009).

9.5 Personally Controlled Electronic Health Records

The quality of some anticoagulant services is limited by the ability (or inability) of health care professionals involved in INR monitoring and anticoagulant patient management to access a current health record with information regarding comorbidities, current medication and INR history. At the time of enrolment into any warfarin management service, the referring practitioner may provide a documented medical and social history. This needs to be maintained regularly because it is likely to change frequently, especially in the predominantly elderly population with AF. Social factors may also be critical to the capability of the patient or carer to undertake dietary or dosage changes. It is important that there is a process for updating the relevant information on a regular basis. Patients should be strongly encouraged and facilitated to have a Personally Controlled Electronic Health Record, which should be accessible to the relevant health professionals caring for the patient.

10 Guidelines and education strategies

This chapter describes existing international guidelines for the management of AF and puts forward a case for an endorsed and comprehensive Australian guideline.

10.1 Clinical practice guidelines for the management of atrial fibrillation

10.1.1 Established international guidelines

In recent years, a number of international guidelines on the management of AF have been published that include detailed discussions on the management of anticoagulation therapy. Examples include guidelines developed by the American College of Cardiology Foundation, the American Heart Association and the Heart Rhythm Society (Writing Group Members et al 2011); the Canadian Cardiovascular Society (Skanes et al 2012); the European Society of Cardiology (Coordinating Committee et al 2012); the National Institute for Health and Clinical Excellence (National Collaborating Centre for Chronic Conditions 2006); the Japanese Circulation Society (Japanese Circulation Society 2010) and the American College of Chest Physicians (Guyatt et al 2012). None of these international guidelines explicitly takes into account the cost or cost-effectiveness of management options, nor do they discuss management in patients with multiple conditions. In addition, these guidelines reflect the particular regulatory, reimbursement and clinical practices of the region for which they were developed.

Section 6.4 discussed the recommendations of the four major international guidelines for patients at different risks of stroke.

10.1.2 The need for Australian guidelines

Throughout the Review process, stakeholders consistently raised the issue of the lack of contemporary, comprehensive Australian guidelines for the management of AF.⁵¹ Resources that are currently available in Australia include a position statement on AF from 2001 (Hankey 2001), 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 (Cardiovascular Expert Group 2012). In addition, 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.

In its feedback on the Issues and Options Paper, the National Stroke Foundation (NSF) stated:

Guidelines should be part of a systematic, comprehensive and multifaceted program (i.e. developing guidelines, setting standards and targets, ongoing monitoring and quality improvement activities across multiple levels) to increase overall and safe use of anticoagulation therapies (both old and new). This would importantly involve patients in all aspects of development and delivery and a clear focus on patient-centred care. This work may draw on international guidelines, though an Australian version that is developed to Australian standards and relevant to local populations and contexts is required.

Guidelines should be developed with consideration of, and funding for, their implementation. Although it is a challenge to change clinical practice, strategies for implementation should follow the evolving evidence base and be underpinned by current evidence. Importantly, strategies should aim to impact multiple levels (individual clinicians, consumers, organisations and regulatory agencies). This may include consideration of barriers, and exploration of models of care, health professional support (including comprehensive package

⁵¹ Submissions to Review from National Stroke Foundation and Society of Hospital Pharmacists of Australia

of effective education provision, tools and resources for clinical use, reminder systems etc), patient education, clinical decision-support tools and data collection (audit and feedback).⁵²

10.1.3 Required scope for an Australian guideline

Guidelines need to be dynamic documents, with regular review and update. They should be comprehensive, and incorporate nationally agreed standard pathways covering aspects such as:⁵³

- awareness of the clinical impact and detection of AF
- initiation of anticoagulation therapy, both in hospital and in the community including:
 - clinical decision-support tools to standardise the decision-making process, including appropriate risk stratification (e.g. stroke risk from AF versus bleeding risk from anticoagulation)
 - a warfarin initiation algorithm (as part of a broader warfarin management algorithm) including addressing additional therapies to cover stroke risk in those patients with a very high risk during the therapy initiation phase
 - addressing the barriers to use, such as risk of falls⁵⁴
 - outlining the situations in which a consultation with a cardiologist, or other specialist, is required, and the role of emergency physicians and specialist cardiologists in initiation and followup
- anticoagulant dosage considerations including:
 - a nationally endorsed warfarin dosing algorithm, which could include advice with regard to the frequency of INR monitoring, and appropriate dosage adjustments or other management options
 - a nationally endorsed dosing algorithm for all anticoagulants, incorporating, for example, appropriate calculation of a patient's glomerular filtration rate
- monitoring of anticoagulant response
- consideration of concomitant medicines and comorbid conditions, including development of a resource listing alternative therapies to medicines shown to interact with warfarin or anticoagulants, and include this resource within prescribing or dispensing software and other systems
- management of abnormal bleeding, taking into account different hospital settings and resources available to mitigate or reverse this adverse effect
- clinical decision making in patients who are on NOAC therapies and may benefit from thrombolysis (e.g. ST segment elevation MI, life-threatening pulmonary embolus or ischaemic stroke)
- potentially incorporating roles for allied health professionals; for example, in identifying patients suitable for anticoagulation therapy, or supporting emergency physicians in initiating anticoagulation therapies.

10.1.4 Guidelines for managing warfarin monitoring and dosing

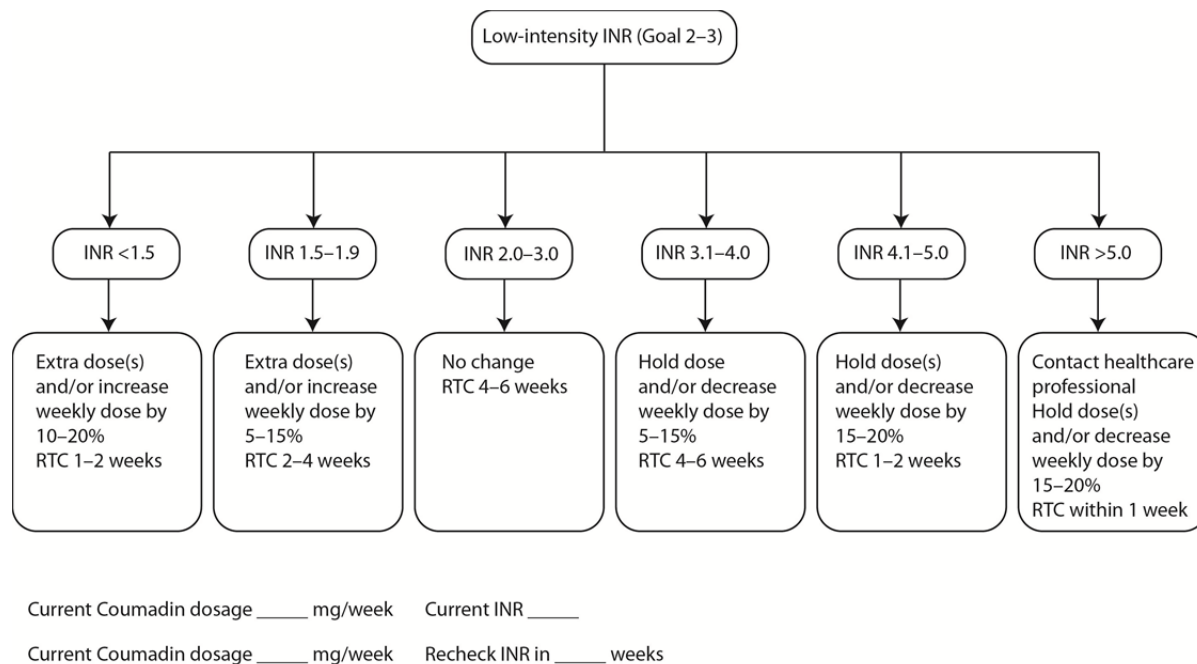
A number of management algorithms (both paper-based and computer software-based) are available to assist in the management of anticoagulation (e.g. see Figure 10.1). Nevertheless, there is a need for a nationally endorsed algorithm that could be used by all health professionals

⁵² Comments on Issues and Options Paper from National Stroke Foundation

⁵³ Comments on Issues and Options Paper from: Australasian College of Emergency Medicine; Paceline Inc. (2012)

⁵⁴ Comments on Issues and Options Paper from R. Gellatly (2012)

and support agencies to assist the development of a wider range of warfarin management services. The aim would be to improve health outcomes and remove some of the inconvenience of regular INR monitoring. The algorithm would also allow decision tools currently being used to be evaluated, assessed and endorsed, as appropriate.



INR = international normalised ratio; RTC = return to check (i.e. next test)
 Source: Adapted from Franke et al 2008

Figure 10.1 Sample warfarin-management algorithm

In addition, national accreditation of warfarin management programs should be required, including standards for the collection of patient-relevant information, reporting of results, management of patients and the reporting of outcomes (including TTR).

It is noted that a number of computer-based software packages for warfarin management are commercially available (e.g. Dawn Clinical Software⁵⁵ and INR Online⁵⁶).

10.2 Integrating patient preferences

The decision to commence anticoagulation therapy is a trade-off between decreased risk of stroke and increased risk of bleeding and burden of treatment. It appears that many patients consider warfarin monitoring to be inconvenient and, as such, their interest in warfarin treatment, as well as their compliance once on treatment, can be poor.

A meta-analysis of patient values and preferences in decision-making for antithrombotic therapy found higher disutility of stroke than with GI bleed. One study found that 20% of patients were willing to accept over 35 additional GI bleeds on warfarin for a 3% absolute risk reduction of stroke. However, on balance, the authors of the meta-analysis found that ‘a reasonable trade-off to assume between stroke and bleeds would be a ratio of disutility of net nonfatal stroke to GI bleeds in the range of 2:1 to 3:1’ (MacLean et al 2012).

⁵⁵ <http://www.4s-dawn.com/dawnac/>

⁵⁶ <http://www.inronline.net/>

Further, (MacLean et al 2012) found that there is a much greater disutility of stroke than of treatment burden. However, many patients place a higher value on avoiding an adverse event that occurs as a consequence of treatment than on avoiding an event (with the same functional consequences) that occurs as a consequence of not using that treatment.

MacLean et al also found that values and preferences for antithrombotic therapy appear to vary appreciably among individuals. For most patients, warfarin does not have important negative effects on quality of life, although many patients worry about the adverse effects associated with warfarin therapy, and patient aversion to warfarin therapy may decrease over time as treatment continues.

10.3 Education strategies

Another issue that was consistently raised by stakeholders was the need for an education strategy for health professionals and patients, to improve understanding and acceptance of anticoagulation therapy. Such a strategy would need to be developed as part of a comprehensive strategy to drive behavioural change.

10.3.1 Consumer education

Consumer education could improve adherence to warfarin (e.g. through providing information about risks and benefits of anticoagulation, and providing accurate information about diet and concomitant medication), and help consumers to make informed choices and play an active role as partners in their health care.⁵⁷ An education program could include provision of standardised information and education to every new patient starting warfarin therapy, and to those already taking warfarin who may not have received sufficient information. A range of patient education materials are currently available (e.g. *Warfarin: Important Information for Patients* booklet produced by Aspen Pharmacare and locally developed resources such as *Living with Warfarin: Information for Patients* produced by the Western Australian Medication Safety Group Anticoagulant Working Group), and these could be consolidated into a single definitive guide.⁵⁸

10.3.2 Prescriber education

Education tools for prescribers should provide guidance on how to:

- improve the diagnosis rate of AF
- identify patients who are at risk of stroke and systemic embolism
- categorise the risk level for stroke and systemic embolism
- categorise the risk level for the potential adverse events of therapeutic intervention, including ensuring that risk factors known to increase the incidence of haemorrhage are addressed as part of a patient's total management
- establish where the balance between the risks and benefits of each possible therapeutic intervention lies for the individual patient, consider the options and select the most appropriate treatment (i.e. providing the right intervention for the right patient)
- most effectively counsel patients.

The tools should also include comprehensive but clear information about potential interactions between anticoagulants and food, medicines and disease states.

⁵⁷ Comments on Issues and Options Paper from: Australasian College of Emergency Medicine; Consumer Health Forum (2012)

⁵⁸ Comments on Issues and Options Paper from: Pharmacy Guild of Australia (2012)

Comprehensive, multifactorial education programs can successfully change the behaviour of clinicians and consumers. For example, this was demonstrated by the results of an education campaign run by Medimark International (a medical education company that was funded to provide an AF educational program by Boehringer Ingelheim, although the funder was not involved in any aspect of the program) titled the Stroke Prevention Results in Atrial Fibrillation Therapy (SPRINT) program. SPRINT was a 5-step education program implemented in the first half of 2011, with participation from almost 1400 GPs.⁵⁹ The confidence of GPs was self-assessed before and after they participated in the program, and the results were recorded on a scale of 1–5 (with 5 being the highest). Results were as follows:

- 16% of GPs ranked their confidence in managing antithrombotic therapy as 5 at the beginning of the program, compared to 46% on completion of the program.
- 7% of GPs ranked their confidence in using CHADS₂ to assess stroke risk as 5 at the beginning of the program, compared to 49% on completion (in addition, the percentage that ranked their confidence as 4 in this area increased from 24% to 45%).
- 3% of GPs ranked their confidence in using HAS-BLED to assess bleeding risk as 5 at the beginning of the program, compared to 34% on completion (in addition, the percentage that ranked their confidence as 4 in this area increased from 11% to 53%).⁶⁰

10.3.3 Integration into practice

Guidelines and education strategies must balance the need to comprehensively cover complex issues and the need for usability in clinical practice.

There are innovative ways through which user-friendly guidelines could be integrated into clinical practice, and education tools into patient-friendly usable resources such as decision-support systems (e.g. medical prescribing software), and mobile phone and tablet technologies (e.g. apps).

⁵⁹ Comments on Issues and Options Paper from: Medimark International (2012)

⁶⁰ Comments on Issues and Options Paper from: Medimark International (2012)

11 The future of new oral anticoagulants in Australia

This chapter considers the registration status of NOACs in Australia and overseas, their mechanism of action, pharmacology and pharmacokinetics and their interactions with other medicines.

As discussed in previous chapters, a number of NOACs for the reduction of stroke risk in patients with AF have been developed and trialled during recent years. These agents appear to be at least as effective as warfarin in reducing stroke risk, and their sponsors state that they do not require monitoring for anticoagulant response and are involved with fewer interactions with other medicines.

A consistent finding in all the pivotal studies of the NOACs was the reduction in the incidence of ICH compared to patients on warfarin (Granger et al 2011, Patel et al 2011, Connolly et al 2010). A number of submissions identified this as an important, clinically relevant difference between warfarin and the newer agents.⁶¹

11.1 Status in Australia

Dabigatran and rivaroxaban are registered with the Therapeutic Goods Administration (TGA) for the prevention of stroke and systemic embolism in patients with NVAF and at least one other risk factor for stroke.

Dabigatran and rivaroxaban are not Pharmaceutical Benefits Scheme (PBS)-listed for stroke prevention; they are currently subsidised for the prevention of venous thromboembolism in patients undergoing total knee or hip replacement. However, since they are TGA-registered for the AF indication, patients have access to them if they pay the nonsubsidised price. Also, the sponsor companies have given the medicines free of charge to some patients under their product familiarisation programs. Currently there are around 25,000 patients receiving dabigatran through this mechanism. The rivaroxaban program recently commenced.

In March 2011, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended that dabigatran should be considered for inclusion on the PBS for the prevention of stroke and systemic embolism in people with AF and at least one additional risk factor for stroke. In making its 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 was 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

⁶¹ Submissions from: Cardiac Society of Australia and New Zealand; National Stroke Foundation; Paceline Inc.; Royal Australasian College of Physicians; Blombery PA (2012)

oral anticoagulation — could be treated with dabigatran, which would be likely to lead to additional benefits and costs not measured in the trial

- people at low risk of stroke and currently managed on aspirin or no treatment may be unnecessarily transferred to dabigatran.

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.⁶²

Rivaroxaban was registered by the TGA for stroke prevention in AF patients on 13 April 2012. PBAC considered a submission for rivaroxaban for this indication at its March 2012 meeting. PBAC rejected the submission because of the uncertainty around the clinical evidence to support the clinical claim and the resultant uncertainty in the economic analysis.⁶³

Apixaban is not registered in Australia for stroke prevention, but the sponsor has applied for parallel TGA–PBS registration and listing.

11.2 International status

Like the TGA, the European Medicines Agency (EMA) has approved dabigatran for stroke prevention in AF patients at two dosages — 110 mg and 150 mg twice daily.⁶⁴ The FDA has approved the 150 mg twice daily and 75 mg twice daily regimens for the AF indication.⁶⁵ It did not approve the 110 mg strength because of its inability to identify any subgroup in which this dose would not represent a substantial disadvantage compared to the 150 mg strength (Beasley et al 2011).

The FDA and EMA have both approved rivaroxaban 15 mg and 20 mg per day for prevention of stroke and embolism in AF patients.^{66,67}

Regulatory agencies are considering applications for apixaban for stroke prevention in AF patients, and it received a positive review for this indication from the EMA's Committee for Medicinal Products for Human Use on 21 September 2012.⁶⁸

The NOACs discussed in this report — dabigatran, rivaroxaban and apixaban — are the first NOACs to be approved, or considered for approval, globally. Other NOACs are in development internationally (e.g. edoxaban), and major clinical trials of these are ongoing.

11.3 Mechanism of action

The new agents act on the clotting cascade at different points to warfarin, as shown in Figure 11.1. Dabigatran is a direct thrombin inhibitor (Hankey and Eikelboom 2011); whereas rivaroxaban and apixaban are direct factor Xa inhibitors.

⁶² <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-dabigatran-march11>

⁶³ <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2012-03/1st-time-decisions>.

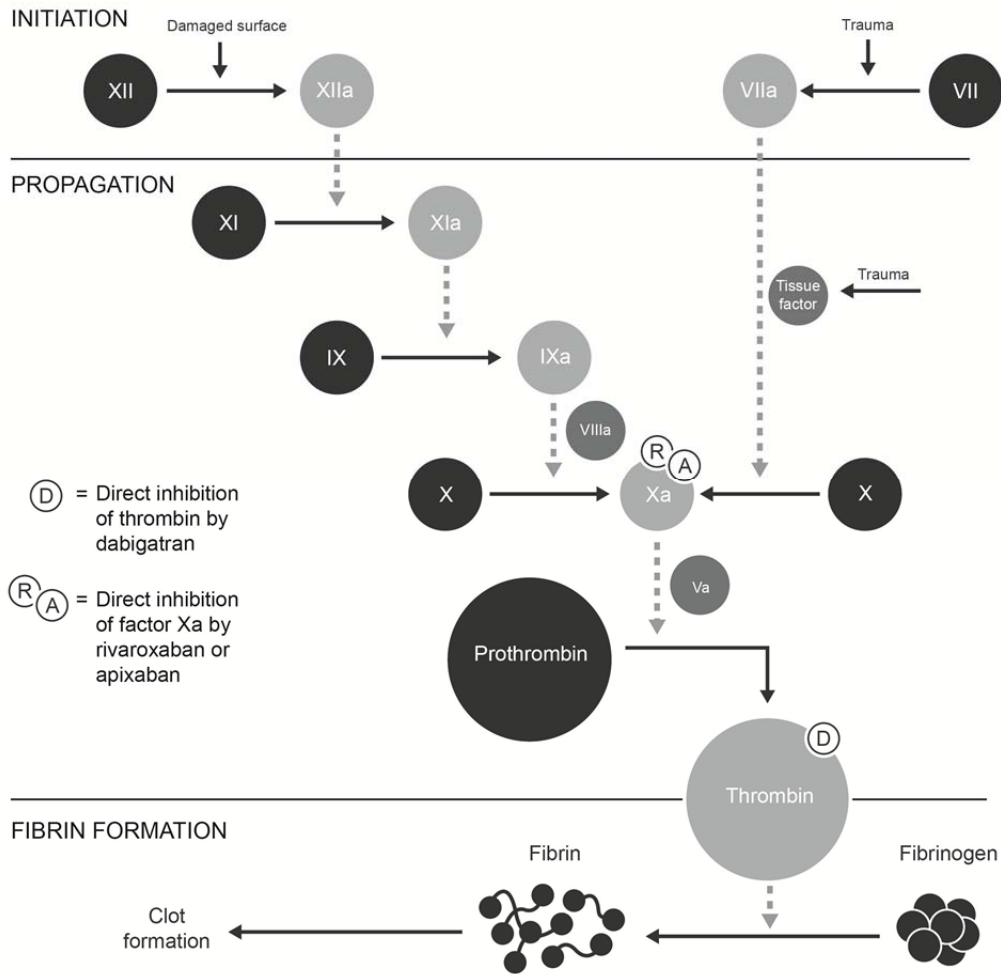
⁶⁴ <http://www.ema.europa.eu/ema>

⁶⁵ <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>

⁶⁶ <http://www.accessdata.fda.gov>

⁶⁷ <http://www.ema.europa.eu/ema>

⁶⁸ Bristol-Myers Squibb. ELIQUIS (apixaban) receives CHMP positive opinion for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation [press release]. September 21, 2012.



Source: Adapted from BPAC NZ (2011)

Figure 11.1 The effect of new oral anticoagulants on the clotting cascade

There is more information available for dabigatran than the other NOACs, because of its earlier availability for stroke prevention worldwide, including in Australia, and therefore this report contains more information regarding dabigatran than the other agents. In the absence of head-to-head trials, and the lesser availability of data for rivaroxaban and apixaban, it is not possible to compare the three agents. The greater amount of information available for dabigatran should not be simply interpreted as evidence of greater concern regarding its clinical effectiveness.

11.4 Pharmacology and pharmacokinetics

Table 11.1 outlines the characteristics of the NOACs.

Table 11.1 Pharmacology and pharmacokinetics of dabigatran, rivaroxaban and apixaban

	Dabigatran	Rivaroxaban	Apixaban
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)	ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation)
Mechanism of action (see Figure 11.1)	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Clearance	80% eliminated unchanged by renal excretion. Dabigatran etexilate (but not the active dabigatran) is a substrate of P-gp	36% excreted unchanged 44% liver metabolism via CYP3A4, CYP2J2 and CYP-independent mechanisms involving P-gp transporter systems	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
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 is 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	Oral bioavailability of 80–100% Oral bioavailability is affected by food; bioavailability of 20 mg tablet is 66% under fasting conditions	Oral bioavailability of approximately 50%.
Half-life	12–14 hours in elderly healthy volunteers; 14–17 hours in surgical patients	5–9 hours in young patients; 11–13 hours in the elderly	12 hours

... Continued

	Dabigatran	Rivaroxaban	Apixaban
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 > 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	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 > 80 years weight < 60 kg
C _{max}	0.5–2.0 hours	2–4 hours	3–4 hours

AF = atrial fibrillation; HPMC = hard gelatin and hypromellose; P-gp = P-glycoprotein; TGA = Therapeutic Goods Administration
Sources: Bayer Australia Limited 2012, Boehringer Ingelheim 2012, Bristol-Myers Squibb Australia Pty Ltd 2012

11.5 Medicine interactions

Interactions can occur between medicines as a result of altered pharmacokinetics and/or pharmacodynamics (PSA 2012). Pharmacokinetic interactions result from an alteration of the rate and/or extent of absorption or from changes in the clearance of a medicine. These factors will result in changes to the plasma concentration profile and depending on the steepness of the dose response curve may result in an increase or decrease in pharmacological response. Pharmacodynamic interactions can result from direct or indirect effects leading to an inhibition or potentiation of response including toxicity.

The plasma concentration of a medicine following chronic administration (C_{ss}) is represented by the following relationship:

$$C_{ss} = Cl \times fD/T$$

where Cl = clearance, f = bioavailability and D/T = dose rate

The pharmacokinetic data shown in Table 11.1 suggest that:

- the clearance of warfarin, rivaroxaban and apixaban may be influenced by CYP3A4 inducers and inhibitors
- the clearance of warfarin may be influenced by inhibitors and inducers of CYP2C9 and CYP1A2
- dabigatran, rivaroxaban and apixaban have the potential to interact with inhibitors or inducers of P-glycoprotein (P-gp).

Table 11.2 lists the inducers and inhibitors of CYP2C9, CYP3A4 and CYP1A2 (AMH 2012).

Table 11.2 Inducers and inhibitors of CYP2C9, CYP3A4 and CYP1A2

CYP2C9 inhibitors	CYP2C9 inducers
Amiodarone (moderate)	Aprepitant
Efavirenz, etravine	Bosentan
Fluconazole (moderate), fluvastatin	Rifampicin
Ritonavir	St John's wort
Teniposide	
Voriconazole	
Fluoxetine	
Fluvoxamine	
CYP3A4 inhibitors	CYP3A4 inducers
Aprepitant (moderate) atazanavir (strong)	Aprepitant
Cimetidine (weak), clarithromycin (strong)	Bosentan
Darunavir, diltiazem ^a (moderate)	Carbamazepine, corticosteroids
Erythromycin (moderate)	Efavirenz, etravirine
Fluconazole, fluvoxamine, fosamprenavir	Modafinil
Grapefruit juice	Nevirapine
Imatinib, indinavir, itraconazole ^a (strong)	Phenobarbitone, phenytoin
Ketoconazole ^a	Rifabutin, rifampicin, ritonavir
lopinavir	St John's wort
Posaconazole ^a	Tipranavir
Ritonavir ^a	
Saquinavir	
Ticagrelor, tipranavir	
Verapamil (moderate), voriconazole ^a	
CYP1A2 inhibitors	CYP1A2 inducers
Cimetidine (weak), ciprofloxacin (moderate)	Omeprazole
Fluvoxamine (strong)	Phenobarbitone, phenytoin
Verapamil (weak)	Tobacco smoke

^a Also strong inhibitors of P-glycoprotein transporter
Source: AMH 2012

The transporter P-gp is localised at the luminal membrane in enterocytes, where it exports its substrate back into the intestinal lumen. It thus reduces the bioavailability of its substrates or increases a medicine's rate of clearance by active secretion into the intestinal lumen. CYP3A4 is also expressed in enterocytes. Intestinal P-gp and CYP3A4 are thought to act together to reduce the oral bioavailability of certain medicines, although there are some differences in their substrates (e.g. digoxin is a substrate for P-gp but is not metabolised by CYP3A4) (Muller and Fromm 2011).

Induction and inhibition of P-gp can occur (Muller and Fromm 2011) with induction resulting in decreased bioavailability, whereas inhibition can increase the bioavailability of medicines that are P-gp substrates. Examples of inhibitors and inducers of P-gp are shown in Table 11.3.

Table 11.3 Inhibitors and inducers of P-glycoprotein

P-glycoprotein inhibitors	P-glycoprotein inducers
Amiodarone, azithromycin	Rifampicin
Carvedilol, clarithromycin, cyclosporin	St John's wort
Erythromycin, everolimus	Tipranavir
Itraconazole, ketoconazole	
Lapatinib	
Naproxen	
Quinidine	
Ritonavir	
Verapamil	

There is potential for many medicines to interact with the NOACs, including many of the same medicines that are reported to significantly interact with warfarin.⁶⁹ In particular, a number of submissions raised the point that dabigatran interacts with two medicines that are commonly used in the management of cardiac rate and/or rhythm in AF patients: amiodarone and verapamil.⁷⁰

The extent and clinical significance of interactions of the NOACs will need to await wider clinical use, with a number of submissions to the review noting that the effects of concomitant medicines on the NOACs have not been studied as extensively as they have for warfarin,⁷¹ and that this is a 'particular problem for people taking many medications, a group not included in the clinical trials'.⁷² In addition, the detection of medicine interactions with the NOACs will be more difficult in view of the current lack of a validated measure of anticoagulant response.

The impact of proton-pump inhibitors (PPI) and H₂-receptor antagonists on the bioavailability of dabigatran is uncertain. The bioavailability of dabigatran is low, and the product is formulated with tartaric acid to aid dissolution. The bioavailability of dabigatran was reduced by 24% in combination with pantoprazole (Stangier et al 2008). Population pharmacokinetic studies indicate an approximate 15% reduction in medicine exposure for PPIs, which was not considered to be clinically relevant (Boehringer Ingelheim 2012). Note that about 45% of AF patients receiving warfarin were also receiving a PPI (unpublished data, Veterans' Medicines Advice and Therapeutics Education Services, University of South Australia, Adelaide, 2012). This figure may be higher with dabigatran in clinical practice, because dyspepsia is a common side effect.

In view of the large proportion of patients with AF who are co-administered inhibitors of gastric acid secretion, this matter needs further consideration.

⁶⁹ Submissions from: Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists; Pillans P; Australian Association of Consultant Pharmacy (2012)

⁷⁰ Submissions from: Cardiac Society of Australia and New Zealand; Australian Association of Consultant Pharmacy; Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (2012)

⁷¹ Submission from Royal Australian College of Physicians (2012)

⁷² Submission from Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (2012)

11.5.1 Pharmacodynamic interactions

Many of the pharmacodynamic interactions reported with currently available anticoagulants have also been reported with NOACs, with increased bleeding observed when NOACs were taken concomitantly with antiplatelets and NSAIDs (Boehringer Ingelheim 2012). The RE-LY (dabigatran) trial protocol strongly discouraged the use of concomitant NSAIDs (Ezekowitz et al 2009), while the ROCKET-AF trial protocol prohibited the long-term (i.e. > two weeks) use of concomitant NSAIDs (ROCKET AF study investigators 2010). As previously mentioned, data from the Australian Government Department of Veterans' Affairs indicate that about 30% of veterans with AF on aspirin, clopidogrel or warfarin monotherapy are taking concomitant NSAIDs or COX-2 inhibitors (unpublished data, Veterans' Medicines Advice and Therapeutics Education Services, University of South Australia, Adelaide, 2012).

12 Efficacy and safety of new oral anticoagulants

This chapter discusses the pivotal clinical trials of the three NOACs that have been compared to warfarin (dabigatran, rivaroxaban and apixaban) and that have shown promise in preventing stroke in AF patients. NOACs have been reported to have several advantages compared to warfarin, including a lower risk of ICH. However, there have been no head-to-head (direct comparison) randomised trials of the three NOACs, and differences in the trials make indirect comparisons between them problematic.

In regard to stroke, data from the three pivotal trials shows that:

- dabigatran 150 mg twice daily was the only regimen to demonstrate a statistically significant reduction in ischaemic stroke compared to warfarin
- dabigatran 110 mg twice daily and rivaroxaban were not inferior to warfarin in relation to total stroke and systemic embolism
- apixaban and dabigatran 150 mg twice daily were superior to warfarin in preventing stroke and systemic embolism
- all the NOACs were associated with a statistically significant reduction in haemorrhagic stroke.

12.1 Clinical trials

Three pivotal clinical trials have compared dabigatran (RE-LY), rivaroxaban (ROCKET-AF) and apixaban (ARISTOTLE) to warfarin in patients with AF. Appendix 1 provides tables that outline:

- the baseline characteristics of the participants of these trials (Table A1)
- the key elements and differences in the design of these trials (Table A2).

Tables A1 and A2 demonstrate that the trial populations for the RE-LY and ARISTOTLE trials were more similar than the trial population included in ROCKET-AF.

All three trials were multinational and recruited patients from about 40 different countries. The proportion of the total trial populations from different regions varied among the trials, as shown in Table 12.1. A potential issue is that the standard of care is likely to be different between and within regions, as has been demonstrated by the significant variation in TTR results in the warfarin arm of the studies in certain countries or regions.

This was further exemplified in a recent analysis of a registry (the RE-LY registry, which was conducted separately to the RE-LY trial of dabigatran), which found that for 15,408 AF patients from 47 countries, there was global variation in mortality rates and stroke risk (Healey 2012).

Table 12.1 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)	15.4	5.3	36.1	25.7	11.7	5.9
ROCKET-AF (rivaroxaban)	14.8 (Asia-Pacific)	13.2	18.8	14.8	38.6	(reported under Asia-Pacific)
ARISTOTLE (apixaban)	14.3	19.0	24.7	16.2	21.8	4.1

Sources: Boehringer Ingelheim 2010, Johnson & Johnson Pharmaceutical Research & Development 2011, Wallentin and Collet 2011

12.2 Comparative efficacy of the new oral anticoagulants

There are no direct comparison trials between the NOACs, and since the pivotal trials of the NOACs were designed differently, indirect comparisons are likely to be confounded. Several indirect comparisons have been published recently but all acknowledge the limitations of such an approach (Miller et al 2012, Banerjee et al 2012, CADTH 2012b, Lip et al 2012a, Schneeweiss et al 2012). The European Sub-Committee Working Group on Thrombosis summarised the differences in the trials as follows (Coordinating Committee et al 2012):

- the moderate-risk populations in the RE-LY and ARISTOTLE trials with dabigatran and apixaban (respectively) 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 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
- there were differences in followup periods because only the ROCKET-AF trial included events up to 30 days after discontinuation of the study medicine
- 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 Multi-center Extension of Dabigatran Treatment in Patients With Atrial Fibrillation Who Completed RE-LY) 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.

In addition, 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 to strengths of dabigatran.

CADTH conducted a therapeutic review of the NOACs, *Safety, Effectiveness, and Cost-effectiveness of New Oral Anticoagulants Compared with Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients with Atrial Fibrillation* ('CADTH Review') (CADTH

2012b). This review, which is referred to throughout this section, did 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. These limitations also apply to the other indirect comparisons referred to throughout this section.

12.3 General safety and efficacy compared to warfarin

The efficacy outcomes of the NOACs compared to warfarin in pivotal trials are shown in Table 12.2.

Table 12.2 Efficacy outcomes of new oral anticoagulant trials

Trial (medicine) RR/HR	Hazard ratio (HR) or relative risk (RR) (95% confidence interval)							
	Total stroke or systemic embolism		Ischaemic stroke		Haemorrhagic stroke		Systemic embolism	
RE-LY (dabigatran)	<u>110 mg</u>	<u>150 mg</u>	<u>110 mg</u>	<u>150 mg</u>	<u>110 mg</u>	<u>150 mg</u>	<u>110 mg</u>	<u>150 mg</u>
RR (Connolly et al 2010)	0.90 (0.74, 1.10)	0.65 (0.52, 0.81)	1.11 (0.88, 1.39)	0.76 (0.59, 0.97)	0.31 (0.17, 0.56)	0.26 (0.14, 0.49)	NA	NA
ROCKET-AF (rivaroxaban)	0.79 (0.66, 0.96)		0.94 (0.75, 1.17) ^a		0.59 (0.37, 0.93)^a		0.23 (0.09, 0.60)	
RR (Patel et al 2011)	ITT: 0.88 (0.75, 1.03)							
ARISTOTLE (apixaban)	0.79 (0.66, 0.95)		0.92 (0.74, 1.13)		0.51 (0.35, 0.75)		0.87 (0.44, 1.75)	
HR (Granger et al 2011)								

ITT = intention to treat; NA = not available

^a Safety on treatment

Note: Numbers are bolded where they are statistically significant ($P < 0.05$).

Table 12.3 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)
- NOACs instead of warfarin (based on point estimates of the event rates from the pivotal trials).

These numbers should be treated as indicative only, given the heterogeneity among the trials.

The greatest benefit in reduction of stroke and systemic embolism occurs when patients move from aspirin to warfarin. However, this switch will cause an increase in the rate of ICH. Assuming a 50:50 split in use of the two strengths of dabigatran (Metcalf and Moodie 2012), the reduction in stroke and systemic embolism with dabigatran compared to warfarin would be around 390 per 100,000 patients per year. Statistically significant benefits in the reduction of ischaemic stroke compared to warfarin were seen only with dabigatran 150 mg twice daily.

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

Table 12.3 Number of events caused (+) or avoided (–) per 100,000 patients per year (including 95% confidence intervals, where available)⁷³

	Stroke or systemic embolism (includes haemorrhagic, ischaemic and unknown stroke)	Haemorrhagic stroke	Ischaemic 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)
Rivaroxaban vs. warfarin	–290 (–600, +70)	–180 (–280, –30) ^b	–90 (–360, +240) ^b	–330 (–660, +40) ^b	–230 (–370, –50) ^b

+ = more events; – = fewer events; ITT = intention to treat; NA = not available; NOAC = new oral anticoagulant

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.

Note: Numbers are bolded where they are statistically significant

Sources: Connolly et al 2010, Granger et al 2011, Patel et al 2011

Table 12.4 shows a similar analysis conducted by CADTH but presented as events per 1000 patients.

⁷³ The absolute risk reduction per 100,000 patients per year and associated 95% CI 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 $(1 - \text{the RR or HR reported}) \times 100,000$. This is equivalent to a RR improvement per patient per year estimate $\times 100,000$. The CIs are based on the RR or HR 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 12.4 Summary of individual study results — absolute risk reduction per 1000 patients treated each year compared to warfarin as seen in the pivotal clinical trials (95% confidence interval)

	Mean followup	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)	2more (5 more, 0 more)
Rivaroxaban 20 mg once daily	1.9 years ITT 1.6 years SOT	3 fewer (1 more, 6 fewer)	1 more ^a (6 more, 3 fewer)	4 fewer (2 more, 8 fewer)	3 fewer^a (1 fewer, 4 fewer)	8 more^a (13 more, 4 more)	2 fewer ^a (1 more, 4 fewer)

ITT = intention to treat; SOT = safety on treatment

^a Safety on treatment population

Note: Numbers are bolded where results are statistically significant

Source: CADTH 2012b

12.4 Specific efficacy compared to warfarin

A number of analyses, including the CADTH Review (CADTH 2012b), have investigated the impact of various factors on the relative efficacy of the NOACs compared to warfarin. Such factors include the quality of warfarin management in the control arm, and patient characteristics such as age, renal impairment and risk of stroke or bleeding.

12.4.1 Impact of trial centre's average time in therapeutic range on efficacy and safety of new oral anticoagulants 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 TTR (cTTR) for the warfarin population (Wallentin et al 2010). Individual patient TTR levels would have been informative, but are not available. 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 the 'net clinical benefit' (unweighted composite outcome of reduction in stroke, systemic embolism, pulmonary embolism, MI, death and major bleeding) (Wallentin et al 2010).

These statistically significant interaction terms indicate that the advantages of dabigatran for some outcomes compared to warfarin were greater at trial sites with poor INR control than at those with better control. The results indicate that local standards of care can affect the relative risks and benefits of dabigatran versus warfarin.

Although the outcome-by-cTTR interaction for stroke or 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 greater than or equal to 65.5%.

Tables 12.5 and 12.6 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 12.5 Hazard ratios (with 95% confidence intervals) for various endpoints as a function of centre's mean time in therapeutic range for dabigatran 150 mg from RE-LY

cTTR (%)	Stroke/systemic embolism	Mortality	Net clinical benefit ^a	Major bleeding	Intracranial haemorrhage
< 57.1	0.57 (0.37, 0.88)	0.67 (0.53, 0.85)	0.67 (0.56, 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)	0.87 (0.73, 1.05)	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)	1.05 (0.87, 1.27)	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)	1.11 (0.91, 1.35)	1.16 (0.88, 1.54)	0.39 (0.18, 0.84)
Interaction P-value	0.20	0.052	0.0006	0.03	0.89

cTTR = centre's mean time in therapeutic range

^a Unweighted composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death and major bleeding.

Note: Numbers are bolded where the results are statistically significant.

Source: Wallentin et al 2010

Table 12.6 Hazard ratios (with 95% confidence intervals) for various endpoints as a function of centre's mean time in therapeutic range for dabigatran 110 mg from RE-LY

cTTR (%)	Stroke/systemic embolism	Mortality	Net clinical benefit ^a	Major bleeding	Intracranial haemorrhage
< 57.1	1.00 (0.68, 1.45)	0.73 (0.58, 0.92)	0.74 (0.62, 0.89)	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)	0.97 (0.81, 1.16)	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 (0.80, 1.17)	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)	1.07 (0.87, 1.30)	0.90 (0.67, 1.21)	0.27 (0.11, 0.66)
Interaction P-value	0.89	0.066	0.036	0.50	0.71

cTTR = centre's mean time in therapeutic range

^a Unweighted composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death and major bleeding.

Note: Numbers are bolded where the results are statistically significant.

Source: Wallentin et al 2010

Data for the outcomes from the ARISTOTLE trial of apixaban as a function of cTTR are also available, and are presented in Table 12.7. 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 (Wallentin and Collet 2011).

Table 12.7 Hazard ratios (95% confidence interval) for various endpoints as a function of centre's mean time in therapeutic range for apixaban from ARISTOTLE

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 (compared to intracranial haemorrhage in Tables 12.5 and 12.6)

Note: Numbers are bolded where the results are statistically significant.

Source: Wallentin and Collet 2011

The available data for rivaroxaban also demonstrated no significant interaction between total stroke and cTTR (Patel et al 2011).

The CADTH Review (CADTH 2012b) 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 12.8.

The report found that for stroke or systemic embolism:

- for cTTRs less than 66%, the absolute risk reduction ranged from 2 to 9 fewer strokes or 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 or systemic embolism ranged from 1 to 5 fewer per 1000 patients.

The report found that for major bleeding:

- for cTTRs less than 66%, the absolute risk reduction ranged from 2 to 11 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, and there were significantly fewer bleeds with apixaban, but significantly more major bleeds with rivaroxaban.

Table 12.8 Summary of individual study results by time in therapeutic range — absolute risk reduction per 1000 patients treated each year (95% confidence interval) compared to warfarin as seen in the pivotal clinical trials

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 once daily ^a	3 fewer (1 more, 6 fewer)	1 more (6 more, 3 fewer)	3 fewer (0 more, 6 fewer)	2 fewer (3 more, 6 fewer)	5 fewer (2 more, 10 fewer)	11 more (25 more, 0 more)

TTR = time in therapeutic range

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

Note: Numbers are bolded where the results are statistically significant.

Source: CADTH 2012b

12.4.2 Impact of patient stroke and bleeding risk on efficacy and safety of new oral anticoagulants compared to warfarin

In clinical judgment regarding the use of any anticoagulants, reducing the incidence of ischaemic stroke and systemic embolism needs to be balanced against the increased risk of 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 Chapter 6, Table 6.2).

A subgroup analysis of the RE-LY trial data investigated the impact of the CHADS₂ score on clinical outcomes (Oldgren et al 2011). In all arms of the trial, as the CHADS₂ score increased, so did the rates of stroke or systemic embolism, major and intracranial bleeding, and vascular and total mortality. 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. It found that apixaban was only statistically significantly superior to warfarin in the reduction of stroke and systemic embolism at CHADS₂ scores of 3 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 (Lopes et al 2012).

Banjeree et al (2012) calculated the net clinical benefit of NOACs, 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). The modelling analysis used patient data from the Danish National Patient Registry and outcome data from the recent clinical trials of the NOACs. The model found:

- 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 scores of greater than or equal to 1 or CHA₂DS₂-VASc scores greater than or equal to 2, the three NOACs appear to be superior to warfarin in terms of net clinical benefit, regardless of risk of bleeding; this is likely to be due mainly to the reduction in ICH seen with all three NOACs.

The model only accounted for ischaemic and haemorrhagic strokes. Outcomes might have been different, had other outcomes (e.g. major bleeding) been included.

The CADTH Review (CADTH 2012b) summarised the absolute risk reduction for particular outcomes per 1000 patients treated per year with each of the NOACs, using patients with a CHADS₂ score of less than 2, and a CHADS₂ score of 2 or more (Table 12.9).

Note: The ROCKET-AF trial of rivaroxaban only included patients with a CHADS₂ score of 2 or more.

The CADTH Review found (CADTH 2012b):

- for stroke or systemic embolism
 - for CHADS₂ scores of less than 2, the absolute risk reduction ranged from 0 to 4 fewer strokes or systemic emboli per 1000 patients treated in a year, but was only statistically significant for dabigatran 150 mg twice daily
 - for CHADS₂ scores of greater than or equal to 2, the absolute risk reduction of stroke or systemic embolism ranged from 2 to 6 fewer strokes or systemic emboli per 1000 patients treated in a year, and was statistically significant for apixaban and dabigatran 150 mg twice daily
- for major bleeding
 - for CHADS₂ scores of less than 2, the absolute risk reduction ranged from 7 to 10 fewer major bleeds per 1000 patients treated in a year; the dabigatran 150 mg results were not statistically significant
 - for CHADS₂ scores of greater than or equal to 2, the absolute risk reduction ranged from 1 more to 8 fewer major bleeds per 1000 patients treated in a year; apixaban was the only agent that showed a statistically significant result.

Table 12.9 Summary of individual study results by CHADS₂ score — absolute risk reduction per 1000 patients treated each year (95% confidence interval) compared to warfarin as seen in the pivotal clinical trials

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 once 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 on treatment population for rivaroxaban subgroups — intention-to-treat data were not available for CHADS₂ subgroups.

Note: Numbers are bolded where the results are statistically significant.

Source: CADTH 2012b

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

In its Safety Advisory of 3 November 2011, the TGA noted that being over the age of 75 is a risk factor for bleeding with dabigatran (TGA 2011c). This increased bleeding risk in the elderly was also raised as an issue in a number of submissions,⁷⁴ and is particularly important since approximately 50% of patients with AF are over the age of 75.⁷⁵

The Australian product information for dabigatran states that 110 mg twice daily should be used in patients aged 75 and over to prevent strokes in patients with AF and at least one other risk factor for stroke (Boehringer Ingelheim 2012).

The CADTH Review (CADTH 2012b) summarises the absolute risk reduction for particular outcomes per 1000 patients treated per year with each of the NOACs by age (< 75 years or ≥ 75 years) (Table 12.10).

⁷⁴ Submissions from: National Stroke Foundation; Cardiac Society of Australia and New Zealand (2012)

⁷⁵ Submission from Pillans P (2012)

Table 12.10 Summary of individual study results by age — absolute risk reduction per 1000 patients treated each year (95% confidence interval) compared to warfarin as seen in the pivotal clinical trials

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 once 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)

Note: Numbers are bolded where the results are statistically significant.

Source: CADTH 2012b

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 (Eikelboom et al 2011):

- dabigatran 110 mg twice daily compared to warfarin was no worse than warfarin in reducing stroke and systemic embolism, and was associated with a lower risk of major bleeding in patients under the age of 75 but a similar risk of bleeding in those aged 75 and over
- dabigatran 150 mg twice daily compared to warfarin was associated with a lower risk of major bleeding in those under the age of 75 and a trend towards a higher risk of major bleeding in those aged 75 and over
- the same relationship to age was also seen for extracranial bleeding but not for intracranial bleeds, which was reduced independent of age for both doses of dabigatran.

Recent data on the clinical (nontrial) use of dabigatran in New Zealand (from July to December 2011) showed that 78% of patients receiving 110 mg twice daily were over the age of 75 while only 20% of those receiving 150 mg twice daily were over the age of 75 (Metcalf and Moodie 2012). Further, patients over the age of 75 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 aged 75 and over. Based on the analyses by (Eikelboom et al 2011) and the CADTH Review (CADTH 2012b), this would indicate that, in regard to this cohort of patients (age ≥ 75 years), the benefit of a reduction in major 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 in the pivotal trials — the mean age was 71 years in RE-LY, 73 years in ROCKET-AF and 70 years in ARISTOTLE.

12.5 Efficacy of new oral anticoagulants compared to aspirin

Apixaban is the only NOAC that has been directly compared to aspirin in a randomised controlled trial, the AVERROES trial, which involved 5599 patients with AF who were deemed to be unsuitable for vitamin K antagonist therapy (Connolly et al 2011b). The most common reasons given in the trial for patient unsuitability for vitamin K antagonist therapy are outlined in Table 12.11 below.

Table 12.11 Most common reasons for unsuitability of vitamin K antagonist therapy

Reason for unsuitability of vitamin K antagonist therapy	Percentage of patients enrolled in study (%)
Multiple reasons for unsuitability of VKA therapy	51.5
Assessment that INR could not or was unlikely to be measured at requested intervals	43
Patient's refusal to take VKA	37.5
CHADS ₂ score of 1 and VKA therapy not recommended by physician	21.5
Assessment that INR could not be maintained in therapeutic range	17
Uncertainty about patient's ability to adhere to instructions regarding VKA therapy	15.5
Patient's refusal to take VKA as only reason for unsuitability	14.5
Expected difficulty in contacting patient for urgent change in dose of VKA	11.5
CHADS ₂ score of 1 as only reason for unsuitability of VKA therapy	11.5

INR = international normalised ratio; VKA = vitamin K antagonist (coumarins; i.e. warfarin in Australia, but internationally, phenprocoumon and acenocoumarol are used)

Source: Connolly et al 2011b

The data and safety monitoring board recommended early termination of the study because of a clear benefit in favour of apixaban. The trial found a significant reduction in stroke/systemic embolism (HR 0.45, CI 0.32–0.62) with no statistically significant increase in major bleeding (HR 1.13, CI 0.74–1.75) with apixaban compared to aspirin.

Table 12.12 Rates of study outcome with apixaban and aspirin in the AVERROES trial

Outcome	Event rate (% per year)		Hazard ratio (95% CI)
	Apixaban	Aspirin	
Stroke/systemic embolism (primary outcome)	1.6	3.7	0.45 (0.32, 0.62)
Ischaemic stroke	1.1	3.0	0.37 (0.25, 0.55)
Haemorrhagic stroke	0.2	0.3	0.67 (0.24, 1.88)
	(6 events)	(9 events)	
Total mortality	3.5	4.4	0.79 (0.62, 1.02)
Major bleeding	1.4	1.2	1.13 (0.74, 1.75)

Note: Numbers are bolded where they are statistically significant

Source: (Connolly et al 2011b)

The average age of patients in the AVERROES trial was 70, which, as discussed in Section 12.4.3, is less than the average age of those taking dabigatran in the non-clinical trial setting in New Zealand, where 50% of patients were aged 75 and over.

This study reaffirms that warfarin is superior to aspirin at reducing stroke and systemic embolism, with the stroke and systemic embolism event rate for aspirin of 3.7% per year in the aspirin arm of AVERROES, compared to 1.6% per year in the warfarin arm of ARISTOTLE (noting that it is difficult to compare the AVERROES and ARISTOTLE trials, particularly because inclusion criteria for the AVERROES trial included patients unable to tolerate

vitamin K antagonist therapy. However, baseline characteristics of patients in the two trials appeared similar.)

12.6 Safety of the new oral anticoagulants

12.6.1 Bleeding risk

The use of anticoagulants in the prevention of stroke in patients with AF involves balancing the risk of ischaemic stroke against the risk of bleeding, particularly ICH. Patients who have a greater risk of stroke (as determined by CHADS₂ score) also have a greater risk of bleeding (a higher HAS-BLED score). Increased risk of bleeding is associated with increasing age, hypertension, history of MI or ischaemic heart disease, cerebrovascular disease, anaemia, history of bleeding and concomitant use of medicines such as antiplatelets and NSAIDs.

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’ (TGA 2011c).

Recently a genetic variant that reduces exposure to active dabigatran with a subsequent reduction in bleeding risk has been reported, and this is discussed later in this chapter (Paré et al 2012).

Major bleeding

The results for major bleeding events from the three recent NOACs trials are given in Table 12.13. In these trials, major bleeding was defined as one or more of the following:

- overt bleeding resulting in a decrease in haemoglobin level of at least 20 g/L
- overt bleeding requiring transfusion of at least two units of blood
- symptomatic bleeding into a critical organ or region of the body (this includes ICH).

Table 12.13 shows that, in the trial population, dabigatran 110 mg twice daily and apixaban caused less major bleeding than warfarin, and that there was no significant difference between dabigatran 150 mg twice daily or rivaroxaban and warfarin. None of the NOACs appeared to cause a greater risk of major bleeding than warfarin, but whether this will be confirmed in widespread clinical use is uncertain. For example, there may be particular groups of patients for whom the risk of major bleeding with NOACs is greater than for warfarin. Data from the RE-LY trial indicates that the number needed to harm (NNH) for major bleeding for dabigatran 150 mg twice daily in patients aged 75 years or over (compared to warfarin) is 137 (as shown in Table 12.14).

Table 12.13 Event rate and number needed to treat for major bleeding for warfarin and new oral anticoagulants

Trial	Warfarin (%/year)	NOAC (%/year)	Relative risk/hazard ratio (95%CI)	NNT to prevent a major bleed
RE-LY — dabigatran 110 mg BD	3.57	2.87	0.80 (0.70, 0.93)	143
RE-LY — dabigatran 150 mg BD	3.57	3.32	0.93 (0.81, 1.07)	400
ROCKET-AF ^a — rivaroxaban	3.4	3.6	1.04 (0.90, 1.20)	-500 (NNH)
ARISTOTLE — apixaban	3.09	2.13	0.69 (0.6, 0.8)	104

CI = confidence interval; NNH = number needed to harm; NNT = number needed to treat; NOAC = new oral anticoagulant; BD = twice daily

Note: Numbers are bolded where they are statistically significant. The ROCKET-AF trial enrolled patients with a higher CHADS₂ score
^a Safety on treatment

Sources: Connolly et al 2010, Granger et al 2011, Patel et al 2011

Based on the subgroup analysis of the RE-LY trial of major bleeding risk in older and younger patients (Eikelboom et al 2011), the number needed to treat (NNT) or NNH, in patients aged less than 75 years, or 75 years or more, are presented in Table 12.14.

Table 12.14 Numbers needed to treat (or harm) based on results of subgroup analyses of the pivotal trials of the new oral anticoagulants compared to warfarin

Agent	Dabigatran 110 mg twice daily	Dabigatran 150 mg twice daily	Rivaroxaban ^a	Apixaban
NNT to prevent one major bleed compared to warfarin in patients aged < 75	87	109	1000	164
NNT to prevent one major bleed compared to warfarin in patients aged ≥ 75	-1667 (NNH)	-137 (NNH)	-217 (NNH)	53
P-value for interaction between age and major bleeding	< 0.001	< 0.001	0.34	0.64

NNH = number needed to harm; NNT = number needed to treat

^a Safety on treatment

Note: These numbers need to be treated with caution as they are based on post-hoc analyses

Sources: Eikelboom et al 2011, Granger et al 2011, Halperin et al 2012.

Distribution of bleeds is different

Table 12.15 shows that the distribution of types of bleeding events differed between the NOACs and warfarin. All NOACs showed lower rates of ICH than warfarin, while dabigatran (150 mg twice daily) and rivaroxaban showed higher rates of GI bleeding than warfarin.

Table 12.15 Odds ratios for bleeding events — new oral anticoagulants 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 (0.69, 0.93)	0.94 (0.81, 1.08)	1.03 (0.89, 1.19)	0.69 (0.60, 0.80)
Major gastrointestinal bleeding	1.08 (0.83, 1.40)	1.45 (1.13, 1.85)	1.60 (1.29, 1.98)	0.88 (0.67, 1.14)
Intracranial haemorrhage	0.30 (0.19, 0.46)	0.41 (0.28, 0.61)	0.65 (0.46, 0.92)	0.42 (0.30, 0.58)

^a Safety on treatment

Note: Numbers are bolded where they are statistically significant

Sources: CADTH 2012b

The underlying mechanism for the variations in sites of bleeding with different anticoagulants has not been established, although a number of theories have been proposed, particularly in regard to the reduction in ICH (see section on intracranial haemorrhage, below).

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 NSF described as ‘unusual and probably important’.⁷⁶

Plasma concentration and bleeding risk

Several recent publications have examined the concentration–response relationships of dabigatran (Douxflis et al 2012, Lindahl et al 2011, Stangier et al 2007). It has been suggested that a trough plasma concentration of dabigatran of greater than 200 ng/mL correlates with increased risk of bleeding. TGA has stated that an activated partial thromboplastin time of more than 80 seconds correlates with increased bleeding risk (TGA 2011b). While the therapeutic range of dabigatran in AF has not been defined, it has been suggested that drug monitoring may be recommended, using, for example, a specific coagulation test to determine whether people are at increased risk of bleeding or as a screening test for the risk of overdose (e.g. HEMOCLOT thrombin inhibitor or activated partial thromboplastin time) (Douxflis et al 2012). The Australian Public Assessment Report for Dabigatran noted that trough plasma concentrations were highly variable in both dose groups from the RE-LY trial, but indicated dose proportionality. In addition, plasma concentrations were 30% higher in female than in male patients, 30% higher in those over the age of 75 than in those aged 65–75 years, and 68% higher in those over the age of 75 than in those under the age of 65. In patients with a glomerular filtration rate (GFR) of 30–50 mL/minute, the mean plasma concentrations were 2.3 times higher than in patients with a GFR of more than 80 mL/minute (TGA 2011b).

The absence of the need for monitoring is frequently cited as a benefit of the NOACs, but a growing body of evidence indicates that some form of therapeutic monitoring may be a useful tool in the clinical management of AF patients receiving NOACs (Duffull et al 2012, Ten Cate 2012).

A recent subanalysis of the RE-LY trial identified that 33% of Europeans are carriers of the variant CES1 gene, single-nucleotide polymorphism (SNP) rs2244613, which blunts the biotransformation of the pro-drug, dabigatran etexilate, to the active moiety dabigatran. These carriers have a 15% decrease in trough concentrations of dabigatran and a 27% decrease in the risk of bleeds. The report stated that the variant influenced the bleeding risk but not dabigatran’s

⁷⁶ Submission from: National Stroke Foundation (2012)

antithrombotic efficacy (Paré et al 2012). Further investigation of this finding will need to be undertaken. In response to this announcement, it has been stated that ‘in order to apply these findings to personalized medicine a point-of-care assay is needed that can be used in outpatients’ (reported by (Stiles 2012)).

Intracranial haemorrhage

Table 12.16 shows that a significant reduction in ICH and haemorrhagic stroke 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.⁷⁷ Whether the magnitude of reduction in ICH would be reduced by an improvement in TTR, especially due to a reduction in INR values of more than 3, is unknown, but it is acknowledged that a significant proportion of ICH with warfarin occurs at an INR of less than 3. The NSF stated that ‘not all bleeding events are clinically equivalent and clinicians may be most concerned with the small but important incidence of ICH’.⁷⁸

The net absolute reduction in the incidence rate of ICH and haemorrhagic strokes are consistent across all three agents, as shown in Table 12.16. Given the high morbidity and mortality associated with these events, this reduction represents a significant clinical advantage of the NOACs compared to dose-adjusted warfarin. However, the NNT to prevent one ICH is high, at about 200 (and 500 for rivaroxaban), and the NNT to prevent one haemorrhagic stroke is about 400. A hypothesis for this difference between NOACs and warfarin has recently been proposed: warfarin affects the initiation, amplification and propagation of coagulation, whereas NOACs have less effect than warfarin on the propagation phase (Weitz 2012). Weitz (2012), and Eikelboom et al (2011) both suggest that a large amount of thrombin needs to be generated in the propagation phase to stabilise the haemostatic plugs, and that the greater inhibition by warfarin in this phase leads to a higher risk of intracranial bleeding. Another theory is that the difference may be associated with factor VII availability (Connolly et al 2009).

Table 12.16 Number needed to treat per year to avoid an intracranial haemorrhage or haemorrhagic stroke, or stroke or systemic embolus with new oral anticoagulants in the pivotal trials compared to warfarin

Trial	Rate of ICH or HS with NOACs (% per year) ^a	Rate of ICH or HS with warfarin (% per year) ^a	Number needed to treat per year to prevent an ICH or HS ^a	Number needed to treat per year to prevent one stroke or systemic embolism
RE-LY dabigatran 110 mg twice daily versus warfarin	0.23/0.12	0.76/0.38	189/385	588
RE-LY dabigatran 150 mg twice daily versus warfarin	0.32/0.1	0.76/0.38	227/357	167
ROCKET-AF ^b rivaroxaban versus warfarin	0.5/0.26	0.7/0.44	500/556	333
ARISTOTLE apixaban versus warfarin	0.33/0.24	0.80/0.47	213/435	303

ICH = intracranial haemorrhage; HS = haemorrhagic stroke; NNT = number needed to treat; NOAC = new oral anticoagulant

^a First number is %ICH; second number is %HS

^b Safety on treatment

Note: There is considerable heterogeneity between trials and the numbers should not be directly compared

Sources: Connolly et al 2010, Granger et al 2011, Patel et al 2011

⁷⁷ Submissions from: Cardiac Society of Australia and New Zealand; National Stroke Foundation; Paceline Inc.; Royal Australasian College of Physicians; Blombery PA (2012)

⁷⁸ Submission from: National Stroke Foundation (2012)

The NNT to prevent a haemorrhagic stroke is about 400. This indicates that, if NOACs were to be used in place of warfarin in AF, there would be a reduction of about 400 haemorrhagic strokes per year, assuming that 150,000 patients receive warfarin as the anticoagulant. If the reduction in haemorrhagic stroke was considered to be the only clinical benefit of the NOACs over warfarin then the incremental cost per haemorrhagic stroke avoided is approximately \$300,000.⁷⁹ This assumes that the patient characteristics in the trials are similar to the Australian population. As discussed previously, this is uncertain.

Gastrointestinal bleeds

Bleeding from the GI tract is not uncommon with anticoagulant therapy and is a well-recognised side effect. The clinical sequelae following a gastric bleed are not considered as serious as for an intracranial bleed.

Table 12.17 shows the GI bleeding event rate observed in each of the pivotal trials.

Table 12.17 Event rate (% per year) gastrointestinal bleeding

Trial	Warfarin	NOAC	RR/HR (95%CI)
RE-LY — dabigatran 110 mg BD	1.07	1.15	1.08 (0.85, 1.38)
RE-LY—dabigatran 150 mg BD	1.07	1.56	1.48 (1.18, 1.85)
ROCKET-AF— rivaroxaban ^a	NA	NA	1.60 (1.29, 1.98)
ARISTOTLE — apixaban	0.86	0.76	0.89 (0.70, 1.15)

BD = twice daily; CI = confidence interval; HR = hazard ratio; RR = relative risk; NA = not available; NOAC = new oral anticoagulant

Note: Numbers are bolded where they are statistically significant ^a Safety on treatment

Sources: Connolly et al 2010, Granger et al 2011, Patel et al 2011

It has been proposed that the increased risk of GI bleeds observed with dabigatran 150 mg twice daily and rivaroxaban may be due to the exacerbation of surface bleeding by the presence of active anticoagulant in the gut (Weitz 2012), and that this may be due to the greater faecal excretion of NOACs compared to warfarin. It has also been suggested that these lesions are more common in the elderly, thereby explaining the increased bleeding rate in those over the age of 75. The oral bioavailability of dabigatran is low (6%); thus, faecal excretion of the pro-drug is likely to be high and some hydrolysis by esterases in the gut could result in gut exposure to active dabigatran. However, the differential effect of the two Factor Xa inhibitors, rivaroxaban and apixaban, does not support this hypothesis. The absorption of rivaroxaban is considered to be almost complete and it is thus considered to have a high oral bioavailability. Of an administered dose, about 70% undergoes metabolism, with 50% of the metabolites excreted in faeces (presumably via biliary secretion or direct intestinal secretion). There is no evidence that these metabolites are pharmacologically active (Bayer Australia Limited 2012). On the other hand, apixaban, which in the ARISTOTLE trial did not show increased GI bleeding, has an absolute bioavailability of only 50% (Bristol-Myers Squibb Australia Pty Ltd 2012). Of the administered dose of apixaban, about 25% is recovered as metabolites, mainly in the faeces. Biliary and direct intestinal secretion was also observed. This would suggest that the gut exposure to apixaban or faecally cleared metabolites is likely to be greater for apixaban than for rivaroxaban. In view of the similar modes of action of the two medicines, the hypothesis does not appear to be consistent with the known biopharmaceutical properties of the medicine. It is


⁷⁹ Based on the current cost of dabigatran as presently listed on the PBS for post-surgical prevention of venous thromboembolism; warfarin usage estimates based on those given in Offbeat: Atrial fibrillation and the cost of preventable stroke (2011) by Deloitte Access Economics; and costs of INR monitoring based on those provided by Boehringer Ingelheim in its submission to the Review (2012).

acknowledged, however, that the ROCKET-AF trial contained patients with a higher CHADS₂ score who would have had a greater bleeding risk than the patients in the ARISTOTLE trial, and the observation may simply reflect the difference in the trial populations.

The impact of co-administered NSAIDs on GI bleeding risk of anticoagulants is unknown. The use of NSAIDs was discouraged in the pivotal trials, but (as discussed in Section 8.7.1) data from the Australian Government Department of Veterans' Affairs database indicates that almost 30% of AF patients on aspirin, clopidogrel or warfarin monotherapy were co-prescribed concomitant NSAIDs or COX-2 inhibitors (12%, 10% and 76%, respectively) (unpublished data, Veterans' Medicines Advice and Therapeutics Education Services, University of South Australia, Adelaide, 2012). It is not known whether the increased incidence of GI bleeding seen with dabigatran 150 mg twice daily and rivaroxaban over warfarin would be further increased in patients receiving NSAIDs or COX-2 inhibitors. Since many patients with AF will also have musculoskeletal comorbidities, this clinical situation is likely to be relatively common. It is uncertain whether the concomitant use of NSAIDs in patients receiving NOACs (particularly those receiving dabigatran or rivaroxaban) will show a greater degree of gastric bleeding.

12.6.2 Myocardial infarction risk

Submissions raised the issue of a meta-analysis linking dabigatran to an increased incidence of MI (heart attack) and angina (chest pains) compared to warfarin.⁸⁰ One submission highlighted that, in New Zealand, there have been uncertainties regarding management approaches to patients with acute MI who are on dabigatran.⁸¹



12.6.3 Safety data from regulatory agencies

The Institute for Safe Medication Practices (in the United States) produces details of adverse event cases reported to 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 cases), and stroke (644 cases). It was also suspect in 15 cases of liver failure' (ISMP 2012). 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 (ISMP 2012).

Spontaneous adverse event reporting data has limitations, 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 at least be 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' (ISMP 2012).

⁸⁰ Submissions from: National Stroke Foundation; Royal Australasian College of Physicians; New South Wales Therapeutic Advisory Group Inc.; Pillans P; Consumers Health Forum of Australia (2012)

⁸¹ Submission from: Pillans P (2012)

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’ (ISMP 2012). These types of sentiments were also raised in a number of submissions to the Review.⁸²

The FDA is currently evaluating postmarketing reports of bleeding events in patients taking dabigatran. In Australia, the TGA has recently begun publishing its Database of Adverse Event Notifications, which comprises reports made to the TGA by patients, consumers, health professionals and sponsors of medicines.⁸³ The database shows that since its registration in Australia (November 2008) until 14 June 2012, there have been 725 adverse event reports made to the TGA regarding dabigatran; of these, there were 124 reports where death was a reported outcome (noting that these reports of death may or may not have been the result of taking dabigatran).⁸⁴ Note that this data is subject to the aforementioned limitations of spontaneous adverse event reporting, and it is noted that many of the reports to the TGA were made by Boehringer Ingelheim as part of its oversight of the dabigatran Product Familiarisation Program. 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 postmarket 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’ (EMA 2012). 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.

12.7 Management

12.7.1 Potential usage outside approved indications

A recent survey in the United States indicated that 37% of current dabigatran use is off-label, predominantly for hypertensive heart disease (14% of use), coronary artery disease (6%) and venous thromboembolism (5%). Further, the survey found that, since the introduction of dabigatran for stroke prevention in AF (in October 2010) the percentage of AF patients not receiving any antithrombotic therapy (i.e. neither an anticoagulant nor an antiplatelet) has remained constant, and so too has the use of antiplatelet monotherapy for AF. The authors concluded that they ‘did not find any evidence that it (dabigatran) has increased overall atrial fibrillation treatment rates’ (Kirley et al 2012). The relevance of these observations to Australia is uncertain, but does raise the issue of uncertainty of the switching patterns used in any economic model where a mixture of comparators is used.

⁸² Submissions from: Society of Hospital Pharmacists of Australia; Australasian Society of Thrombosis and Haemostasis, Haematology Society of Australia and New Zealand, Australian and New Zealand Society of Blood Transfusions; New South Wales Therapeutic Advisory Group Inc.; Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (2012)

⁸³ <http://www.tga.gov.au/safety/daen.htm>

⁸⁴ <http://www.tga.gov.au/daen/daen-report.aspx>

12.7.2 Patient compliance and continuation

Warfarin is administered once daily. A number of submissions noted that twice daily dosages (as required for apixaban and dabigatran) require increased patient adherence.⁸⁵ In its submission to the Review, CSANZ stated:

... it should be noted that nonadherence 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.⁸⁶

A number of submissions to the Review stated that dabigatran should not be repackaged into dose-administration aids or unit-dose systems (e.g. in residential aged-care facilities and hospitals)⁸⁷, because if exposed to moisture, the capsules could 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’.⁸⁸ The capsule shell must be left intact (Boehringer Ingelheim 2012). This will be relevant to patients with dysphagia who may need their medication to be taken out of its capsule shell before administration.

Dabigatran has been reported to cause dyspepsia in a significant number of patients, which was reported as a common reason for discontinuation (Connolly et al 2009). The NOAC discontinuation rates seen in the key pivotal trials were similar to those in the warfarin-arms of the trials. Table 12.18 summarises these trial discontinuation rates.

Table 12.18 Summary of patient discontinuation rates in the pivotal trials for the new agents

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

Note: There are key differences between the trials, so it is difficult to compare across the trials. For example, the rivaroxaban trial enrolled patients at higher stroke risk (see Table A1) than the other trials, and this is likely to be the reason for the higher patient discontinuation rates in the ROCKET-AF trial.

Sources: Connolly et al 2009, Granger et al 2011, Patel et al 2011

12.7.3 Renal function

Because dabigatran is predominantly cleared renally, its pharmacokinetics will be influenced by the degree of renal function; a number of submissions raised the issue that careful consideration of renal function will be required before prescribing dabigatran.⁸⁹

⁸⁵ Submissions from: Cardiac Society of Australia and New Zealand; New South Wales Therapeutic Advisory Group; Australasian Society of Thrombosis and Haemostasis, Haematology Society of Australia and New Zealand, and Australian and New Zealand Society of Blood Transfusions (2012)

⁸⁶ Submission from Cardiac Society of Australia and New Zealand (2012)

⁸⁷ Submissions from: National Stroke Foundation; Society of Hospital Pharmacists of Australia (2012)

⁸⁸ Submission from: Society of Hospital Pharmacists of Australia (2012)

⁸⁹ Submissions to review: Cardiac Society of Australia and New Zealand; National Stroke Foundation; Australian Association of Consultant Pharmacy; Society of Hospital Pharmacists of Australia; Australasian Society of Thrombosis and Haemostasis, Haematology Society of Australia and New Zealand, and Australian and New Zealand Society of Blood Transfusions (2012)

On 3 November 2011, 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’ (TGA 2011a). A summary of these new recommendations is provided in Box 12.1.

Box 12.1 Dabigatran (Pradaxa[®]) and the risk of bleeding: summary of new recommendations for monitoring kidney function

- Kidney function should be assessed in all patients by measuring the creatinine clearance (CrCL) 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 (aged > 75 years) or in patients with moderate kidney impairment, kidney function should be assessed at least once a year.

Source: TGA 2011a

Dabigatran dosage in patients with reduced renal function

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 (Boehringer Ingelheim 2012).

However, in its analysis of the RE-LY trial, FDA noted that patients with poor renal function (GFR 30–50 mL/min) had a similar bleeding risk independent of dosage, but had an increased incidence of stroke and systemic embolism at dosages of 110 mg twice daily compared to 150 mg twice daily. The data 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 would reduce the efficacy in regards to the primary outcome.

The reduction in stroke and systemic embolism risk at the higher level of drug exposure is not unexpected in view of the relationship between trough concentration and clinical outcomes. However the inability to demonstrate any reduction in bleeding risk at the lower dose is unexpected.

Therefore, 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.

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.⁹⁰

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. 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 weight⁹¹ or where renal function is not

⁹⁰ Submission from: Pillans P (2012)

⁹¹ Submission from: Pillans P (2012)

appropriately calculated by prescribers⁹² (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).

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. Declining renal function may not be identified until the patient's next renal function test, which — according to the TGA advice — would be once per year in elderly patients (> 75 years) or in patients with moderate renal impairment (TGA 2011a). In the ROCKET-AF trial, patients randomised to rivaroxaban received the lower dose if their renal function was less than 50 mL/min (ROCKET AF study investigators 2010). 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 over 80 years and/or weight less than 60 kg (Granger et al 2011).

12.7.4 Bleeding control and management

There is no clinically proven antidote to reverse the effects of the new agents; this is particularly an issue in cases of bleeding or overdose, or where emergency surgery or switching between agents is required. The lack of an antidote was raised as an issue in a number of submissions,⁹³ and one submission outlined that this was a particular concern because GI bleeds are more frequent with dabigatran than with warfarin.⁹⁴

In its submission to the Review, the Cardiac Society of Australia and New Zealand outlined that the current management approach to serious bleeding with dabigatran is, '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'.⁹⁵

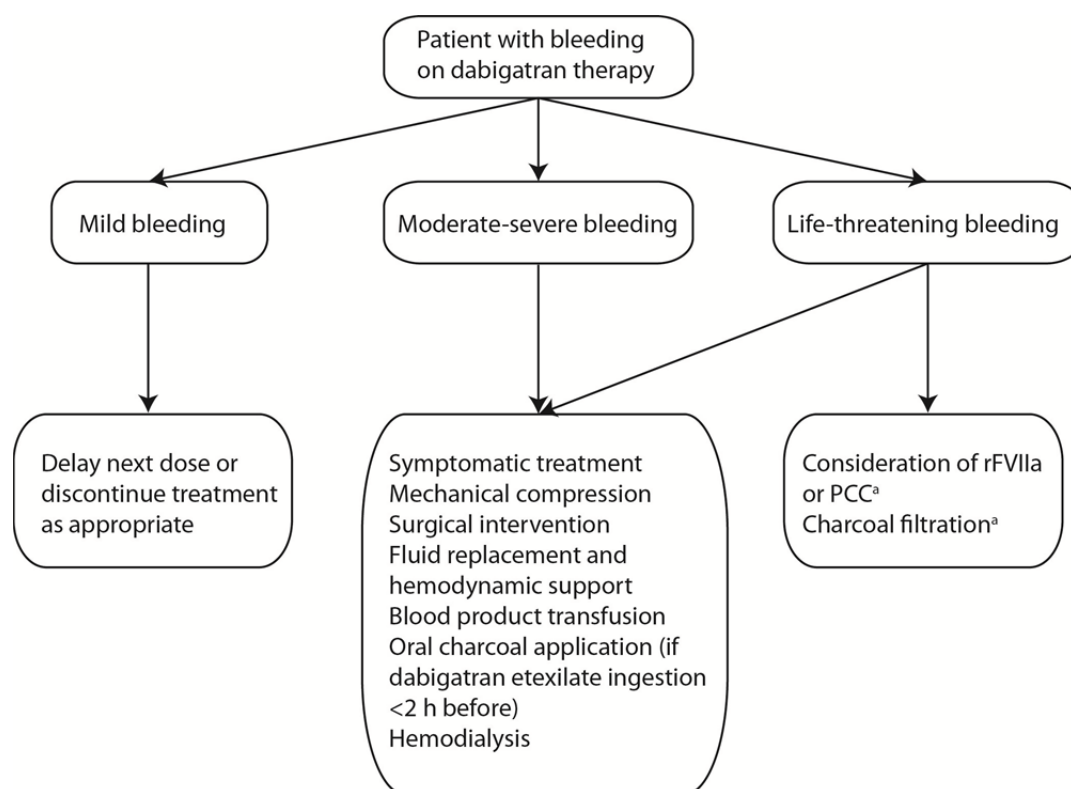
Potential strategies for managing bleeding events in patients who are on dabigatran have been suggested, including administering prothrombin complex concentrate and recombinant activated factor VIIa, and these have been incorporated into various local guidelines, such as the Queensland Health Guidelines for Managing Patients on Dabigatran (Pradaxa[®]) who Present to Hospital (Safe and Quality Use of Medicines and Anticoagulant Working Party 2011), which are similar to that shown in Figure 12.1.

⁹² Submission from Blombery PA (2012)

⁹³ Submissions from: National Stroke Foundation, Society of Hospital Pharmacists of Australia; Royal Australasian College of Physicians; Australasian Society of Thrombosis and Haemostasis, Haematology Society of Australia and New Zealand, and Australian and New Zealand Society of Blood Transfusions; New South Wales Therapeutic Advisory Group; Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists; Council of Australian Therapeutic Advisory Groups (2012)

⁹⁴ Submission from: Royal Australasian College of Physicians (2012)

⁹⁵ Submission from: Cardiac Society of Australia and New Zealand (2012)



PCC = prothrombin complex concentrations (non-activated or activated); rFVIIa = recombinant activated factor VII.
 a Recommendations base only on limited nonclinical data, there is no experience in volunteers or patients
 Source: Adapted from van Ryn et al 2010

Figure 12.1 Management of dabigatran in cases of bleeding

However, these strategies are based on limited nonclinical data. 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’ (CADTH 2012a). There is some evidence that prothrombin complex concentrate may reverse anticoagulation with rivaroxaban (Erenberg et al 2011), and this was identified in some submissions.⁹⁶ However, this evidence was from a trial of 12 healthy volunteers, and effectiveness was measured based on laboratory markers, the clinical meaningfulness of which are uncertain (CADTH 2012a).

Some authors have commented that ‘time is an important antidote with the NOACs’ due to their half-lives of less than 12 hours (Granger 2012); however, it must be acknowledged that these half-lives will be prolonged as renal function declines, particularly for dabigatran.

In its comments on the Issues and Options Paper, the Australasian College for Emergency Medicine stated:

A half-life of around 12 hours for NOACs, whilst shorter than warfarin, is still too long to wait for the anticoagulant to be cleared from a patient suffering an abnormal bleeding event, so reversal strategies are required. Vitamin K is cheap and easy to administer for abnormal bleeding during warfarin therapy, while recombinant factor VIIa, haemodialysis or charcoal haemofiltration are expensive and hard to administer.

The CADTH review acknowledged that reversal strategies for the NOACs are emerging; however, these are currently only supported by anecdotal case reports published as conference

⁹⁶ Submissions from: Flecknoe-Brown S; Australasian Society of Thrombosis and Haemostasis, Haematology Society of Australia and New Zealand, and Australian and New Zealand Society of Blood Transfusions (2012)

abstracts (CADTH 2012a). 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.

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. This is likely to be more relevant in patients aged 75 years and over receiving the higher dose of dabigatran since the NNH, with respect to major bleeding, is only 137.

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.

Perioperative management

The lack of reversal agent for dabigatran was raised as a specific concern in emergency settings⁹⁷ and perioperative settings⁹⁸, 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’.⁹⁹

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 (Healey et al 2012).

In its submission to the Review, the Cardiac Society of Australia and New Zealand discuss a report by (Lakkireddy et al 2012), which 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’.¹⁰⁰

12.7.5 Switching between anticoagulants

The issue of switching between anticoagulants was highlighted in the ROCKET-AF trial of rivaroxaban, where a greater number of strokes and systemic emboli were recorded in people switching from rivaroxaban to warfarin at the end of the trial (Fleming and Emerson 2011). The national guideline on AF management will need to address the issue of switching between anticoagulants.

12.8 Lack of a validated test for anticoagulation intensity

A number of submissions discussed the lack of a need for regular monitoring of therapeutic effect as an advantage of NOACs.¹⁰¹ This situation was identified as being a particular advantage in some groups of patients, including those for whom warfarin INR monitoring may limit work opportunities, those with poor venous access, rural patients and those who are travelling.

⁹⁷ Submission from: Australasian College for Emergency Medicine (2012)

⁹⁸ Submission from Nayagam (2012)

⁹⁹ Submission from: Royal Australasian College of Physicians (2012)

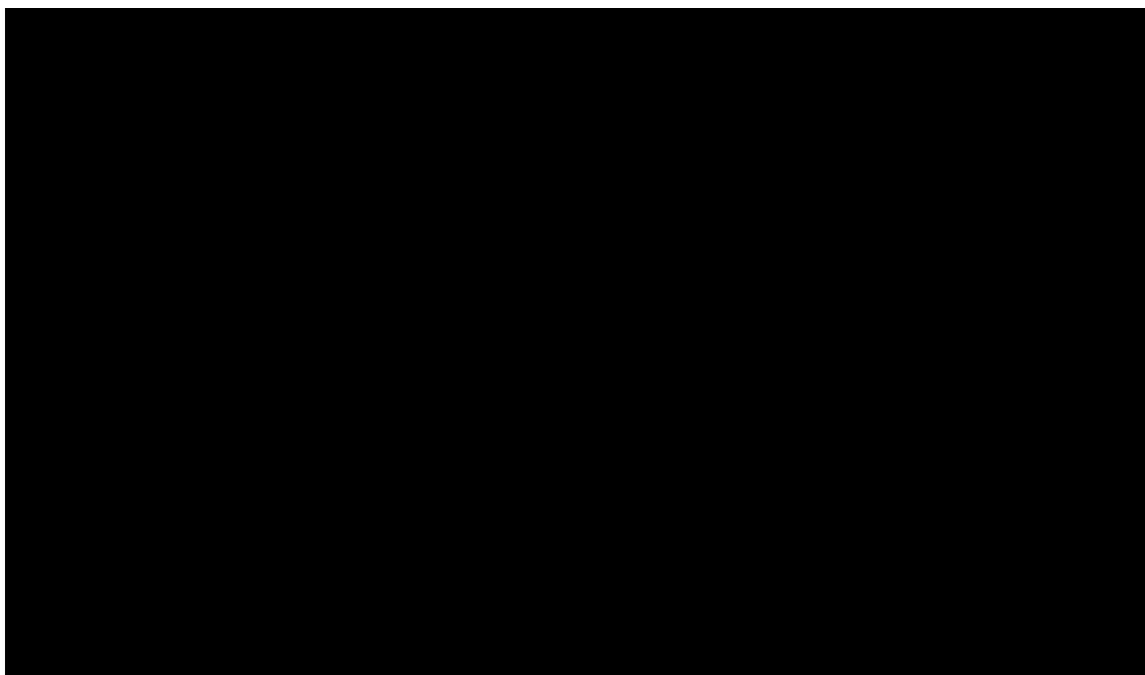
¹⁰⁰ Submission from: Cardiac Society of Australia and New Zealand (2012)

¹⁰¹ Submissions from: Cardiac Society of Australia and New Zealand; Stroke Society of Australia; National Stroke Foundation; Atrial Fibrillation Association; Blombery PA; Levendel A; Rao S; Australasian Society of Thrombosis and Haemostasis, Haematology Society of Australia and New Zealand, and Australian and New Zealand Society of Blood Transfusions; Victorian Government Cardiac Clinical Network; consumer; consumer; Motala IS; Amerena J; Rouhead D; Jones A; Bailey I (2012)

However, there is currently no routine tool for monitoring an individual patient on NOACs for under- or over-anticoagulation. This may be important because the effectiveness of dabigatran, in particular, depends on renal function, and the effectiveness of all NOACs may be influenced by interactions with other medicines and depends on patient compliance. Monitoring would also be of clinical benefit in situations such as overdose or serious bleeding, emergency surgery and in patients at the extremities of size.¹⁰²

Some coagulation assays provide a linear, dose-dependent correlation to the plasma concentration of the specific anticoagulant; for example, the HEMOCLOT thrombin-inhibitors assay for dabigatran (Douxflis et al 2012, Stangier and Feuring 2012, van Ryn et al 2010). However, a relationship such as the one between INR and clinical outcome for warfarin has not been established or validated for NOACs (CADTH 2012a). In particular, guidance is lacking on a link between plasma-concentration levels of NOACs, and set therapeutic ranges or bleeding risk ranges (CADTH 2012a). Also, not all coagulation assays are commercially available, and they lack standardisation and validation (CADTH 2012a).

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’ (Ten Cate 2012).



In contrast, the ability to measure the INR is a useful way to monitor the extent of anticoagulation in an individual patient taking warfarin. For example, a low INR can indicate poor compliance or increased dosage requirements; and an elevated INR can indicate the increased probability of the patient having a bleeding event, meaning that appropriate action can be taken (e.g. omitting a dose or reducing the dosage) to reduce the risk of bleeds.

¹⁰² Submissions from: Australasian Society of Thrombosis and Haemostasis, Haematology Society of Australia and New Zealand, and Australian and New Zealand Society of Blood Transfusions; Tideman P, St John A, Tirimacco R; Royal Australasian College of Physicians; Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists; Pillans P; Council of Australian Therapeutic Advisory Groups; Australian Association of Consultant Pharmacy (2012)

12.9 Interpatient variability in response to new oral anticoagulants

As discussed in Section 11.5, NOACs interact with a range of medicines, including those that also interact with warfarin. As NOACs become part of wider clinical use, interactions with other medicines will be identified. However, in the absence of a suitable surrogate measure, these interactions will not be identified until adverse reactions (i.e. strokes and bleeding) are seen. At this stage, NOACs lack the efficacy or toxicity safety signal that is available for warfarin and is used to identify patients who may be at greater risk.

Appendix 1 New oral anticoagulation agents — further information

Table A1 compares the baseline characteristics of trial participants in the three pivotal trials of new oral anticoagulants (NOACs).

Table A1 Comparison of baseline characteristics of trial participants for new oral anticoagulants

Baseline characteristics of study participants (active arm)	RE-LY (dabigatran)		ROCKET-AF (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 ischaemic attack; VKA = vitamin K antagonist (coumarins; i.e. warfarin in Australia, but internationally, phenprocoumon and acenocoumarol are used)

Table A2 outlines key elements of the design of each of the pivotal trials of the NOACs.

Table A2 Design of new oral anticoagulant trials

	RE-LY (dabigatran)	ROCKET-AF (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 followup (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 • aged > 74 years • aged 65–74 years 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% • aged > 74 years • 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 • aged > 74 years • 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 ischaemic attack; TTR = time in therapeutic range

Appendix 2 Community pharmacist-led anticoagulation services in New Zealand

The 'Community Pharmacist-led Anticoagulation Management Service' project demonstrated that a warfarin management system through accredited community pharmacies in New Zealand using point-of-care testing and a shared-care model led to a significant increase in the time in therapeutic range and a high degree of patient satisfaction (Shaw et al 2011). This trial was discussed in Section 9.3.2 under 'Pharmacist-led anticoagulation services'.

Pursuant to the success of this trial, Community Pharmacy Anticoagulation Management (CPAM) Services were included in the New Zealand Community Pharmacy Services Agreement that came into effect from 1 July 2012.¹⁰³

Objective

The objective of the CPAM Service is the provision of INR point-of-care testing by community pharmacy and adjustment of warfarin doses within a defined range with the aid of an approved decision-support system (*INR Online*¹⁰⁴) to:

- support patients and their families to better understand and manage their warfarin medication
- reduce warfarin-related adverse medication events
- improve accessibility and convenience for patients
- improve multidisciplinary management of patients prescribed warfarin in the community and
- reduce the burden on medical practitioners.

The CPAM Services model is part of a broader effort in New Zealand to develop a new patient-centred community pharmacy service model.

Funding

The funding levels for this service are up to NZ\$1.5million for 2012-13, NZ\$2.5million for 2013-14 and NZ\$3.5million for 2014-15.

Each community pharmacy that provides CPAM will receive NZ\$40.75 per month or NZ\$489 per year for each patient, and new providers are entitled to claim a NZ\$1,000 establishment fee. The average number of patients registered in the program per pharmacy is anticipated to be approximately 45.

Currently 16 pharmacies are offering this service, and an additional 50 pharmacies will be able to offer this in 2012-13. Increases will follow 2013-14 and 2014-15.

Shared care arrangements and management algorithms

The *INR Online* software that is being used for this program includes dosing algorithms, however patients with INRs outside the range of 1.5-4.0 are automatically referred back to the GP for review. The *INR Online* software is programmed to schedule testing every 4 weeks, with the maximum interval being 6 weeks.

¹⁰³ <http://www.centraltas.co.nz/LinkClick.aspx?fileticket=C98uzFAzSJQ%3d&tabid=242&mid=874>

¹⁰⁴ <http://www.inronline.net/>

The recommendation in the Standing Orders will be that patients who are referred to the service are already stable. The fee to pharmacists does not cover the test strips if the patient is tested frequently over the month.

Safety considerations/roles and responsibilities

- The Medical Practitioner retains overall responsibility for the patient's anticoagulation management but delegates that care to the pharmacist through a standing order. A strong professional relationship must be in place between the Medical Practitioner and pharmacy/pharmacist providing this service.
- Only accredited pharmacists trained by the approved CPAM Services training course (outlined further below) are able to provide this Service.
- The pharmacist is responsible for the quality assurance program that ensures the test device is providing reliable results. As an additional quality check it is recommended that the pharmacist works with an agreed local laboratory at least once a year to review quality assurance performance.

Operation of the service

Provision of the CPAM Service involves:

- undertaking patient assessment each time the test is undertaken in order to establish the patient's history and any symptoms, and if any patient factors may influence the results (e.g. a missed dose of warfarin)
- performing the INR test using a drop of blood on the test strip of an approved testing device
- dose adjustment made by the supervising pharmacist supported by an approved decision support tool with a validated dosing algorithm supported by published data
- giving the patient the results of the test and providing advice on the dose of warfarin to take each day until the next test as a hard copy dosing calendar
- giving the patient counselling and education about warfarin medication when required using an approved Warfarin Education Programme
- electronically providing the Medical Practitioner with information on the results of the monitoring and changes to the warfarin regime
- requesting medical review by the patient's Medical Practitioner if any INR is < 1.5 and > 4.0
- contacting the patient's Medical Practitioner directly if the pharmacist is concerned about the patient's symptoms, results, or the dose recommendation
- keeping a full record of the patient's care management plan as provided by the approved on-line decision support tool
- participation in a quality assurance programme
- auditing anticoagulant management by regularly monitoring anticoagulant control of individual patients and cumulative results using approved decision support software
- auditing compliance for timeliness of testing to identify patients with compliance issues using the approved decision support software, and
- recording the incidence of adverse events (in particular the incidence of bleeding) including hospital admissions using the approved decision support software.

Key performance indicators

Pharmacists are required to provide quarterly reports to the New Zealand Ministry of Health with information including documentation of the following Key Performance Indicators:

- compliance (tests on time, 1–3 days, 4–7 days, 7+ days)
- control (tests in range, tests above, tests below)
- adverse events.

Pharmacist training

The training requirement for pharmacists wishing to be accredited to provide CPAM services will be in the form of a one-day course which will be provided by the New Zealand College of Pharmacists and includes the following components:

- anticoagulation management knowledge, provided by a haematologist, with assessment exam
- training on using the hardware
- training on the Clinical Decision Support Software
- patient consultation demonstration.

Criteria for pharmacy participation

Successful providers will be chosen by a national panel and the District Health Boards as part of an expression of interest process. They will be selected according to the following criteria:

- quality — the ability to provide a high quality, value-added service.
- accessibility — location, hours of operation, servicing of priority groups.
- staffing — the minimum staffing is at least 2.0 full time equivalent pharmacists per pharmacy.
- numbers of patients on warfarin — demonstration that up to 45 patients would be registered in the service within each site.
- evidence of strong local primary care support for the service.
- geographical spread — an equitable number of providers within each district and across New Zealand.

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