Submission to the Review of Anticoagulation Therapies in Atrial Fibrillation

February 2012

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Australia

TABLE OF CONTENTS

Appendix A: Dabigatran Product Information

Appendix B: Dabigatran Public Summary Document

Appendix C: Consumer Market Research Report

Appendix D: Interventions to Improve Warfarin Use: Literature Search Methodology

TABLES

FIGURES

ABBREVIATIONS

AACP	Australian Association of Consultant Pharmacists
ACS	Acute coronary syndrome
AE	Adverse event
AF	Atrial fibrillation
ACE	Angiotensin converting enzyme
AIHW	Australian Institute of Health and Welfare
ALM	Active learning module
ANZHSN	Australia and New Zealand Horizon Scanning Network
ATRA	Angiotensin II receptor antagonist
AUC	Area under the curve
bid	bis in die (twice daily)
CADTH	Canadian Agency for Drugs and Technologies in Health
$CHADS_2$	Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke (or TIA) doubled
CHA_2DS_2-VASc	Cardiac failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled) – Vascular disease, Age 65-74 and Sex category (female)
CMWG	Compliance with Medicines Working Group
CPAMS	Community Pharmacist-led Anticoagulation Management Service
CPD	Continued professional development
CrCl	Creatinine clearance
CSANZ	Cardiac Society of Australia and New Zealand
cTTR	Centre time in therapeutic range
DASS	Duke Anticoagulation Satisfaction Scale
DVA	Department of Veterans Affairs
DVT	Deep vein thrombosis
EMA	European Medicines Agency
EQ-5D	EuroQoL – 5 dimensions
ESC	European Society of Cardiology
FTE	Full time equivalent
GP	General Practitioner
GPCE	General Practitioner Conference and Exhibition
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR,Elderly (>65), Drugs/alcohol concomitantly
HMR	Home Medicines Review
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial haemorrhage
INR	International normalised ratio
MBS	Medicare Benefits Schedule
MPR	Medication possession ratio
MEMS	Medication event monitoring system
MGSM	Macquarie Graduate School of Management
MI	Myocardial infarction
NICE	National Institute for Health and Clinical Excellence
NHMRC	National Health and Medical Research Council
NPS	National Prescribing Service
NR	Not reported
NS	Not significant

NSF	National Stroke Foundation
NVAF	Non-valvular atrial fibrillation
OR	Odds ratio
OTC	Over the counter
PBS	Pharmaceutical Benefits Scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PDC	Proportion of days covered
PFP	Product familiarisation program
PGA	Pharmacy Guild of Australia
PoCT	Point-of-care testing
PROBE	Prospective, Randomised, Open-label, Blinded Endpoints
PSA	Pharmaceutical Society of Australia
PSD	Public Summary Document
PSM	Patient self management
PST	Patient self testing
PSUR	Periodic Safety Update Report
PwC	PricewaterhouseCoopers
QUM	Quality use of medicine
RACGP	Royal Australian College of General Practitioners
RCT	Randomised controlled trial
RE-LY	Randomized Evaluation of Long-term anticoagulation therapY
SHPA	Society of Hospital Pharmacists of Australia
SNP	Single nucleotide polymorphism
TABS	Tool for Adherence Behaviour Screening
TACT	The Ambulatory Care Team
TGA	Therapeutic Goods Administration
TIA	Transient ischaemic attack
TTR	Time in therapeutic range
VKA	Vitamin K antagonist
WHO	World Health Organisation

1. OVERVIEW

Despite over 50 years of clinical experience managing warfarin there still remains a significant unmet need for new stroke prevention medicines. This submission is made so that patients can have access to dabigatran via the Pharmaceutical Benefits Scheme (PBS). Without the PBS, patients who are mainly seniors, will not be able to afford a medicine proven to prevent more strokes and to cause fewer life-threatening bleeds than warfarin. Dabigatran eliminates the need for routine blood monitoring and dietary restrictions, and importantly dabigatran is cost-effective versus currently available medicines. Based on the available evidence of cost-effectiveness, and in accordance with the PBAC's recommendation, dabigatran should be listed without delay while efforts are ongoing to demonstrate the cost-effectiveness of any interventions to improve the use of warfarin. It is important to note there has been no new class of oral anticoagulants for over 50 years until dabigatran was approved. There is a clinical need for new oral anticoagulants like dabigatran, which are less problematic for patients to take than warfarin. The Review needs to consider the patient-relevant issues in addition to the clinical and safety benefits for dabigatran. Given the significant clinical need, new stroke prevention medicines like dabigatran are needed now, rather than subject to delayed access.

Dabigatran etexilate is a direct thrombin inhibitor which received approval for the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (NVAF) from the Therapeutic Goods Administration (TGA) in April 2011. This followed the results of the 18,000 patient RE-LY study, comparing two doses of dabigatran (110 mg and 150 mg) taken twice daily with well controlled, dose-adjusted warfarin in patients with NVAF at moderate-to-high risk of stroke. Dabigatran received a positive recommendation from the Pharmaceutical Benefits Advisory Committee (PBAC) in March 2011, and has received approval for stroke prevention from over 50 regulatory agencies globally, including major markets such as the US, Canada, and the UK. To date, over half a million atrial fibrillation patients around the world have been treated with dabigatran for the prevention of stroke. Dabigatran is listed on the PBS for the prevention of venous thromboembolism following hip or knee replacement surgery. Further information on dabigatran can be found in the approved Product Information (Appendix A).

Clinical need for new anticoagulants

Patients with atrial fibrillation (AF) are at an increased risk of stroke. Strokes experienced by these patients are severe, and result in high rates of mortality and functional disability. Of all hospitalised ischaemic strokes 25% are AF related, with a mortality rate of around 20% at 30

days post stroke. The cost of strokes in patients with AF is estimated at around $400 million per year.

Despite several extensive educational campaigns by bodies such as the National Prescribing Service (NPS), over 20% of patients with moderate-to-high stroke risk do not receive any stroke prevention medicines. Many moderate-to-high risk patients receive aspirin even where warfarin is indicated. A recent clinical audit conducted by the National Stroke Foundation reported that 70% of patients admitted to hospital as a result of an AF-related stroke were not receiving any anticoagulant. Only 34% of those patients admitted for a recurrent stroke were taking an anticoagulant. This is consistent with overseas data. Reasons for underuse of anticoagulants includes the narrow International Normalised Ratio (INR) range for warfarin and the resources needed to keep patients controlled, the inconvenience of regular monitoring, the fear of catastrophic bleeding, poor patient compliance, the complicated dosing and titration of warfarin with multiple strengths taken concurrently, as well as drug and food interactions. There is clear evidence that a significant clinical unmet need exists for effective, well tolerated anticoagulants that are easier to manage than warfarin, particularly due to the high proportion of patients who remain untreated or are on suboptimal treatments. This appears to be even more important in rural and regional areas where the use of warfarin is very low.

Positive PBAC recommendation for dabigatran

The PBAC at its March 2011 meeting recommended the listing of dabigatran as an Authority (streamlined) item for the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation who are at moderate-to-high risk of developing stroke or systemic embolism as evidenced by one or more risk factors. Further information on the PBAC's evaluation of dabigatran can be found in the Dabigatran Public Summary Document (Appendix B).

The evaluation of medicines to establish cost-effectiveness by the PBAC is widely regarded as one of the most rigorous health technology assessment processes in the world. In establishing the cost-effectiveness of medicines for the Australian public the PBAC undertakes a thorough review of clinical and economic data to establish the effectiveness, and cost-effectiveness of medicines proposed for listing. In making its recommendations the PBAC has the option to recommend listing, to reject a listing or to defer a decision. Under the *National Health Act (1953)*, the PBAC has to consider the *"effectiveness and cost of therapy"* and has to be satisfied that the new medicine provides a significant improvement in efficacy or a reduction in toxicity over alternative medicines.

In 2011, the PBAC rejected over 40 submissions and deferred around 8 submissions. The commonly cited reasons for a rejection include uncertain clinical need, uncertain cost-effectiveness, uncertain clinical benefit, and uncertain clinical place of therapy. Reasons for deferrals have included the need for further discussions with sponsors or clinicians, and to seek advice from Medicare Australia to implement a listing. If the Committee believed that there were any reasons to reject or to defer the listing of dabigatran then it would have made that recommendation as it is able to under the Act. It is not unusual for the PBAC to also comment on other issues for consideration when recommending a new medicine for listing. Any wider issues considered for dabigatran were not considered sufficient to lead to a rejection or a deferral by the PBAC. It is clear that the PBAC was satisfied that dabigatran met all requirements, including cost effectiveness, to allow it to be listed on the PBS, and made its recommendation accordingly. The PBAC noted in the minutes from its March 2011 meeting, *"dabigatran represents a safe, efficacious and cost effective therapy for 'at risk' patients with atrial fibrillation for the reduction of stroke and systemic thromboembolism. These reductions represent important reductions in morbidity, and can be expected to result in mortality reductions."*

Impact on patients with non-valvular atrial fibrillation

The vast majority of patients with atrial fibrillation are likely to be seniors (on concessional or veteran benefits) and will therefore be the least able to afford the cost of dabigatran while it is not listed on the PBS. Thus, the decision to delay the listing of dabigatran disproportionately affects the most vulnerable patients. Consequently, many of these patients will remain at high risk of stroke; especially those who are treated with less effective stroke prevention medicines such as aspirin and clopidogrel, those unable to be controlled on warfarin, or the significant proportion that remain untreated due to no other treatment options being available. Patients currently treated with warfarin who may be prescribed dabigatran will also benefit from a reduced risk of stroke and lower risk of serious bleeding events such as intracranial haemorrhage.

Stroke prevention treatment is individualised for each patient based on the balance of stroke and bleeding risk. There is no justifiable reason to restrict the population eligible for dabigatran based on a higher stroke risk profile or a need to take and fail on other stroke prevention treatments before being eligible for dabigatran. Any such recommendation by the Review would in essence lead AF patients to unnecessarily experience poor health outcomes before being eligible for dabigatran, which has already been deemed to be a cost-effective first-line treatment for patients at moderate-to-high risk of stroke by the PBAC.

Safety Advisory Alerts for dabigatran

The background to the Terms of Reference for the Review states that there have been Safety Advisory Alerts issued by the TGA for dabigatran to highlight bleeding-related adverse events and renal monitoring requirements. It is important to note that Safety Advisory Alerts are commonly issued by the TGA for new medicines, with over 50 alerts issued in 2011. The TGA is the appropriate regulatory body to evaluate the adverse events of all medicines. As the TGA has noted, the purpose of these reports is to advise consumers, health professionals and industry about new safety information and that an alert does not necessarily mean that a product is considered to be unsafe. The TGA has noted (3 November 2011) that as more patients commenced on dabigatran a corresponding increase in the number of bleeding-related adverse event cases were reported. The TGA also noted that in clinical trials for stroke prevention in atrial fibrillation, there was a lower risk of bleeding with dabigatran compared to warfarin. The second Safety Advisory Alert (3 November 2011) reinforces the importance of assessing kidney function to minimise the risk of bleeding. This alert was issued following the action by the company to voluntarily request an update to the approved Product Information to highlight this advice. This information was also proactively communicated by the company to healthcare professionals. These TGA reports as well as post-marketing data from around the world are discussed in further detail in this submission. The types of adverse events observed for dabigatran are consistent with those outlined in the approved Product Information. Most of the reports in Australia have been actively reported by the company as our representatives and other employees frequently interact with prescribers participating in the Product Familiarisation Program. In summary, these alerts identify the types of adverse events reported to the TGA, which are outlined in the approved Product Information, and reinforce that patients should be selected for treatment based on guidance in the approved Product Information.

Anticoagulants by nature increase the potential for bleeding. Intracranial haemorrhage is one of the most feared consequences of treatment with warfarin, and one of the main reasons for its limited use. In RE-LY, dabigatran significantly reduced the risk of intracranial haemorrhage by up to 70%, as well as significantly reducing the risk of life-threatening bleeding compared to warfarin. The higher 150 mg dose of dabigatran (taken twice daily) significantly increased gastrointestinal bleeding (GI) while the 110 mg dose (taken twice daily) had a similar level of GI bleeding and significantly less major bleeding than well controlled warfarin. The net clinical benefit in terms of stroke reduction and bleeding for dabigatran was superior to warfarin, and led to registration in over 50 countries. Since dabigatran has become available around the world, Boehringer Ingelheim has closely monitored and regularly shares the latest adverse event data with agencies such as the

TGA. With any new medicine, healthcare professionals would be expected to be particularly vigilant with regards to adverse events. Since launch the adverse events reported for dabigatran are consistent with what would be anticipated from the extensive clinical trial program.

Boehringer Ingelheim has taken a very proactive approach both with healthcare professionals and regulatory authorities to advocate appropriate prescribing, through appropriate patient and dose selection, and reporting of adverse events. While much rigour is being employed in the monitoring of dabigatran there is sparse high quality data to assess the impact of adverse events due to warfarin in Australia, as noted recently in Parliament. The submission discusses recent overseas data to demonstrate that warfarin is a leading cause of hospitalisations for adverse drug events in the US, accounting for one third of all drug-related hospitalisations. Vitamin K antagonists are the second most common cause of hospital admissions for drug reactions in the UK. Similar research data is not readily available in Australia, but there is no reason to believe that the data would differ. In 1999, it was estimated that warfarin-related hospitalisations cost the health budget around $100 million per annum. This cost is likely to be much higher now.

Boehringer Ingelheim has undertaken an extensive program of educational activities for general practitioners, a wide range of specialist physicians, pharmacists and patients to encourage the quality use of medicines. These initiatives, including examples, are discussed in detail in this submission.

Interventions to improve the use of warfarin

Boehringer Ingelheim supports the evidence based approach advocated by Government through the established PBAC evaluation process. We also support that the current Review should be evidence based. The RE-LY study, which found a significant reduction in key clinical outcomes such as haemorrhagic stroke, intracranial haemorrhage and other bleeding events when patients were followed for up to 36 months, is regarded as high level clinical evidence, and forms the basis of the cost-effectiveness evaluation undertaken by the PBAC. Data from RE-LY is directly applicable to the Australian population. The time-in-therapeutic range (TTR) from RE-LY (mean TTR of 64%) is comparable to studies of Australian clinical practice (range in TTR of 50-69%). This is further discussed in the submission. The cost-effectiveness of interventions such as community-based education, point-of-care testing, home medication reviews, anticoagulation clinics, and pharmacogenetic testing need to be evaluated thoroughly to demonstrate efficient health outcomes. This evaluation has to be considered in the context of the forgone health outcomes by delaying the listing of cost-effective medicines such as dabigatran.

This submission presents a systematic review of the literature in order to identify interventions which could be used to improve the use of anticoagulants in the Australian clinical setting. This included new strategies for anticoagulant management as well as methods of optimising existing models of care and currently available interventions. The systematic literature review was conducted in order to identify all Australian studies which met these criteria. The effectiveness of these interventions is presented and discussed in detail in this submission. A review of the international literature was also conducted.

Only one intervention has been formally assessed in Australia: point-of-care testing. This was assessed by Medical Services Advisory Committee (MSAC) in 2005 and was not considered cost-effective. The other interventions identified in the literature search had varying levels of clinical effectiveness and cost effectiveness. The trials were generally lower level evidence (i.e., there were few randomised controlled trials) and were of short term duration. This is particularly relevant given the chronic nature of treatment in AF patients. The short term improvements in outcomes seen in some studies may not be maintained over the longer term. The outcomes assessed in the trials were generally not patient relevant, typically assessing intermediate outcomes such as INR control rather than clinically relevant outcomes such as strokes and bleeding events. The international evidence is confounded by the differences in health care systems. Interventions which are effective overseas may not be as effective in the Australian clinical setting, highlighting applicability issues. Strategies such as anticoagulation clinics, for example, would need to be piloted and evaluated in Australia prior to being introduced nationally so that optimum continuum of care could be ensured. It is not appropriate to recommend any intervention to improve warfarin's use that has not been evaluated to the same rigorous level and evidence based evaluations undertaken by the PBAC.

In terms of interventions studied in Australia, although some hospital based interventions may be beneficial at the level of an individual hospital, they do not address the issue of achieving and sustaining a longer term therapeutic INR. There was no evidence that community prescriber training improved INR control and limited evidence that it could improve the rate of warfarin prescribing for patients in which it was appropriate. The overall evidence indicates that point-of-care testing is less effective than laboratory testing. There was a reduction in bleeding outcomes associated with home medication reviews and patient education; however the interventions were assessed over a limited time period.

The key limitation of the literature is the lack of long-term data assessing clinically relevant outcomes. An important difference between medicines and interventions is that the impact of an intervention often attenuates over time, as demonstrated in some studies. This is not unexpected given that these interventions often require a change in behaviour or additional

clinical processes, which if not reinforced may not be effective. Data from a study may represent the best practice, with data collected while prescribers and patients are being monitored and reminded of the intervention being assessed. This is particularly relevant in the studies discussed in the submission, which were all unblinded and suffer from selection and other biases. It is therefore likely that the clinical benefits described in the publications would not be as large if an intervention was introduced to all prescribers and patients in Australia.

An additional limitation is the accessibility issues associated with implementing these interventions, particularly if introduced in preference to medicines which are available through all pharmacies in Australia. In contrast, not all prescribers or pharmacists are willing or able to provide the additional services required for the interventions. This is most strikingly demonstrated by the low uptake of Government funded home medication reviews (HMRs). A report commissioned by the Department of Health and Ageing to evaluate the HMR program concluded that less than 10% of general practitioners participated in the program. There is also evidence presented in the submission that some interventions are only applicable to a subset of patients prescribed warfarin.

In terms of the costs of implementing the interventions, it is important to note that the costs presented in this submission are additional to the costs of warfarin and in most cases monitoring costs. The costs are conservative in that many costs associated with the implementation of the programs are not accounted for (e.g., costs of pilot programs, administration costs, costs of reviews). Some programs, such as the introduction of specialised anticoagulation clinics would need to be trialled in Australia before being adopted given the significant differences in Australian treatment practices and geography compared to the overseas environments in which they have previously been operated.

In summary, evidence for the efficacy of dabigatran comes from a high quality clinical trial which found a significant reduction in key clinical outcomes such as ischaemic and haemorrhagic strokes, and bleeding events when patients were followed long term. In contrast, there is no evidence that any intervention assessed to date is associated with a significant long-term improvement in clinically relevant outcomes. While the absolute cost of many of these interventions may appear lower than that for new oral anticoagulants, making health care decisions based purely upon budget impact is not reasonable. Inefficient spending on interventions that are not cost-effective represents poor investment in the delivery of health outcomes. There is no evidence of acceptable cost-effectiveness for any of the warfarin interventions discussed in the submission.

There are also significant barriers to ensuring that any intervention is available to all warfarin patients. Any intervention aimed at improving warfarin's use will most likely only be appropriate for some patients. Therefore, any recommendation for patients to undertake an intervention to improve warfarin's use prior to gaining access to new medicines like dabigatran would place some patients at higher risk of developing poor health outcomes such as stroke and bleeds, while establishing which patients improve on the intervention. These issues, as well as the cost-effectiveness of interventions must be considered when evaluating the relative merits of warfarin interventions. This and the clinical need for new stroke prevention medicines means that it would be unacceptable for all patients to also wait until cost-effectiveness can be demonstrated for any of the interventions for warfarin patients, before access is permitted. High quality evidence for medicines such as dabigatran exists, demonstrating cost-effectiveness over current medicines such as warfarin and aspirin. The implementation of any intervention throughout Australia also needs to be considered especially in rural and remote areas where warfarin use is lowest. Furthermore, the vast majority of patients with AF are likely to be seniors who are least likely to be able to afford the cost of dabigatran while it remains unlisted on the PBS. In failing to recognise the PBAC's recommendation the Government is creating a division between those who can afford new, effective stroke prevention medicines and those who are left vulnerable.

Issues raised in Parliament

The Government has noted several reasons that led it to initiate the Review. It is important to note that the PBAC has considered all the relevant matters to enable the Committee to recommend the listing of dabigatran on the PBS. This submission presents a systematic review of the warfarin interventions as well as an estimation of some of the direct costs involved. While some interventions have a low cost as a one-off intervention, for example education, to truly consider any of the interventions as representing value for money, a detailed cost-effectiveness analysis is required. There is no evidence that any of the interventions represent cost-effective options. The Government has also noted that dabigatran will cost $1 billion over the forward estimates (over five years). This statement is misleading as it ignores the costs associated with the reductions in strokes, major bleeds, and the use of medicines such as warfarin and aspirin as well as the ongoing monitoring costs for warfarin. This also ignores the wider indirect costs such as productivity costs forgone or carer costs associated with caring for patients disabled by stroke. This also ignores the chronic nature of treatment of stroke prevention, which is similar to the treatment of other important risk factors such as the treatment of hypertension and elevated lipids. Over the past five years the Commonwealth has spent around $8 billion on antihypertensive medicines and lipid-lowering medicines. Since dabigatran is the first to be approved for PBS

listing, the costs to the Commonwealth will be capped to an agreed level that will be shared by all subsequent entrants. Finally, the Government has raised the issue of safety concerns for dabigatran. This is discussed above and in detail in the submission. Boehringer Ingelheim remains concerned that safety is being used as a reason for this review. As noted above the TGA is the appropriate regulatory agency to consider safety.

Policy implications

It is unprecedented that following rigorous evaluation of dabigatran by the PBAC, through a well established process, the Government should decide to initiate an additonal review. In essence the Government has initiated a review of its own highly respected health technology evaluation process. This establishes a dangerous precedent for all future medicines submitted for PBAC evaluation in that the Government can impose a review of a positive recommendation from the PBAC before the listing of a new medicine on the PBS.

The Government decision to initiate the Review, despite the recommendation of the PBAC, is another form of politicisation of the reimbursement process, following from the deferrals of several drugs in early 2011. The delaying of new medicines for financial reasons is poor policy and will adversely impact the health of Australians. This is also contrary to the National Medicines Policy as it withholds affordable access to patients and impacts the viability of the industry. The aim of this policy is to improve the health outcomes for all Australians. In its submission to the Senate, Deakin Health Economics noted *"...it could be argued that when the PBAC makes a determination that a drug is cost-effective, this means that it can be expected that the returns (in terms of impact on the overall economy from gains in the health of the population) justify the investment....the decision to defer the listing of drugs that have been accepted to be superior to the alternatives currently available and that have been accepted as representing value for money, is therefore perplexing."* The decision to delay the listing of dabigatran pending further review is no different to the PBS deferrals of last year. It is just an evolution of a policy deemed to be unacceptable by all stakeholders except the Government.

The Government's decision to delay the listing of dabigatran will lead to poor health outcomes in many patients especially those who will experience stroke as a result of the delayed listing. There is no justifiable reason to delay the listing of dabigatran while the Government considers the benefits of improving the use of warfarin. The Government's decision to delay the listing until this Review is complete and has issued a report that is considered by the PBAC, and again by Government, is also placing significant additional hurdles on sponsors such as Boehringer Ingelheim to provide Australians with affordable access to new medicines.

2. CLINICAL NEED FOR NEW STROKE PREVENTION MEDICINES

Atrial fibrillation (AF) is a cardiac arrhythmia characterised by uncoordinated atrial activation with consequent deterioration of mechanical function. Dabigatran is used to prevent stroke or systemic embolism in non-valvular atrial fibrillation (NVAF) in patients at moderate-to-high risk of stroke. This submission will use the terms AF and NVAF throughout. Warfarin and aspirin are not restricted for use for any indication. AF is associated with a hypercoaguable state and a predisposition to thrombus formation.

AF is estimated to have a prevalence of around 2% of the population (Sturm *et al* 2002). The prevalence of AF will increase over time as the Australian population ages. AF is the leading cause of ischaemic stroke and AF patients have an approximate five-fold risk of stroke compared to those in sinus rhythm (Wolf *et al* 1991). Many patients only have AF diagnosed once they suffer a stroke or systemic embolism. Atrial fibrillation is the third most common risk factor for developing stroke (National Stroke Foundation 2011).

The majority of strokes in the presence of AF result from haemostasis in the left atrium leading to thrombus formation and embolism. The strokes experienced in AF patients are severe and have high rates of mortality and functional disability (Lin *et al* 1996). Strokes in patients with AF are more likely to affect the cerebral cortex, the part of the brain most directly responsible for consciousness, with essential roles in perception, memory, thought, and mental ability.

Gattellari found that 25% of all hospitalised ischaemic strokes are AF related. Australian patients with AF were significantly more likely to die from their stroke at 30 days (19.4% versus 11.5%, respectively), at 90 days (20.9% versus 15.8%, respectively), and at 365 days (38.5% versus 22.6%, respectively) than those without AF. Patients with AF accessed more in-hospital rehabilitation than those without AF ($p<0.0001$). 90-day stroke survivors with AF spent an average 21.5 days in hospital versus 16.6 days in those without AF (Gattellari *et al* 2011). Recurrent strokes are also more common in patients with AF.

The costs and Quality Adjusted Life Year (QALY) burden of stroke

The National Stroke Foundation (2011), estimated that there will be around 60,000 strokes in Australia in 2011 and that the cost of stroke is $2.14 billion. Around $400 million in stroke costs each year will be due to strokes in patients with AF. AF imposes a significant economic burden on the Australian population, including direct healthcare

costs and indirect costs such as lost productivity. Average QALY losses for first-ever stroke were estimated at 5.09 for ischaemic stroke and 6.17 for intracerebral haemorrhage (Cadilhac *et al* 2010).

Cadilhac estimated the direct five-year costs (2004 figures) for first-time stroke to be $57,106 and $49,995 for ischaemic stroke and intracerebral haemorrhagic stroke, respectively (Cadilhac *et al* 2009).

Stroke prevention medicines listed on the PBS and the need for new treatments

On the PBS the main medicines used in the prevention of stroke for NVAF patients are aspirin and warfarin. Clopidogrel is used off label. However, this will not be considered any further in this submission for the Review since the PBAC did not assess it as a relevant comparator. In terms of the currently listed drugs on the PBS, low risk patients are treated with aspirin. Moderate-to-high risk patients are treated with warfarin or aspirin. The decision to treat a patient is made on an individual patient basis, with the treating clinician balancing the risks and benefits of warfarin versus aspirin. Moderate-to-high risk patients can be prescribed warfarin. Any patients who are eligible for warfarin therapy, but are contraindicated to it, receive aspirin or remain untreated. The key guidelines available overseas are discussed in Section 3. All these guidelines now include the use of dabigatran for moderate-to-high risk patients.

While the Review will largely focus on warfarin and interventions to improve its use, asper the Review Terms of Reference, it is important for the Review to also consider the high proportion of patients on aspirin which is much less effective than warfarin, as well as the proportion of patients receiving other medicines off-label and particularly those who remain untreated. The submission to the PBAC for dabigatran used a conservative proportion of 50% of patients on warfarin and 50% on aspirin. In addition, the main sensitivity analysis assessed 40% on warfarin; 40% on aspirin and 20% on no treatment. These proportions are very conservative. These proportions for the year ending in 2011 would equate to around 127,000 patients on warfarin, around 127,000 patients on aspirin, and around 64,000 untreated patients with a diagnosis of NVAF. Note these patient numbers exclude those with low risk of stroke and those with valvular AF, with the prevalence based on Sturm *et al,* 2002. The proportion of untreated patients in Australia is likely to be much greater than 20% as will be discussed below. If the Government is genuine about improving the health outcomes of Australians with NVAF then it would not delay the listing of dabigatran as the clinical need for newer stroke prevention medicines

is great, with many patients untreated or on sub-optimal treatments such as aspirin despite being eligible for warfarin.

Warfarin

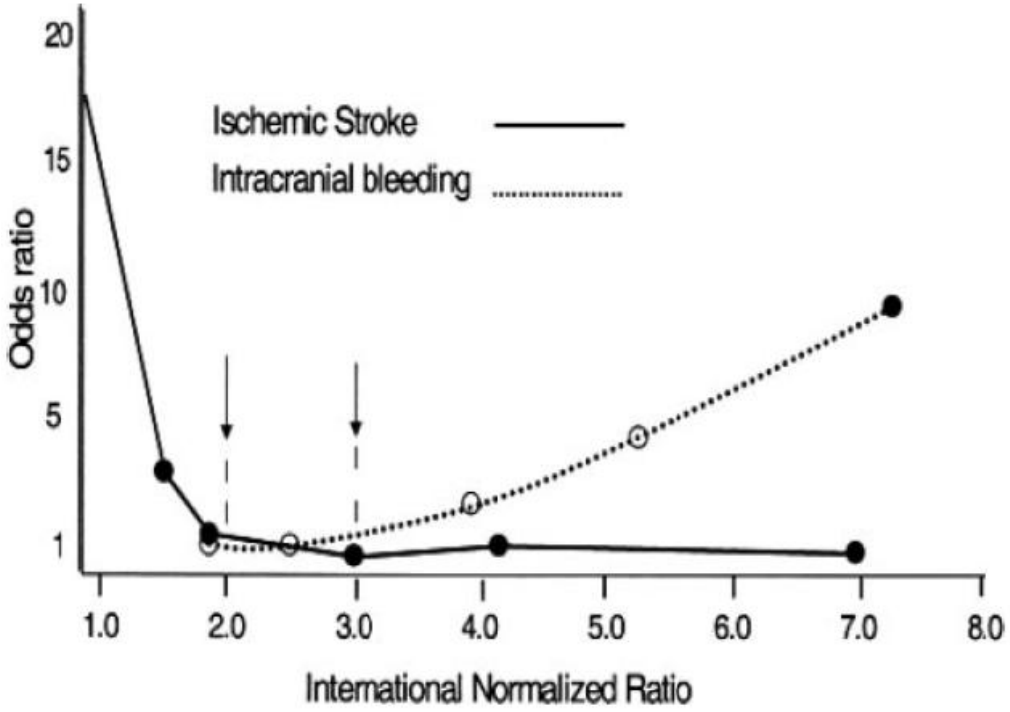
Warfarin is an efficacious antithrombotic drug, but is associated with a number of issues which limit its effective use. These include its narrow therapeutic range, high rate of adverse events, the inconvenience of frequent monitoring, and many drug-drug and drug-food interactions. Consequently, a significant proportion of eligible AF patients do not receive appropriate therapy which will be discussed below.

Warfarin is a vitamin K antagonist (VKA) which causes an anticoagulant effect by inhibiting synthesis of four vitamin K-dependent clotting factors: II, VII, IX and X. Warfarin has been available for more than 50 years, and has a well known efficacy and safety profile. A meta-analysis of 29 published randomised trials of 28,044 patients with NVAF described the efficacy and safety of currently available antithrombotic agents for stroke prevention (Hart *et al* 2007). Compared with placebo or no treatment, warfarin (six trials, 2,900 participants) reduced the risk of stroke by 64%. In comparison, aspirin reduced the risk of stroke by 21%.

Narrow therapeutic margin of warfarin

A major disadvantage of warfarin is its narrow therapeutic margin. The intensity of anticoagulant therapy is measured using INR (International Normalised Ratio). For stroke prophylaxis in patients with AF, the recommended target INR range is 2.0 to 3.0. In order to achieve a balance between optimising the therapeutic effect and minimising the risk of serious adverse events such as bleeding, patients must have their INR monitored regularly in order to ensure the INR is maintained within this range. Warfarin is only effective within a relatively narrow therapeutic margin: under-anticoagulation increases the risk of stroke and over-anticoagulation increase the risk of bleeding, including intracranial haemorrhage (ICH). The relationship between INR and stroke and intracranial bleeding is shown in Figure 1.

Figure 1 Relationship between anticoagulation intensity (INR) and risk of ischaemic stroke or intracranial bleeding



Source: Fuster *et al* 2006

The risks associated with poor INR control are particularly relevant as it is well established that the degree of INR control is highly variable across patients receiving warfarin. The level of INR control in Australia will be discussed in more detail below.

One of the reasons for poor INR control is that patients are often on warfarin while they are in hospital. INR is often poorly controlled at hospital discharge, which may reflect the trend for early hospital discharges (Jackson *et al* 2004d). Jackson found that found that 33% and 26% of patients in usual care were in the sub-therapeutic or supra-therapeutic range, respectively. Another Australian study reported that when 62% of patients were discharged from hospital, their INR was outside of the therapeutic range (Bereznicki *et al* 2007).

A number of factors affect the ability to maintain INR within the target therapeutic range. These include i) variable response of patients to warfarin, ii) warfarin has many drug-drug and drug-food interactions and iii) a complex dosing regimen, requiring patient education as well as increasing the risk of overdose or under-dosing.

INR monitoring and dose adjustments

As the dose-response relationship with warfarin is unpredictable, the recommended initiation dose for oral anticoagulation is between 5 mg and 10 mg for the first 1-2 days for most patients, with subsequent dosing based on the INR response. Warfarin is available in four strengths (1mg, 2 mg, 3mg and 5 mg); many patients have to take multiple strengths at the same time so that their INR is controlled. The inter-individual variability of response to warfarin and the multitude of patient-specific factors influence the anticoagulant effect, therefore dosing needs to be titrated.

Intensive INR monitoring is required for the duration of therapy to ensure that anticoagulation is maintained within the recommended target therapeutic range. Testing is required several times a week (often daily) at the start of therapy until the target INR has been achieved and maintained for at least 2 consecutive days; then two or three times weekly for 1 to 2 weeks; and may be reduced gradually to once every 3-4 weeks during the maintenance phase once the INR is stabilised. If dose adjustments are required during the maintenance phase, monitoring should be increased until INR is stable.

Visits to pathology labs and/or general practitioners for coagulation monitoring can be inconvenient for many patients and represents a significant burden and barrier to effective treatment. Monitoring requirements also impose a considerable financial burden on the patient in terms of time and travelling costs (Jowett *et al* 2008). In addition to the unpredictable anti-coagulation effects offered by warfarin, the burden of monitoring can lead to poor adherence to warfarin. This creates a major source of unstable anticoagulation control, resulting in sub-optimal stroke prevention and an increased risk of warfarin-related adverse events, most importantly, haemorrhagic events. There is a significant clinical need for alternatives to warfarin which do not require intensive monitoring.

Warfarin related adverse events

Warfarin is commonly associated with adverse drug reactions, many of which require hospitalisation, and some of which are fatal. Vitamin K antagonists (VKAs) are the most common medications causing emergency department visits for adverse drug reactions in the US, causing 17.3% of all such visits (Budnitz *et al* 2007). Warfarin is also the leading cause of hospitalisations for adverse drug events in the US (20 hospitalisations per 10,000 medication visits), representing around one-third of all drug-related

hospitalisations (Budnitz *et al* 2011). VKAs are the second most common cause of hospital admissions for adverse drug reactions in the UK (Pirmohamed *et al* 2004).

The adverse events caused by warfarin result in an economic burden to the Australian healthcare system. Rigby *et al* (1999) estimated adverse events caused by warfarin to cost Australia over $100 million (at 1999) per annum in direct hospital costs alone. The authors noted that this was the second most costly cause of adverse events in Australia.

Haemorrhage risk associated with warfarin

The bleeding risk for warfarin is much higher in clinical practice where INR is less likely to remain in the therapeutic range. Van Walraven *et al* (2007) conducted a retrospective cohort study in eastern Ontario using population-based administrative databases to measure the proportion of serious haemorrhagic and thromboembolic events that would be avoided if anticoagulation was perfect. During the study period, totalling 6,422 years of exposure time, patients on anticoagulant therapy spent 14.2% of the time with INR values >3. The population-attributable risk of critically high anticoagulation intensity for serious haemorrhagic events was 25.6% in patients who had received anticoagulation therapy and 2.0% in the entire elderly population. This would translate into an annual decrease of 67 serious haemorrhagic events in eastern Ontario alone if the time spent with a critically high INR was avoided. Similarly, the population-attributable risk of critically high INRs for lethal haemorrhages was 28.1% and 1.8% for the anticoagulated and entire population, respectively. Bereznicki noted that based on these Canadian data, 2,500 hospital admissions for bleeding and thromboembolic events could be avoided in Australia if INR control was improved (Pharmaceutical Society of Australia 2009).

The most important haemorrhagic complication is intracranial haemorrhage (ICH). This is the main bleeding outcome that can result in deficits greater than those produced by the ischaemic strokes (i.e., the outcome that warfarin treatment aims to prevent) (Singer *et al* 2008 and Fang *et al* 2007). The severity of ICH compared with other bleeding outcomes such as extracranial haemorrhage was described in Fang *et al* 2007, where 76% of patients with ICH had a severe disability or died, compared with 3% of those with extracranial haemorrhage. The majority of deaths and disabilities among patients with a warfarin-associated haemorrhage were due to ICH (88%). ICH was found to represent 5.6% of warfarin-related hospitalisations (Budnitz *et al* 2011). Out of 1,053 bleeding-related hospitalisations in 871 Australian patients, approximately 15% were cerebral bleedings (Vitry *et al* 2011).

Compared to warfarin, dabigatran 110 mg had a relative risk (RR) of 0.30 (0.19, 0.45) and dabigatran 150 mg RR 0.41 (0.28, 0.60) for intracranial haemorrhage (Connolly *et al* 2010). Given the significant impact of dabigatran on intracranial haemorrhage, it is very disappointing that Australian patients are missing out on cost-effective medicines such as dabigatran.

It is difficult to determine the bleeding risk for an individual patient. It depends on the intensity of the anticoagulant effect, the patient characteristics or comorbid conditions, the concomitant use of drugs that interfere with haemostasis and the length of time the patient has been on warfarin therapy (Schulman *et al* 2008). Once any clinically significant bleeding is observed, the need for ongoing anticoagulation therapy needs to be carefully reassessed.

Rural use of warfarin and anticoagulation control

Warfarin use appears to be lower in rural and regional areas. In a study of five Queensland hospitals (Read and Levy 2005), there were startling differences in the proportions of AF patients discharged on warfarin treatment (metropolitan 83.3% versus regional 25.0%) and those discharged on no antithrombotic treatment (metropolitan 16.7% versus regional 33.3%). In a study of 818 Australian veterans, those patients living in remote and outer regional areas had significantly lower time in therapeutic range (TTR) than veterans living in regional and metropolitan areas (49.9% versus 65.3%, $p< 0.01$) (Bereznicki *et al,* 2011). Similar findings were reported in the US with patients in metropolitan areas more likely to receive antithrombotic therapy than those in rural areas (58% versus 47%, respectively) (Flaker *et al* 1999).

Underutilisation of anticoagulants in AF

Warfarin remains underutilised despite its efficacy in AF patients with an elevated risk of stroke and decades of experience in clinical use. The National Health and Medical Research Council has highlighted the underuse of anticoagulants such as warfarin noting *"the number of recent Australian publications on the underuse of anticoagulation in stroke prevention points to a growing awareness of this evidence-practice gap among health services researchers"* and *"this particular evidence-practice gap remains a challenging one because it involves balancing competing risks. We need to know more about the reasons why warfarin is under-prescribed from both the perspective of at-risk patients and clinicians. Patients and health professionals often experience uncertainty and frustration about the information available to help them with day-to-day warfarin management"* (National Institute of Clinical Studies 2008). The underutilisation of warfarin

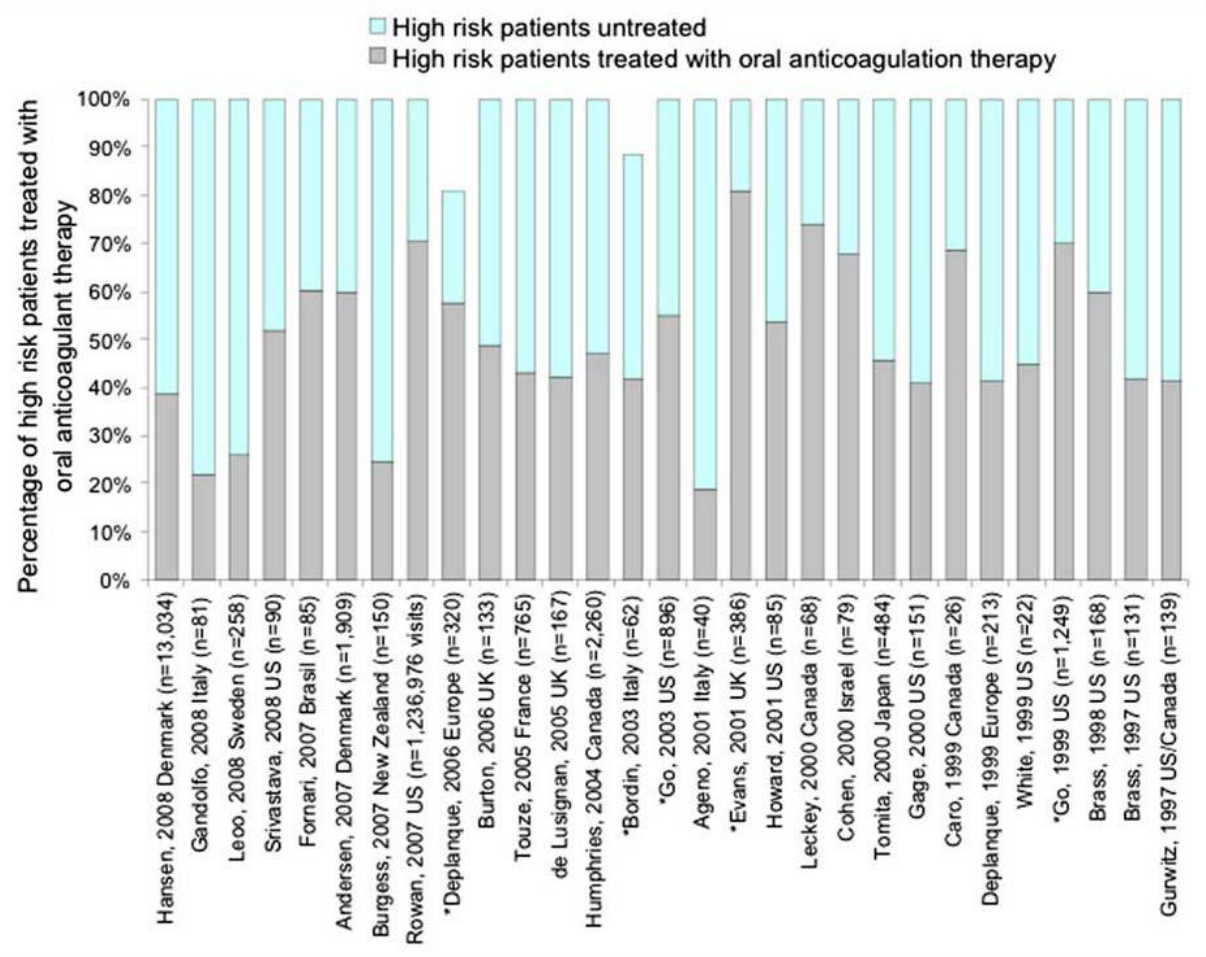
has also been highlighted by the National Prescribing Service (NPS) in its educational intervention to improve warfarin's use (Mandryk *et al* 2008). It is therefore unacceptable that the Government has decided to delay the listing of dabigatran given its own researchers have identified on many occasions the underutilisation of anticoagulants in patients with atrial fibrillation.

Bereznicki (2010) in his expert report for the dabigatran PBAC submission noted that *"despite the proven benefit of anticoagulation for stroke prevention in AF, available data show that of those patients with AF and no contraindications to warfarin therapy, only about half are prescribed warfarin."*

The available evidence also suggests a low rate of stroke prevention treatments among patients with AF. The National Stroke Foundation (NSF) found that out of all the AF patients admitted to hospital for first-time stroke only 30% were receiving any form of stroke prevention medicine and for a recurrent stroke only 34% were on an anticoagulant (NSF 2011). This evidence again highlights the significant clinical need for new stroke prevention medicines such as dabigatran.

A recent systematic review of 54 studies (Figure 2) found that less than 60% of patients with a high risk of stroke were receiving adequate treatment for stroke prevention (Ogilvie *et al* 2010). Ogilvie noted that reasons for underuse of anticoagulants include low levels of therapy initiation, the narrow INR range for warfarin, inconvenience of regular monitoring, fear of catastrophic bleeding, and patient compliance.

Figure 2 Oral anticoagulant usage in high risk patients with AF and prior stroke/TIA



Source: Ogilvie *et al* 2010

A recent study of patients from a US medical claims database showed that less than half of the patients with an atrial fibrillation indication had received warfarin even those patients at higher risk of stroke (Zimetbaum *et al* 2010). Similar results were observed in a Canadian study from the Registry of the Canadian Stroke Network with 40% of high-risk AF patients on warfarin, 30% on antiplatelets and 29% on no treatment. Of the patients on warfarin around 75% were on subtherapeutic INR values (Gladstone *et al* 2008). Jackson *et al* (2001) reported that only 34% of Australian patients who are considered to have a high stroke risk were receiving warfarin (see Table 1).

Table 1 Use of anti-thrombotic treatments in patients with NVAF in Australia

Risk group	% in risk group	% on warfarin (or with aspirin)		% on aspirin	% on no treatment
		All	With no contra-indications		
High risk Recommended therapy: warfarin (target INR 2.0-3.0) if no contraindication)	79%	34%	43%	42%	24%
Moderate risk Recommended therapy: warfarin or aspirin)	18%	38%	na	42%	20%
Low risk Recommended therapy: aspirin 75–300mg/day)	3%	8%	na	15%	77%

Source: Jackson *et al* 2001

A summary of the proportion of patients on warfarin, aspirin and no treatment from Australian studies is presented in Table 2.

Table 2 Stroke prevention treatments in AF patients in Australia

Study	Risk	% in risk group	% contraindicated to warfarin	% on warfarin (or with aspirin)		% on aspirin	% on no treatment
				All	No contra-indications		
Ang 1998	High risk	91%	32.5% of all patients [a]	28%	37%	41%	31%
	Moderate risk	7%		23%	na	62%	15.4%
	Low risk	2%		0%	na	33%	67%
Jackson 2001	High risk	79%	39%[b]	34%	43%	42%	24%
	Moderate risk	18%	24% [b]	38%	na	42%	20%
	Low risk	3%	Na	8%	na	15%	77%
Kelly 2001	High risk	54% (only those at high risk and not contraindicated)	44% of all patients	na	66%	22%	12%
Jackson 2004a	High risk	78%	Na	33%	39%	44%	22%
	Medium risk	15%	Na	30%	na	41%	30%
	Low risk	7%	Na	na	na	na	na
Inglis 2002	Not available (na)	74% of those without heart failure at high risk	Na	~44%	na	na	na
Jackson 2011	High risk	73%	Na	36%	44%	33%	22%
	Medium risk	22%	Na	36%	na	33%	26%
	Low risk	6%	Na	16%	na	16%	68%

[a] At least one documented reason not to prescribe warfarin (e.g., bleeding tendency, alcohol abuse, previous problem, liver disease, cognitive ability, blood dyscrasias, uncontrolled hypertension, falls, surgery, allergy). Only non-valvular AF patients were included in Ang *et al* (1998).
[b] At least one documented reason not to prescribe warfarin (e.g., recent overt bleeding, bleeding tendency, alcoholism, previous discontinuation, liver disease, blood dyscrasia, refractory hypertension).

The above studies highlight that many patients at higher risk of stroke are taking aspirin or are untreated despite requiring treatment with warfarin. This unnecessarily exposes them to an elevated risk of stroke. There is a clear clinical need for newer stroke prevention medicines.

Many prescribers use potential contraindications and the possibility of litigation as reasons for poor warfarin prescribing, many are also fearful of prescribing treatments that may lead to bleeds such as intracranial bleeds. Gattellari found that 30% of family physicians often were not sure whether or not to prescribe warfarin, with 15.8% of family physicians reported having an AF patient experience an intracranial haemorrhage with anticoagulation and 45.8% had a patient with AF experience stroke without prior anticoagulation (Gattellari *et al* 2008). The NPS through its educational intervention captured many of the prescriber barriers which are presented below in Table 3 (Mandryk *et al* 2008). For patients, the barriers to warfarin treatment include: frequent blood testing, the potential for warfarin adverse events and the multiple drug-drug and drug-food interactions leading to dietary and alcohol restrictions.

Warfarin is subject to multiple interactions. It is extensively metabolised by the CYP450 enzyme system. The absorption or metabolic clearance of warfarin is affected by many drug interactions as summarised by Bereznicki (Pharmaceutical Society of Australia 2009). The NPS has published a list of possible herbal products that interact with warfarin (NPS 2003). Warfarin is also subject to many food interactions. Patients on warfarin need to adhere to their normal diets and avoid drastic changes. Foods with high vitamin K content interact with warfarin and dosing changes are necessary. Examples of high vitamin K foods include beetroot, broccoli, lettuce, cabbage, liver, spinach and edible oils. In contrast, there are no dietary precautions for dabigatran.

Table 3 Perceived barriers to antithrombotics prescribing [a]

- GPs reluctant to cease warfarin and aspirin initiated by specialists
- GPs find warfarin a difficult drug to manage
- Resistance of GPs to initiate warfarin when there are dangers of bleeding, and arduous monitoring requirements
- INR monitoring is difficult in some remote areas, and consequently GPs may be reluctant to use warfarin
- Monitoring of INR therapy is time consuming and not renumerated via current government policies
- Problems because NPS guidelines for initiating warfarin differ from some pathology laboratories (which manage patients)
- Warfarin counselling and education is extremely time consuming
- Some GPs do not consider aspirin very effective
- Because aspirin is an older, cheaper, OTC drug, it is viewed as being not as good as newer products
- Confusion over aspirin use because of media attention regarding bleeding in the elderly
- Aggressive marketing of clopidogrel by pharmaceutical companies (pushed quite strongly by representatives)
- High prescribing of clopidogrel by cardiologists
- Clopidogrel is often started by specialist and GPs were reluctant to change therapy
- Many GPs think clopidogrel is better than aspirin
- GPs reluctant to cease dual therapy of clopidogrel and aspirin initiated by specialists
- Lack of information comparing dipyridamole and clopidogrel for those patients where aspirin is not the best therapy
- Aspirin, clopidogrel and dipyridamole (and combinations) being used in different ways by different specialists
- GPs report conflicting prescribing patterns of antithrombotics by cardiac specialists
- Specialists often prescribe outside guidelines but GPs have to support such prescribing

[a] Brief summary list obtained from GP Divisional 'Activity Completion Reports' to NPS regarding the antithrombotics programme (Mandryk *et al* 2008)

The above barriers are supported by other Australian researchers. Peterson found that the principal barriers to the prescribing of anticoagulants include: active gastrointestinal bleeding; previous intracranial haemorrhage; alcoholism; history of daily falls; liver disease; severe anaemia and concurrent use of non-steroidal anti-inflammatory drugs (Peterson *et al* 2002). Bereznicki *et al* (2010) noted three main categories of barriers to warfarin prescribing: patient (such as age and frailty), physician (including risk of adverse events, labour-intensiveness of monitoring INR control) and healthcare system-related barriers.

The clinical need for new anticoagulants is clear given the high proportion of patients on suboptimal treatments or no stroke-prevention at all.

Consumer views

Boehringer Ingelheim commissioned an independent market research agency to conduct market research of consumer attitudes to treatment options including warfarin and the need for additional stroke prevention medicines (see Appendix C). The methodology for the research included qualitative in-depth interviews and a focus group with consumers diagnosed with atrial fibrillation. The consumers ranged from those currently receiving warfarin, those who had received warfarin the past and those not receiving warfarin. This latter group may have been receiving other therapies for their AF.

The second stage of the research involved a larger scale on-line survey of 200 consumers (40% female and 60% male) over the age of 50 years with a diagnosis of atrial fibrillation. The majority of consumers were aged 55 to 75 years of age with a median age of 67 years. Consumers represented all the States and Territories, with NSW, Victoria and Queensland the most common States. Only 13% of consumers were not concessional or Veteran card holders which is quite representative of current warfarin use on the PBS. Many of the consumers had other medical conditions with arthritis, pain, hearing loss as common conditions. Around 6% have had a previous stroke with around 14% also reporting a previous transient ischaemic attack. 57% of the consumers had their atrial fibrillation diagnosed by a cardiologist or other specialist physician and almost 40% by their General Practitioner. The majority of consumers had been diagnosed with AF for 5 years or more.

Consumers that were taking stroke prevention treatments mentioned warfarin and aspirin as the most commonly used treatments. 52% of the consumers were on aspirin and 31% on warfarin. 15% of consumers surveyed had used warfarin at some stage during their treatment for atrial fibrillation but had discontinued its use. Warfarin and aspirin had a high level of awareness by consumers with over 85% prompted awareness for each drug in all consumers.

Those consumers who had used warfarin in the past but not currently reported reasons for ceasing its use as difficulties in its use including regular monitoring, the need for regular dose review as well as bleeding events. This is shown in Figure 3.

Consumers that had heard of warfarin but never used it gave similar reasons for their lack of use, with the primary reasons being concerns about bleeding, the difficulty in using warfarin and interactions with other medications and foods. In addition a major reason for non-use was that the consumer's doctor advised against warfarin use. Other reasons given related primarily to doctors not prescribing warfarin for their patients.

Figure 3 Consumer research: reasons for not using warfarin

You have indicated that you have used Warfarin in the past but not anymore. Why is that?

N = 29

Description	%
It causes bleeding	28%
It is a difficult therapy to use (requires regular blood testing)	52%
There are dosing problems as it interacts with some foods and alcohol	21%
It interacts with other medications	21%
It requires regular dose review with a doctor	41%
My dose could not be stabilised by my doctor	10%
Other (please specify)	48%

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N = 29

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There are dosing problems as it interacts with some foods and alcohol	21%
It interacts with other medications	21%
It requires regular dose review with a doctor	41%
My dose could not be stabilised by my doctor	10%
Other (please specify)	48%

The most important attributes of an anticoagulant reported by consumers were effective reduction of stroke and improvement in quality of life. 61% of consumers surveyed considered that there was a high or very high need for new alternatives for managing the risk of stroke as a result of atrial fibrillation. When prompted for feedback, the consumers noted safety concerns, the need for regular monitoring, dietary restrictions, fear of stroke and warfarin as being some of the key reasons for the need for new treatments.

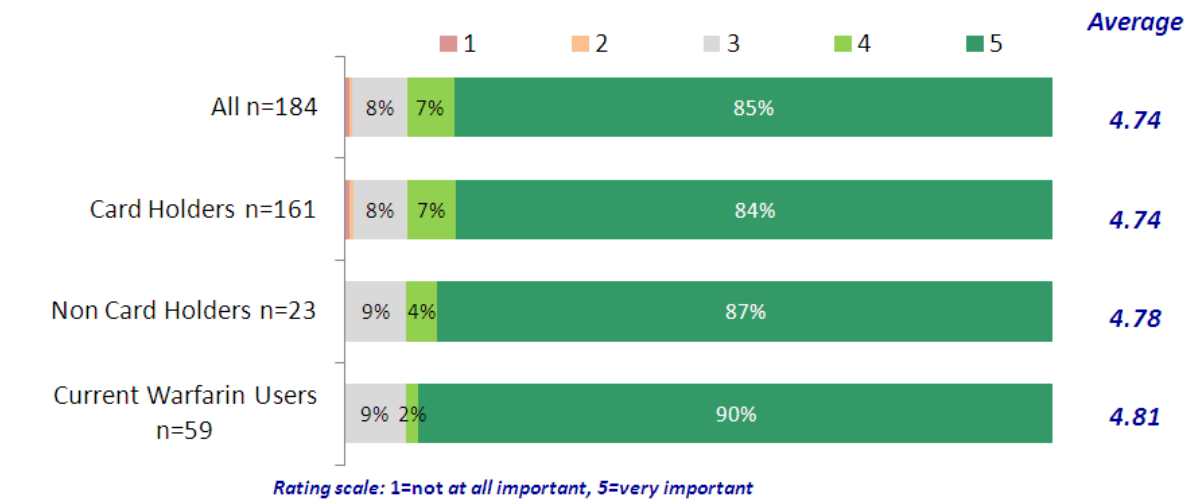
A key issue for consumers in regard to new alternatives is cost. Nonetheless over 70% of consumers would speak to their General Practitioner about a new stroke prevention medicine such as dabigatran.

Following the compelling evidence from a similar survey conducted in mid 2011 demonstrating public opposition to Government deferrals of PBAC recommended medicines, consumers were also asked in this research to provide responses on the Government

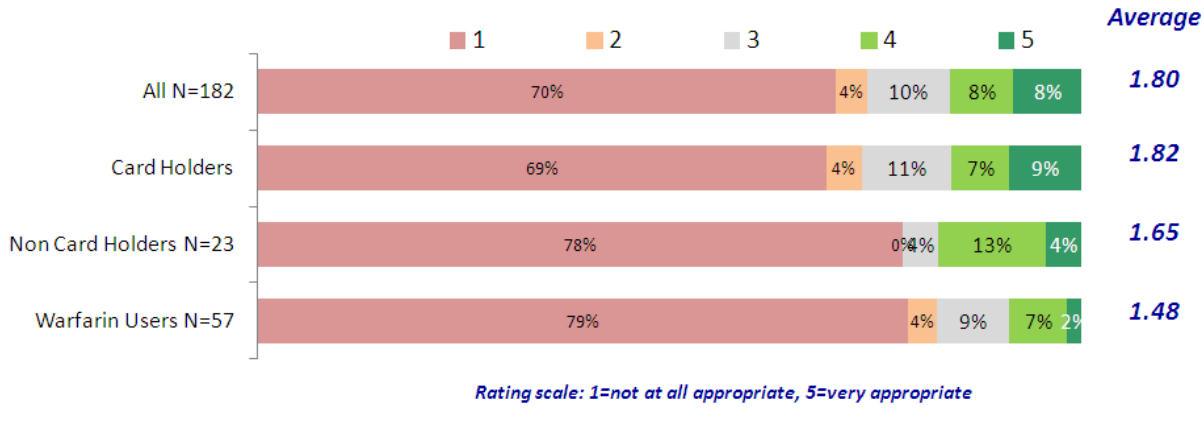
delaying access to a new stroke prevention medicine. Over 80% noted that it would be very important to them to make the new medicine available to them on the PBS. Only 16% of consumers believed it was appropriate for the Government to delay the PBS listing of a new stroke prevention medicine that has been recommended for listing by its own committees. This is shown in Figure 4.

Figure 4 Consumer research: delayed PBS listing

Knowing that this product has proven treatment advantages over warfarin how important would it be to you, for the government to approve access to this product through the PBS?



Reflecting on your answer to the previous question, please rate the appropriateness of the decision by the government to delay listing given that its specialist advisory committees recommended listing the new product on the PBS?



When prompted for more feedback, it was clear that consumers believed that the Government should follow the advice of its own expert committee (Table 4).

Table 4 Consumer research: additional feedback on delayed PBS listing

- The government are a only interested in cutting costs to feather their own nests eg: wage rises for themselves.They should support any treatment that can save lives.
- that is what i think
- Anything that reduces stroke incidence significantly must be supported
- any proven drug which provides better outcomes should be on pbs
- It would help alot of people who take Warafrin
- if it works better!!!!!
- Because at my age and income I need all the help I can get. Very selfish reason of course.
- Governments should be accountable for making medicines available to all people New products are pushed by the Drug Companies because they are better than the others(?) and they are a lot more expensive because only one company is making them Most people live on a fixed income
- We should all be entitled to effective medication at the PBS price particularly if it is proven to prevent strokes which will reduce the cost to the government of post stroke care
- a lot of older folk cant afford to pay the full cost up front
- anything that will improve the heart health of australians should not be held back from release
- yhe government procrastinates
- needs to be tested fully
- If it works it should be made available
- They should list if it is for a better quality of life in people
- If it is proven it should be made available to keep the aging population out of hospitals and nusing homes as a result of strokes
- I am a pensioner
- this is what governments do delay to save money
- This is a very serious condition mainly affecting the elderly. Maybe the governement

thinks us oldies are not important enough to look after. I mean this is a common complaint I have 2 friends with this condition

- Because this type of prescription would be so helpful to so many people
- PBS doesn't care about saving lives, it's all about COST!!
- i am on a disability pension so i would need it on the pbs
- I can never understand why they have committees if they don't follow their recommendations. Yet they had no problem listing VIAGRA & yet this and other life-saving drugs are deied it just doen't make sense.
- some can not aford
- If it's better and safer it should replace other drugs. I don't know the reason the Govt won't list it but I suppose it's financial. Seems like an easy decision to me.
- If it is superior to existing medication it should be there.
- Warfarin is not a safe drug for everyone and should be replaced.
- same
- If this is a tested and proven medication which will help people with stroke prevention then it most certainly should be on PBS - problems with Warfarin have been well now for many years, if blood tests to monitor the dose could be shortened then it would be obvious to all (except the government) that in the end it would be less expensive and more beneficial to patients.
- Mabey a lot of people can't afford the full price.
- There are people out there that cannot afford anything above the PBS and therefore are left out in the cold when it comes to a new drug like this
- I don't know
- it is not appropriate when you consider the wastage by the govt in other areas. surely people's health is of more importance

Notes: N = 136. Displaying answers 1 to 20. Text is as provided by consumers.

In addition, Boehringer Ingelheim has received comments from prescribers that have prescribed dabigatran under the Product Familiarisation Program (PFP) as well as those not participating in the PFP. These comments are presented in Appendix N (commercial-in-confidence). It is clear from the comments that there is clinical need for an alternative to warfarin and aspirin, many prescribers highlight the difficulties managing warfarin titration,

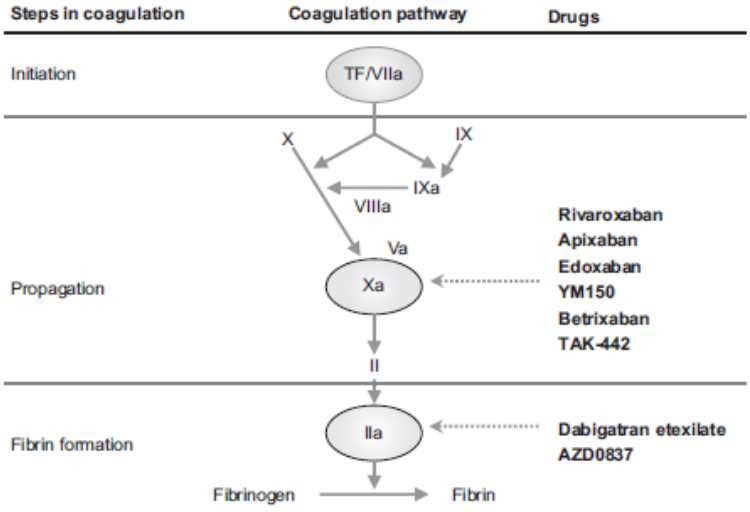
ongoing monitoring and the time taken up to deal with managing warfarin patients. This is particularly so in rural and regional areas. Many prescribers focus on the patient-related benefits of reduced drug interactions and no drug-food interactions. Many prescribers are frustrated with the delay of PBS listing of dabigatran and the actions of the Government.

Finally Boehringer Ingelheim has also received comments from Australian consumers outside of the market research discussed above. These comments are also included in Appendix N (commercial-in-confidence).

Dabigatran

Dabigatran etexilate is a prodrug that is rapidly absorbed and converted to dabigatran which is an oral potent, reversible direct thrombin inhibitor. Dabigatran is available in two capsule strengths for the prevention of stroke or systemic embolism in patients with atrial fibrillation, 110 mg and 150 mg, taken orally twice daily. Dabigatran has a fast onset of action with maximum plasma concentrations reached within 0.5 to 2 hours post administration unlike warfarin which takes over 36 hours. Dabigatran binds to the active site of thrombin inactivating both fibrin-bound and unbound thrombin (Figure 5). By inhibiting thrombin, dabigatran prevents the conversion of fibrinogen into fibrin. Dabigatran has a predictable anticoagulant effect and does not require coagulation monitoring. It is mainly eliminated by the kidneys with urinary excretion accounting for up to 85% of the dose administered intravenously. The recommended daily dose is 150 mg twice daily. 110 mg twice daily is recommended for patients 75 years and over, those at higher risk of bleeding and potentially those with moderate renal impairment.

Figure 5 Sites of action of new anticoagulants



Source: Hankey and Eikelboom 2011

Dabigatran was approved by the PBAC at its March 2011 meeting and the Therapeutic Goods Administration (TGA) on 29 April 2011.

The TGA approved AF indication is as follows: *prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one risk factor for stroke.*

The PBAC recommended dabigatran be listed on the PBS for the indication below on the basis of acceptable cost-effectiveness when compared to warfarin and aspirin. The clinical evidence for dabigatran versus warfarin is the RE-LY trial a phase III, multi-centre, prospective, randomised, open-label, trial with blinded evaluation of all outcomes (PROBE), in 18,113 patients (Connolly *et al* 2009; 2010) and for dabigatran versus aspirin using an indirect comparison using a meta-analysis of aspirin trials in AF (Dabigatran Public Summary Document, Appendix B). The impact of dabigatran on stroke is clinically significant. For the primary outcome of stroke or systemic embolism, when compared to adjusted-dose warfarin, the RR for dabigatran 110 mg bid is 0.90 (0.74, 1.10) and for 150 mg bid 0.65 (0.52, 0.81). Based on a network meta-analysis and indirect comparisons, when compared to aspirin, the RR for dabigatran 110 mg bid for all strokes is 0.52 (0.28, 0.96) and for dabigatran 150 mg bid the RR is 0.37 (0.20, 0.69). When compared to no treatment, for all strokes, the RR for dabigatran 110mg bid is 0.35 (0.17, 0.71), and for dabigatran 150 mg bid RR 0.25 (0.12, 0.51) (Roskell *et al* 2011). These are important results given the high proportions of patients on aspirin and the significant proportion that take no stroke prevention treatment in Australia.

The PBAC recommended listing is as follows:

<u>Authority Required (STREAMLINED)</u>

Prevention of stroke or systemic embolism in a patient with non-valvular atrial fibrillation who are at moderate-to-high risk of developing stroke or systemic embolism as evidenced by one or more of the following risk factors:

i. Age ≥ 75 years;

ii. Hypertension;

iii. Diabetes mellitus;

iv. Heart failure or left ventricular dysfunction (ejection fraction less than 40%) or history of coronary artery disease;

v. *Previous stroke or transient ischaemic attack or systemic embolism.*

The above restriction is consistent with the approved TGA indication as well as the evidence presented in the RE-LY trial. There is no justifiable reason to further restrict the eligible population based on a higher stroke risk profile or based on the need to take prior stroke

prevention treatments before being eligible for dabigatran. Any such recommendation made by the Review is in essence leading atrial fibrillation patients to experience poor health outcomes before being eligible for dabigatran, which has been deemed to be a cost-effective first-line treatment for patients at moderate-to-high risk of stroke.

Further information on dabigatran can be found in the approved Product Information (Appendix A) and the basis for the PBAC recommendation in the Dabigatran Public Summary Document (Appendix B). A copy of the submission to the PBAC has been provided as commercial-in-confidence (Appendix E). The submission to the PBAC provides a detailed presentation of all the efficacy and safety outcomes for dabigatran versus warfarin and aspirin.

3. INTERNATIONAL STROKE PREVENTION GUIDELINES

In order to maximise the health outcomes for patients with AF, various expert bodies from around the world publish guidelines to promote best clinical practice when treating these patients. Several recent updates to such guidelines have considered dabigatran's role in stroke prevention for AF patients.

In early 2011 the American College of Cardiology published an update on the management of patients with AF, with a specific section relating to dabigatran (Wann *et al*, 2011). The update noted that *"both dabigatran doses appeared to be non-inferior to warfarin with respect to the primary efficacy outcome of stroke or systemic embolism. In addition, the 150 mg twice-daily dose was superior to warfarin with respect to stroke or systemic embolism, and the 110 mg twice-daily dose was superior to warfarin with respect to major bleeding."* With respect to the clinical place of dabigatran the update stated: *"patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran. Selection of patients with AF and at least 1 additional risk factor for stroke who could benefit from treatment with dabigatran as opposed to warfarin should consider individual clinical features, including the ability to comply with twice-daily dosing, availability of an anticoagulation management program to sustain routine monitoring of INR, patient preferences, cost, and other factors."* This final statement clearly demonstrates that decisions about anticoagulation therapy are complex and require consideration of multiple factors in an individualised patient-physician interaction, of which the anticipated quality of warfarin control is only one such issue.

The European Society of Cardiology (ESC) issued an update to their guidelines for the management of AF in 2010 (Camm *et al* 2010). At the time of publication, the results of the RE-LY trial were published, however regulatory approval for dabigatran had not yet been granted. Therefore the suggested approach to oral anticoagulation (OAC) was contingent on regulatory approval, *"should both doses of dabigatran etexilate receive regulatory approval for stroke prevention in AF, the recommendations for thromboprophylaxis could evolve as follows considering stroke and bleeding risk stratification."* The ESC guidelines also propose new risk measurement tools for stroke risk (CHA_2DS_2-VASc[1]) and bleeding risk (HAS-BLED[2]) where a higher score is correlated with greater risk for both measures. OAC was recommended for patients in the highest stroke risk category, while those with a CHA_2DS_2-VASc score of 1 had a choice of aspirin or OAC, with OAC preferred (see Figure 6). [1]

[1] CHA_2DS_2-VASc: Cardiac failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled) – Vascular disease, Age 65-74 and Sex category (female)

Figure 6 European Society of Cardiology suggested approach to thromboprophylaxis in patients with AF

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥2 'clinically relevant non-major' risk factors	≥ 2	OAC[a]
One 'clinically relevant non-major' risk factor	1	Either OAC[a] or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

The resulting suggestion from the ESC is as follows: *"Where oral anticoagulation is appropriate therapy, dabigatran may be considered, as an alternative to adjusted dose VKA therapy. (i) If a patient is at low risk of bleeding (e.g. HAS-BLED score of 0–2; see Table 10 for HAS-BLED score definition), dabigatran 150 mg b.i.d. may be considered, in view of the improved efficacy in the prevention of stroke and systemic embolism (but lower rates of intracranial haemorrhage and similar rates of major bleeding events, when compared with warfarin); and (ii) If a patient has a measurable risk of bleeding (e.g. HAS-BLED score of ≥3), dabigatran etexilate 110 mg b.i.d. may be considered, in view of a similar efficacy in the prevention of stroke and systemic embolism (but lower rates of intracranial haemorrhage and of major bleeding compared with VKA). (b) In patients with one 'clinically relevant non-major' stroke risk factor, dabigatran 110 mg b.i.d. may be considered, in view of a similar efficacy with VKA in the prevention of stroke and systemic embolism but lower rates of intracranial haemorrhage and major bleeding compared with the VKA and (probably) aspirin."* Thus the updated guidelines demonstrate the clinical utility of dabigatran and its potential benefits in various AF populations at a moderate-to-high risk of stroke.

The Canadian Cardiovascular Society (CCS) has also published updated AF guidelines subsequent to dabigatran's approval in Canada (Cairns *et al* 2011). The CCS recommends dabigatran be used preferentially to warfarin in the majority of patients. *"We recommend that when an OAC is indicated for stroke prevention, most patients should receive dabigatran in preference to warfarin. Possible exceptions would include patients with a propensity to dyspepsia, gastrointestinal bleeding, or both and those at substantial risk of coronary events.*

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[2] HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR,Elderly (>65), Drugs/alcohol concomitantly.

The dose of 150 mg twice a day is preferable to 110 mg twice a day, except in patients of low body weight, decreased renal function, or at increased risk of major bleeding." The authors of the CCS guidelines placed a high value on the greater efficacy of dabigatran, especially in patients who had not previously been treated with an OAC, and the lower incidence of intracranial bleeding with dabigatran while the long safety experience with warfarin was less valued. The analysis presented in the dabigatran PBAC submission supports this rationale with the impact of strokes (particularly those of a haemorrhagic aetiology) on patient morbidity and mortality being much greater than that caused by other adverse events.

The most recently published guideline for the management of stroke prevention in NVAF comes from the American College of Chest Physicians (Guyatt *et al* 2012). Where oral anticoagulation is appropriate for NVAF patients the guidelines state, *"we suggest dabigatran 150 mg twice daily rather than adjusted-dose VKA therapy (target INR range, 2.0-3.0)."* This clear preference for dabigatran over adjusted-dose warfarin echoes the CCS guidelines in placing dabigatran as the preferred OAC for most NVAF patients.

No Australian AF guidelines have been published since the release of the RE-LY results and therefore no Australian-specific guidance is available. However the various international guidelines all clearly support the use of dabigatran as an appropriate treatment alternative to adjusted-dose warfarin in AF patients at moderate-to-high risk of stroke. The guidelines consistently highlight that the decision as to which OAC therapy to utilise requires consideration of numerous factors including patient age, stroke risk, bleeding risk, preferences, comorbidities, OAC history, renal function, concomitant medications etc. Overall the guidelines serve to reinforce the role of dabigatran in improving the health outcomes of patients with AF.

The decision to deny Australians with NVAF at moderate-to-high of stroke affordable access to dabigatran deprives them of a treatment option that the major international treatment guidelines consistently recommend.

4. INTERVENTIONS TO IMPROVE THE USE OF WARFARIN

A review of the literature was conducted in order to identify interventions which could be used to improve the use of anticoagulants, specifically warfarin. This included new strategies for anticoagulant management as well as methods of optimising existing models of care and currently available interventions. A systematic literature review was conducted in order to identify all Australian studies which met these criteria. The effectiveness of these interventions are presented and discussed. A review of the international literature was also conducted. Key interventions were identified and are discussed in more detail. The costs of implementing these interventions are presented in Section 4.

Only one intervention has been formally assessed in Australia: point-of-care testing. This was assessed by MSAC in 2005 and was not considered cost-effective. The other interventions identified in the literature search had varying levels of clinical effectiveness and cost effectiveness. The trials were generally lower level evidence (i.e., there were few randomised controlled trials) and had a short duration. This is particularly relevant given the length of time that AF patients receive anticoagulants. Short term improvements in outcomes may not be maintained over the longer term. The outcomes assessed in the trials were generally not patient relevant, typically assessing surrogate outcomes such as INR control rather than clinical outcomes such as strokes and bleeding events. The international evidence is confounded by the differences in health care systems. Interventions which are effective overseas may not be as effective in the Australian clinical setting. Strategies such as anticoagulation clinics would first need to be piloted and evaluated in Australia prior to being introduced nationally. The additional costs associated with pilot programs and evaluations of the program must be considered, in addition to the lost opportunity costs associated with delaying the introduction of these programs while they are evaluated.

4.1. A systematic review of Australian warfarin studies

A systemic literature search was conducted in order to identify all Australian studies which aimed to improve warfarin use in the clinical setting. The search strategy and inclusion criteria are shown in Appendix D. The interventions could be broadly classified into four categories: hospital based interventions, community prescriber training, point-of-care testing and home medication reviews.

Publications evaluating hospital based interventions

The literature search identified nine trials which evaluated hospital based intervention (Bajorek 2005, Bereznicki 2007, Coombes 2009, Duff 2010, Elliott 2002, Jackson 2011, Lubliner 2005, Roberts 2006 and Van De Vreede 2003). The publications are summarised in

Table 5. All publications were either case series (level IV evidence), comparing warfarin use on admission with warfarin use after the intervention, or historical control studies (level III evidence), comparing warfarin prior to the introduction of an intervention with warfarin use after the introduction of the intervention. Most trials evaluated the intervention in any patient receiving warfarin, irrespective of the reason for warfarin use.

There was a range of interventions evaluated in the trials. These included changing treatment algorithms (Bajorek 2005), modifying drug charts (Bereznicki 2007, Coombes 2009 and Duff 2010), and changing hospital procedures around warfarin administration (Lubliner 2005 and Van De Vreede 2003). Other trials audited medical records (Elliott 2002), incorporate stroke assessments (Jackson 2011) or implemented academic detailing (Roberts 2006). The interventions often included multiple components and varying degrees of staff training. Although the duration of the data collection ranged from 2 months to 24 months, most trials did not follow patients after their discharge from hospital.

Table 5 Summary of studies evaluating hospital based interventions

Study ID	NHMRC Level of evidence	Population and location	Description of program Duration	Intervention	Control
Bajorek 2005	Level IV Case series with pre-test/post-test outcomes	Elderly patients with atrial fibrillation admitted to Royal North Shore Hospital, Sydney N=218	Algorithm to determine the requirement for antithrombotic therapy. 6 months	Subjects after assessment with the algorithm N=all subjects (case series)	Subjects prior to the introduction of the algorithm N=all subjects (case series)
Bereznicki 2007	Level III-3 Historical control study	Patients initiated on warfarin at Royal Hobart Hospital N=454	Modification to warfarin drug chart and hospital staff education program. 13 months	Subjects managed using the modified warfarin protocol and warfarin drug chart N=183	Subjects managed using the pre-existing warfarin protocol and drug chart N=271
Coombes 2009	Level III-3 Historical control study	Patients prescribed warfarin at 7 hospitals in Brisbane N=1,481	Development and implantation of a standard medication chart with a specific section for warfarin. 24 months	Subjects managed after the intervention N=730	Subjects managed prior to the intervention N=751
Duff 2010	Level III-3 Historical control study	Patients prescribed warfarin at an acute care private hospital in Sydney N=NR	Nomogram to guide loading dose selection, checklist for medical interventions and education for patients and staff. 12 months	Subjects treated after intervention N=NR	Subjects treated prior to intervention N=NR
Elliott 2002	Level III-3 Historical control study	Hospital inpatients prescribed antithrombotics aged 65 and over in 9 public teaching hospitals in Australia N=1,416	Audit of medical notes to assess appropriateness of antithrombotic prescribing, which were presented to staff with an education session. 6 months	Subjects managed after staff received feedback of audit of medical notes and training N=594	Subjects managed by staff prior to the intervention N=563

Study ID	NHMRC Level of evidence	Population and location	Description of program Duration	Intervention	Control
Jackson 2011	Level III-3 Historical control study (pre vs. post intervention) Level IV Case series with pre-test/post-test outcomes (admission vs. discharge)	Patients with atrial fibrillation at Royal Hobart Hospital N=528	Stroke assessment by a pharmacist. 16 months	Subjects treated after initiation of stroke assessment N=134 Subjects after initiation of stroke assessment at discharge N=134 (case series)	Subjects treated prior to initiation of stroke assessment N=394 Subjects after initiation of stroke assessment at admission N=134 (case series)
Lubliner 2005	Level III-3 Historical control study	Patients prescribed warfarin at the Alfred Hospital, Melbourne N=NR	Changing warfarin dosing from 2000 hours to 1600 hours and using an alert sticker on drug charts. 10 months	Subjects treated after the intervention N=NR	Subjects treated prior to the intervention N=NR
Roberts 2006	Level III-3 Historical control study	Patients receiving or initiating warfarin at four hospitals in Australia N=562	Academic detailing, including information on warfarin initiation, over coagulation and deep vein thrombosis prophylaxis. 6 months	Subjects treated after the intervention N=365	Subjects treated prior to the intervention N=197
Van De Vreede 2003	Level IV Case series with pre-test/post-test outcomes	Patients receiving warfarin at 3 hospitals in Melbourne N=NR	Changing warfarin dosing from 2000 hours to 1600 hours and using an alert sticker on drug charts. 2 months	Subjects treated after the intervention N=NR	Subjects treated prior to the intervention N=NR

Abbreviations: NHMRC: National Health and Medical Research Council, NR: Not reported

Summary of key results

Bajorek 2005 evaluated an evidence-based algorithm to determine stroke risk and recommend appropriate antithrombotic use. There was no significant difference in the proportion of patients receiving warfarin on admission (20.7%) compared with the period after the review (17.4%, p=0.37). The proportion of patients receiving warfarin at the three month (16.1%) and six month (15.5%) follow-up point was similar. There was a significant increase in antithrombotic use at admission compared with discharge (57% vs. 81% p<0.001), predominately due to an increase in the use of aspirin.

Bereznicki 2007 evaluated a modified warfarin drug chart, which was sent to each patient's GP post discharge. Education sessions were provided to staff. There was no change in the proportion of patients discharged from hospital with a non-therapeutic INR (61% in the pre intervention group vs. 63% in the post intervention group, p=0.65). There was a significant reduction in the proportion of patients with an INR >4 during initiation in the pre-intervention group (8.5%) compared with the post-intervention group (3.8%, p<0.05). The intervention was associated with a significant reduction in thromboembolic and major bleeding complications within 90 days (OR 0.24, p=0.03).

Coombes 2009 described the development and implementation of a standard medication chart with a designated section for warfarin, and modifying hospital policy to administer warfarin at 1600h rather than 1800h. There was no change in the proportion of patients prescribed warfarin pre-intervention (6.6%) and post-intervention (7.1%, p=NR). The proportion of patients with an INR >5 during initiation decreased from 1.9% in the year pre-intervention to 1.45% in the year post-intervention (p=0.004).

Duff 2010 introduced a range of interventions, including a clinical audit and feedback, patients and provider education, and decision support aides. The proportion of patients with an INR >5 during initiation was 3.7% pre-intervention compared with 1.1% post-intervention (p=NR). The proportion of patients who experienced abnormal bleeding was 1.2% pre-intervention and 0% post-intervention (p=NR).

Elliott 2002 audited the medical records of patients with atrial fibrillation to assess antithrombotic use and then provided feedback to hospital staff in conjunction with an education session. There was no change in the proportion of patients who were prescribed warfarin pre-audit (34%) compared with post-audit (40%, p=0.46). There was a significant increase in the proportion of subjects prescribed aspirin pre-audit (60%) compared with post-audit (87%, p=0.001).

Jackson 2011 discussed the use of a stroke assessment for hospital in-patients with atrial fibrillation. During the pre-intervention period, there was no change in the proportion of

patients receiving warfarin at admission (30%) compared with discharge (29%, p=NR). There was a significant increase in warfarin use in the post-intervention period, with 43% of patients receiving warfarin at admission and 58% receiving warfarin at discharge (p=0.05). There was no difference in the use of aspirin pre-intervention (32% at admission vs. 35% at discharge, p=NR), and a reduction in the use of warfarin post-intervention (48% at admission vs. 39% at discharge, p=0.08).

Lubliner 2005 evaluated changing the time of warfarin dosing from 2000h to 1600h and using an alert sticker on drug charts. The proportion of patients with an INR >5 pre-intervention compared with post intervention was 3.75% vs. 0.67% (p=NS). A warfarin sticker was used appropriately on 92% of appropriate charts.

Roberts 2006 discussed the use of academic detailing performed by specifically trained pharmacists and doctors. Prescribers were given one-on-one detailing sessions for up to an hour. Large group sessions were also conducted. The education included discussion of guidelines, DVT prophylaxis, warfarin initiation and warfarin over coagulation. The use of Vitamin K to reverse INRs >6 was significantly reduced from 74.4% pre intervention to 48.1% post intervention (p=0.007). The following INR was <4 in 48.7% of pre intervention subjects compared with 61.1% of post intervention subjects. The time to stable therapeutic INR was significantly greater in newly initiated patients post intervention (p=0.03). There were also significantly less episodes of over coagulation in the first week of initiation in the pre intervention (18.7%) compared with post intervention (31.8%) patients (p=0.03).

Van De Vreede 2003 evaluated changing the time of warfarin dosing from 2000h to 1600h, and using an alert sticker on drug charts. There was an 82% reduction in patients with an INR >5 on at least two consecutive days.

Discussion

There was limited evidence for the effectiveness of hospital based protocols and staff training. The publications reported a reduction in the proportion of patients with very high INRs, although this was only significant in Bereznicki 2007 (INR >4) and Coombes 2009 (INR >5). Roberts 2006 reported a significantly shorter time to stable therapeutic INR, and significantly fewer episodes of over coagulation. Bereznicki 2007 found a significant reduction in the rate of thromboembolic and major bleeding complications.

The main limitation of these studies was the short time frame in which patients were evaluated. Outcomes were typically measured over the duration of the hospital stay, with limited or no follow-up after discharge. This is reflected by most studies assessing the reduction in the proportion of patients with an INR >5, or >4. This is well outside the optimal range of 2-3, and while important in the initial phase of warfarin use this outcome is of limited

clinical relevance over the longer term. The only study to assess time to therapeutic INR was Roberts 2006, however this was assessed in the days post discharge. A more clinically meaningful outcome would have been the proportion of patients who achieved and maintained an INR of 2-3 over a period of months following the intervention. There are a number of limitations with using INR as the only measure of clinical efficacy. The only publication which assessed clinical events was Bereznicki 2007, which reported a significant reduction in thrombotic and bleeding events in the three months post discharge. It was one of the few interventions to include improved communication with GP, which could highlight the importance of interventions including more than hospital based components to achieve meaningful outcomes.

There was no consistent evidence that hospital based interventions improved the use of warfarin or aspirin in appropriate patients. Although Jackson 2011 reported a significant increase in the proportion of patients prescribed warfarin, this was not found in Bajorek 2005, Coombes 2009 or Elliott 2002. Conversely, Bajorek 2005 and Elliott 2002 found a significant increase in the use of aspirin while Jackson 2011 reported a significant decrease in aspirin prescribing. These differences are likely to be due to the varying sample sizes, as well as clinically relevant differences in the demographics and clinical characteristics of the patients in each trial (particularly the reason for warfarin use). Extrapolating these findings to the broader Australian medical setting has a number of difficulties. The studies were all considered Level III or lower levels of evidence, indicating that the control cohort was not evaluated concurrently to the intervention cohort. This has a number of limitations, including difference in patients and disease characteristics due to lack of randomisation and confounding factors such as changes in hospital practice over time. This is particularly relevant in historical control studies, where differences between groups could be due to other factors not related to the specific intervention (such as changes in standard treatment practices). Most studies were performed at a single hospital with an intervention specifically designed around the pre-existing protocols at that site. The interventions had different components, such as the type of staff training, specific materials used and level of interdisciplinary support (eg sending charts to GPs on discharge). Therefore, the studies may not be relevant or appropriate to all hospitals in Australia.

Based on the evidence from these publications, there is insufficient evidence to conclude that the use of optimised protocols and staff training within hospitals would lead to improved long-term clinical outcomes in patients, or an increase in the appropriate use of warfarin and aspirin.

Publications evaluating community prescriber training

The literature search identified three trials which evaluated community prescriber training (Crotty 2004, Jackson 2004a and Mandryk 2008). The publications are summarised in Table 6. The trials had varied levels of evidence. Crotty 2004 was a pseudo randomised controlled trial (Level III-1), Jackson 2004a described a non randomised comparison (Level III-2) and a historical controlled comparison (Level III-3), while Mandryk 2008 was an interrupted time series (Level III-3). Crotty 2004 and Jackson 2004a were conducted at a single centre, in contrast to Mandryk 2004 which was aimed at all Australian GPs. Crotty 2004 described a physician and nurse training program at a residential care facility, while Jackson 2004a and Mandryk 2008 evaluated GP education programs.

Table 6 Summary of studies evaluating community prescriber training

Study ID	NHMRC Level of evidence	Population and location	Description of program Duration	Intervention	Control
Crotty 2004	Level III-1 Pseudo randomised controlled trial (regions were randomised, centres were matched to other centres in different regions)	Patients in 20 residential care facilities in Adelaide N=715	Two 30 minute detailing visits by pharmacists to physicians, four 2 hour training sessions for one nurse per faculty and a talk by a pharmacist to all staff. 7 months	Subjects in facilities allocated to the outreach intervention N=381	Subjects in facilities allocated to the control N=334
Jackson 2004a	Level III-2 Non-randomised controlled trial (North vs. South Tasmania) Level III-3 Historical control study (Pre vs. post intervention in South Tasmania)	Patients with AF admitted to hospital with atrial fibrillation in Tasmania N South Tasmania (intervention)=402 N North Tasmania (control)=NR	Stroke prevention guidelines for AF sent to GPs and academic detailing visit by research pharmacist. 12 months	Subjects in Southern Tasmania post intervention N=245 Subjects in Northern Tasmania post intervention N=NR	Subjects in Southern Tasmania pre intervention N=157 Subjects in Northern Tasmania pre intervention N=NR
Mandryk 2008	Level III-3 Interrupted time series without a parallel control group	GPs in Australia N=~20,000	Mail outs and educational visits. 26 months	PBS prescribing data after intervention N=NR	PBS prescribing data prior to intervention N=NR

Abbreviations: GP: General practitioner, NHMRC: National Health and Medical Research Council, NR: Not reported, PBS: Pharmaceutical Benefits Scheme

Summary of key results

Crotty 2004 evaluated an outreach program in which physicians at residential care facilities received two visits by a pharmacist, which included an education session about fall prevention and stroke reduction. An audit of fall rates and prescribing patterns (including aspirin and warfarin use) was conducted at each facility and the information fed back to the physician. One nurse per facility was also given training in change management. The proportion of patients with AF receiving warfarin was not well matched at baseline in the control and intervention facilities (22.6% in the control and 8.6% in the intervention facilities). At the end of the trial, the proportion of patients receiving warfarin was 17.1% in the control facilities and 16.7% in the intervention facilities, which was not statistically significant (p=0.90).

Jackson 2004a described a comprehensive GP education program. GPs in Southern Tasmania were mailed stroke prevention guidelines and received an educational visit by a pharmacist. The proportion of patients with chronic AF using warfarin when admitted to hospital was significantly higher post-intervention compared with pre intervention (40% vs. 59%, p=0.008). There was a significant increase in the proportion of patients with chronic AF at a high risk of stroke receiving warfarin pre and post intervention (41% vs. 66%, p=0.01). There was no significant increase in the proportion of patients receiving aspirin. A comparison of PBS and RPBS dispensing data in Southern Tasmania and Northern Tasmania (the control region) was also presented. Although there was a significant increase in warfarin dispensing occasions in both Southern and Northern Tasmania over the duration of the intervention, the increase in Southern Tasmania was significantly higher (p<0.001).

Mandryk 2008 evaluated the impact of educational activities run by the National Prescribing Service (NPS). The activities included mail outs to all GPs in Australia and one-on-one or small group educational sessions. PBS data was analysed to determine if there were any changes in warfarin prescribing patterns. There was no evidence that the NPS educational program had any impact in the use of warfarin or the number of INR tests requested.

Discussion

Overall, there was insufficient evidence to conclude that community prescriber training would significantly improve warfarin use in Australia. Crotty 2004 found no difference in the proportion of patients prescribed warfarin when residential care staff were trained. Mandryk 2008 concluded that there was no change in prescribing behaviour as a result of GP training. Jackson 2004a reported a significant increase in warfarin use over a 12 month period. However, at the end of the study only 66% of high risk subjects with no contraindications to warfarin were receiving warfarin. This shows that a substantial proportion of subjects in

Southern Tasmania were not being appropriately treated despite the intervention. A further limitation of the study is that Jackson 2004a did not assess the effectiveness of warfarin treatment e.g., an assessment of INR control or bleeding events. In order for this type of education to be beneficial over the longer term, the educational messages would need to be regularly reinforced, and potentially changed over time to ensure it remains effective. These factors were not explored in the trial. The cost-effectiveness of community prescriber training was not evaluated.

Publications evaluating point-of-care testing

The literature search identified three trials which evaluated post of care testing (Bereznicki 2010, Bubner 2009 and McLachlan 2005). The Point-of-Care Testing (PoCT) trial reported relevant outcomes in three publications: Bubner 2009, Gialamas 2009 and Laurence 2010. The publications are summarised in Table 7.

The three studies used different study designs. Bereznicki 2010 was a Level IV study, comparing pre and post test outcomes in the same cohort of subjects, while Bubner 2009 was a Level II cluster randomised controlled trial. McLachlan 2005 compared subjects pre and post intervention as well as comparing intervention subjects with a cohort of historical control subjects. Bereznicki 2010 and McLachlan 2005 evaluated point –of-care testing in the pharmacy setting, working in collaboration with GPs to adjust dosing. INR testing was performed by pharmacists in McLachlan 2005, while patients self-monitored INR following training by a pharmacist in Bereznicki 2010. Both interventions had pharmacist and patient training components. In contrast, Bubner 2009 evaluated point-of care-testing conducted by GPs. Clinicians were trained in the use of point-of-care testing devices and did not receive any warfarin specific education.

Table 7 Summary of studies evaluating point-of-care testing

Study ID	NHMRC Level of evidence	Population and location	Description of program Duration	Intervention	Control
Bereznicki 2010	Level IV Case series with pre-test/post-test outcomes	Patients taking warfarin for ≥6 months in Tasmania and NSW N=28	Pharmacist and patient training in point-of-care testing, patient self-monitoring. 6 months	Subjects after receiving the intervention N=all subjects (case series)	Subjects prior to the intervention N=all subjects (case series)
Bubner 2009 Gialamas 2009 Laurence 2010	Level II Cluster randomised controlled trial	Patients receiving and/or anticoagulation therapy from 53 practices in NSW, SA and Victoria N=944	Point-of-care INR testing performed in general practices. 18 months	Subjects who received point-of-care testing N=572	Subjects who received laboratory testing N=372
McLachlan 2005	Level III-3 Historical control study Level IV Case series with pre-test/post-test outcomes	Patients attending community pharmacies and GPs N=53	Pharmacists providing patient education, support and INR monitoring in collaboration with GPs. 10 months (mean)	Subjects treated after the intervention N=41	Intervention subjects treated prior to the intervention N=20 (of the 41 intervention subjects) Separate cohort of subjects who received usual care N=12

Abbreviations: GP: General practitioner, INR: International normalised ratio, NHMRC: National Health and Medical Research Council, NSW: New South Wales, SA: South Australia

Summary of key results

Point-of-care testing was evaluated by three publications (Bereznicki 2010, Bubner 2009 and McLachlan 2005). Bereznicki 2010 provided an education session to pharmacists, which included identifying patients who would be suitable for self monitoring and providing them with training in the use of point-of-care testing. Pharmacists referred patients to their GP, with the recommendation to set up a home medicine review. The mean TTR at baseline was 57.8%, which increased to 72.5% post intervention, although this was not statistically significant (p=0.11). There was a significant improvement in the mean proportion of tests in range for each patient (55.2% at baseline vs. 71.7% post intervention, p=0.03). There was a significant increase in the number of INR tests per month (1.2 at baseline vs. 2.7 post intervention, p<0.001). Quality of life was measured using the EQ5D, with no significant change over the study (p=0.37).

Bubner 2009 described the results of the PoCT trial. The trial compared point-of-care testing in general practices with laboratory testing for a number of outcomes, including the use of warfarin. There were fewer patients with an INR of 2-3 for point-of-care vs. laboratory testing (57.0 vs. 61.5% p=0.24). The proportion of tests with an INR of 2-3 was significantly lower for point-of-care vs. laboratory testing (55.8% vs. 57.6% p<0.001). A cost effectiveness analysis found point-of-care INR testing to be less effective and more costly than laboratory testing, and therefore not cost-effective. This is discussed in more detail in Section 5.

McLachlan 2005 evaluated the use of point-of-care testing in the pharmacy setting. Pharmacists provided patient education, support and INR monitoring. Results were discussed with the patient's GP. There was no statistically significant difference in the length of time that INR readings were within 2-3 (75% pre intervention vs. 78% post intervention, p=0.66). Quality of life was evaluated using a published assessment tool, with no significant difference reported by patients pre vs. post intervention (p=0.102). Patients in the control arm had a mean of 2.1 INR tests per month, which was higher than patients in the intervention arm (pre intervention 1.7 vs. post intervention 1.6). An economic comparison showed a pharmacist managed anticoagulation service to be more expensive than usual care in the first year, but less expensive in subsequent years due to reduction in the INR testing costs.

Discussion

Overall, there was limited evidence that point-of-care testing was effective. The intervention was not associated with improved quality of life. Although Bereznicki 2011 reported a non-significant increase in the mean TTR and a significant increase in the mean proportion of tests in range for each patient, this was based on a very small sample of patients (N=28).

This data should also be considered in the context of its limited applicability to the wider Australian population. Eligible patients in Bereznicki 2010 were selected by pharmacists, with the report noting that this is not a model of warfarin management suitable for all patients. McLachlan 2005 recruited a larger patient population (N=53) and found no difference in the length of time INR readings were 2-3. The most rigorous study was conducted by Bubner 2009, recruiting 944 patients from 53 practices around Australia, including urban, rural and remote locations. It was a cluster randomised trial, which represents high level evidence (Level II). It was conducted over an 18 month period. Point-of-care testing was associated with a lower proportion of patients with an INR of 2-3 and a significantly lower proportion of tests with an INR of 2-3. The authors concluded that point-of-care testing was less effective than laboratory testing. The report found a significant improvement in outcomes associated with other point-of-care tests, such as HbA1c. This highlights the importance of evaluating INR point-of-care testing and not extrapolating data from point-of-care testing in general.

Bubner 2009 conducted a cost effectiveness analysis and concluded that point-of-care testing was not cost-effective. McLachlan 2005 found point-of-care testing to be more expensive than usual care in the first year, but less expensive in subsequent years. The economic implications of point-of-care testing are discussed in more detail in Section 2.3.

Publications evaluating home medication reviews and patient education

The literature search identified four trials which evaluated home medication reviews and patient education (Peterson 2006, Mullan 2005, Peterson 2010 and Roughead 2011). Jackson 2004b describes a pilot study of 128 patients, with the full dataset of 161 patients described in Peterson 2006. Therefore the trial is referred to as Peterson 2006 throughout. Peterson 2010 and Stafford 2011 presented data from the same trial. The publications are summarised in Table 8. Peterson 2006 was a randomised controlled trial, Mullan 2005 and Peterson 2010 were non-randomised controlled study and Roughhead 2011 was a historical controlled study. Peterson 2006 evaluated the effectiveness of home based educational visits for patients newly initiated on warfarin. Peterson 2010 describes an expanded program evaluating the same intervention. Mullan 2005 describes a warfarin management program which included patient education and a medication review. Roughead 2011 evaluates the effectiveness of Government funded home medication reviews.

Table 8 Summary of studies evaluating home medication reviews and patient education

Study ID	NHMRC Level of evidence	Population and location	Description of program Duration	Intervention	Control
Jackson 2004b Peterson 2006	Level II Randomised controlled trial	Patients initiated on warfarin at Royal Hobart Hospital N=161	4 home based educational visits by a pharmacist. 3 months	Subjects given post discharge INR monitoring N=75	Subjects given usual care N=86
Mullan 2005	Level III-2 Non-randomised controlled trial	Patients prescribed warfarin at Wollongong Hospital N=102	Improved warfarin management program, including patient education, medication review, patient follow-up and community of care between hospital and community setting. 3 months	Subjects managed with the improved warfarin program N=50	Subjects managed with the pre-existing warfarin program N=52
Peterson 2010 Stafford 2011	Level III-2 Non-randomised controlled trial	Patients discharged from 8 hospitals in Australia N=268	2 -3 home visits by a pharmacist, which included INR monitoring and warfarin education. 3 months	Subjects who received post discharge service N=129	Subjects who received usual care N=139
Roughead 2011	Level III-3 Historical control study	Patients making medical claims through the Australian Department of Veteran's affairs N=17,136	Government funded home medical review. 18 months	Subjects who had a home medical review N=816	Subjects who did not have a home medical review N=16,320

Abbreviations: NHMRC: National Health and Medical Research Council, NR: Not reported

Summary of key results

Peterson 2006 evaluated the effectiveness of home based educational visits for patients newly initiated on warfarin at Royal Hobart Hospital. Peterson 2010 describes an expanded program, conducted at eight hospitals in Australia. Peterson 2006 was a randomised controlled trial (RCT), while Peterson 2010 was a non-randomised controlled trial (patients were recruited either during an initial control phase or a subsequent intervention phase). In both studies, the intervention was a home-based visit by a trained pharmacist. Subjects in Peterson 2006 were visited on four occasions, while subjects in Peterson 2010 were visited on two or three occasions depending on risk status. The pharmacist tested the INR and educated the patient on warfarin therapy. The pharmacist contacted the GP with the results of the INR testing, who modified the warfarin dose if appropriate.

Both trials assessed the proportion of patients who had a therapeutic INR. This was defined as an INR of 2.0-3.0 for the majority of patients, and 2.5-3.5 for patients with mechanical heart valves. In Peterson 2006 the proportion of usual care vs. home monitoring patients with a sub-therapeutic INR eight days after discharge was 35% vs. 26%, a therapeutic INR was 38% vs. 67% and a supra-therapeutic INR was 27% vs. 8%. There was a significant difference between the usual care compared with home monitoring groups ($p<0.0008$). In contrast, there was no significant difference in INR control at day eight in the larger Peterson 2010 trial. The proportion of usual care vs. home monitoring patients with a sub-therapeutic INR was 36% vs. 30%, a therapeutic INR was 42% vs. 48% and a supra-therapeutic INR was 22% vs. 22% ($p=0.536$). There was also no significant difference in INR control at day 90. The time in therapeutic range was 55% vs. 56% $p=0.922$, the time below range was 29% vs. 31% $p=0.527$ and the time above range was 16% vs. 13% ($p=0.299$).

Peterson 2006 assessed adverse events 90 days after discharge in the usual care vs. home monitoring groups. The rate of bleeding events was 34% vs. 14% ($p=0.004$), the rate of embolic events was 9% vs. 7% ($p=0.56$) and the rate of unplanned hospital readmissions was 22% vs. 26% ($p=0.56$). Peterson 2010 reported no difference in the rate of major bleeding or thrombotic events (10% in the usual care group vs. 3% in the home monitoring group, $p=0.072$) or unplanned hospital readmissions (28% in the usual care group vs. 28% in the home monitoring group, $p=0.947$) in the 90 days after discharge. The proportion of patients with any bleeding event was significantly lower in the home monitoring compared with usual care (14.7%) group (5.3% vs. 14.7%, $p=0.03$). The rate of thrombotic events was also lower (6% usual care vs. 1% home monitoring), although this was not statistically significant ($p=0.06$). There was also no difference in warfarin adherence (Tool for Adherence Behaviour Screening (TABS) score out of 20) at either day eight (18.7 vs. 18.9, $p=0.560$) or day 90 (18.7 vs. 17.9, $p=0.236$).

Peterson 2010 also assessed quality of life using the EuroQoL – 5 Dimensions (EQ-5D) and the Duke Anticoagulation Satisfaction Scale (DASS). There was no significant difference in the EQ-5D or the DASS scores overall or for the individual domains.

Both publications also undertook an economic analysis. Peterson 2006 calculated a cost saving of $9 million per annum due to a reduction in major bleeds in the three months post discharge for the 20,000 patients initiated on warfarin in public hospitals. The cost of the program was estimated at $4 million per annum. Peterson 2010 performed a more detailed economic analysis and calculated the cost of the program to be approximately $9 million in the first year. The intervention was not cost saving when all healthcare costs were considered. The control arm had total healthcare costs of $4 427.26 per patient, while the intervention arm had total healthcare costs of $5 248.77. The cost per patient of a

percentage reduction in major bleeding events was $391.20, any bleeding event was $87.39 and any bleeding or thrombotic event was $65.20. The costs were lower in the control arm when only warfarin-related costs were considered. This is discussed in more detail in Section 5.

Mullan 2005 evaluated a patient education program run through Illawarra Health's The Ambulatory Care Team (TACT), which provides a community-based healthcare service. Patients were allocated to the control or intervention group depending on the day of the week they were admitted to TACT. An education session was conducted at the patient's house within four days of admission. The education session included a complete medication review, use of a warfarin information booklet, examples of how to combine tablets to get different warfarin doses and improved communication between TACT and the patient's GP. There was no difference in hospital visits between control and intervention patients (21% vs. 18%) or emergency department visits (11.5% of control and 8% of intervention patients). There was no difference in the proportion of INR tests within the range of 2-3: 69.4% in the control group and 71.9% in the intervention group (p=0.56).

Roughhead 2011 retrospectively reviewed the Department of Veterans' Affairs claims database to compare patients who had received a Home Medicines Review (HMR) and those who had not. The HMRs were conducted as part of the government funded HMR program. The outcome measure was hospitalisation as a result of bleeding. There was no significant difference in hospitalisations the first two months after an HMR (HR=1.13, p=0.68). There was a significant reduction in the rate of hospitalisations for bleeding at 2-6 months (HR=0.21, p=0.03), however this effect was not maintained at 6-12 months (HR=1.07, p=0.79). The risk of hospitalisation for bleeding was significantly higher at >12 months (HR=1.61, p=0.003).

Discussion

Overall, there was some evidence that expanded home medicine reviews, including warfarin education and point-of-care testing, can be effective in reducing bleeding events in the short term. A significant improvement in the proportion of patients with a therapeutic INR eight days after discharge was reported in Peterson 2006, but not Peterson 2010. There was also no significant difference in INR control at day 90. However, both Peterson 2006 and Peterson 2010 reported a significantly lower rate of bleeding events although there was no improvement in quality of life. In contrast, Mullan 2005 found no difference in INR control, hospitalisations or emergency room visits. Both interventions featured similar components such as detailed patient education, a review of warfarin dosing and a review of the use of medications by a specifically trained pharmacist. The intervention assessed in Peterson

2006 and Peterson 2010 was more intensive, with patients receiving 2 – 4 visits in the week following discharge. In contrast, patients in Mullan 2005 received a single education session. Peterson 2006 and Peterson 2010 included point-of-care INR testing, which was not a component of Mullan 2005.

The main limitation of these studies is the short duration of follow-up. As highlighted by Roughhead 2011, a significant improvement in outcomes in the short term is often not maintained over long periods. Although this paper reported a significant reduction in hospitalisations for bleeding at 2-6 months post intervention, there was a significantly higher rate of hospitalisations for bleeding after 12 months. Given that most patients would be prescribed warfarin for more than 12 months, establishing the long term efficacy of these interventions is critical. It may be that the lower rate of bleeding events seen in Peterson 2006 and Peterson 2010 is not be maintained past 6 months.

Peterson 2006 and Peterson 2010 concluded that home medicine reviews were cost saving due to the reduction in bleeding events. However Peterson 2010 found that the intervention was more expensive than the control arm when all healthcare costs were considered. This is discussed in more detail in Section 5.

Conclusions

A number of interventions which aim to improve warfarin use have been trialled in Australia. However, there is not sufficient evidence to support the assertion made by the PBAC that warfarin use could be improved by means of an education campaign, or indeed any other intervention. Although some hospital based interventions may be beneficial at the level of an individual hospital, they do not address the issue of achieving and sustaining a longer term therapeutic INR. There was no evidence that community prescriber training improved INR control and limited evidence that it could improve the rate of warfarin prescribing for patients in which it was appropriate. The overall evidence indicates that point-of-care testing is less effective than laboratory testing. There was a reduction in bleeding outcomes associated with home medication reviews and patient education, however the intervention was assessed over a very short time period of 3 months. There was no evidence that this would be maintained without regular reinforcement of the educational message.

The key limitation of the Australian literature is the lack of long term data assessing clinically relevant outcomes. An important difference between medicines and interventions is that the impact of an intervention often attenuates over time, as demonstrated by Roughead 2011. This is not unexpected given that these interventions often require a change in behaviour or additional clinical processes, which if not reinforced may not be maintained. Data from a clinical trial may represent the best practice, with data collected while prescribers and

patients are being monitored and reminded of the intervention being assessed. This is particularly relevant in the studies discussed here, which were all unblinded and therefore have an inherent bias. It is therefore likely that the clinical benefits described in the publications would not be as large if the intervention was introduced for all prescribers and patients in Australia.

An additional limitation is the accessibility issues associated with implementing these interventions, particularly if introduced in preference to medications which are available through all pharmacies in Australia. In contrast, not all GPs or pharmacists are willing or able to provide the additional services required for these interventions. This is most strikingly demonstrated by the low uptake of Government funded home medication reviews (HMRs). A report commissioned by the Department of Health and Ageing to evaluate the HMR program concluded that *"Participation by health professionals has been patchy at best. Even now, after five years of implementation, less than 10% of GPs are participating in the HMR Program"* (Home Medicines Review Program Qualitative Research Project Final Report, 2008). There is currently a shortage of GPs, with existing GPs less able to allocate time to additional training and procedures. Similarly, there is a shortage of trained HMR pharmacists, as acknowledged in Peterson 2010. All of the pharmacy based interventions described here were trialled in pharmacies which had agreed to participate in the trial. It is unlikely that all pharmacies in Australia would choose to participate in a warfarin program, or they may not have sufficient resources. The lack of available medical and pharmacy staff would be even more pronounced in rural and remote settings. As noted in Peterson 2010, there are also accessibility issues for patients from a non-English speaking background given the shortage of multilingual GPs and pharmacists. It is therefore extremely unlikely that the interventions discussed here could be introduced in enough pharmacists and/or medical practices to ensure that all Australians taking warfarin had access.

There is also evidence that some interventions are only applicable to a subset of patients prescribed warfarin. For example, in Bereznicki 2010 patients were selected by a health professional on the basis of being highly motivated and interested in becoming involved in their own healthcare. The report noted that this is not a representative sample of patients prescribed warfarin and that the intervention is not a model of management suitable for all patients. This is an inherent limitation of interventions which require patient involvement, especially as NVAF patients are typically elderly.

Evidence for the efficacy of dabigatran comes from a high quality clinical trial (Connolly, 2009) which found a significant reduction in key clinical outcomes such as haemorrhagic stroke, intracranial haemorrhage and bleeding events when patients were followed for up to 36 months (RELY, Connolly *et al* 2010). In contrast, there is no evidence that any

intervention assessed to date is associated with a significant improvement in long term, clinically relevant outcomes in patients receiving warfarin. There are also significant barriers to ensuring that any intervention is available to all Australian warfarin patients. These issues must be considered when evaluating the relative merits of warfarin interventions.

4.2. International research

A review of the international literature was conducted. Key interventions and publications were identified and are discussed in more detail.

- Anticoagulation clinics: Dedicated anticoagulation clinics with specially trained staff are a common model of care in countries in some countries. A review of the effectiveness of anticoagulation clinics is presented, as well as a discussion of some of the considerations associated with introducing similar clinics in Australia.
- Pharmacogenetic testing: A link between specific genes and differences in warfarin metabolism has recently been researched. This section discusses the clinical effectiveness and cost effectiveness of pharmacogenetic testing.
- Community Pharmacist-led Anticoagulation Management Service (CPAMS) study: This recent study from New Zealand evaluated pharmacist-led anticoagulation management. Point-of-care INR monitoring was performed by pharmacists who shared care with clinicians.
- Canadian Agency for Drugs and Technologies in Health (CADTH) systematic review and economic evaluation: This recent systematic review evaluated of models of warfarin management. An economic evaluation was also conducted.

Applicability concerns

The results of international trials are broadly informative, but it is not appropriate to automatically assume that the results are directly applicable to the Australian health care setting. International health care intervention trials are conducted within a different health care system which will have a significant influence on the reported outcomes. For example, clinicians may use different treatment algorithms, treat different patient populations or have access to medicines not available or widely used in Australia. Patient populations must be closely compared, particularly in terms of baseline disease and demographic characteristics. Treatment may be given in different settings, for example INR testing may be routinely performed as an inpatient procedure in some countries, or may be performed in specialist anticoagulation clinics. Care must be taken when extrapolating findings from these types of studies. For example, changes to a procedure in a specialist anticoagulation clinic may not be applicable to the Australian setting where these clinics are not available. Alternately, the

results must be considered in the context of the feasibility, cost and evidence for setting up similar clinics in Australia. Generally, international studies would first have to be replicated in Australia prior to being introduced more widely. The additional costs associated with pilot programs and evaluations of the program must be considered, in addition to the opportunity costs associated with delaying the introduction of new anticoagulants or these programs while they are evaluated.

Anticoagulation clinics

An anticoagulation clinic is a specialised program of patient management focused predominantly, if not exclusively, on managing oral anticoagulation (Ansell and Hughes 1998). These clinics have been developed in response to the increasing recognition of the difficulties with providing safe and effective anticoagulation control with currently available anticoagulants. Dedicated anticoagulation clinics are not common in Australia, but in a number of other countries they are the most frequently used model of care for patients receiving anticoagulants. This following section of this report includes recent systematic reviews and meta-analyses of the effectiveness of anticoagulation clinics in comparisons to other models of care. The relative cost-effectiveness of clinics is also discussed. The subsequent sections describe the different types of anticoagulation clinics used worldwide, and the issues for consideration if anticoagulation clinics were to be introduced in Australia.

Systematic reviews, meta-analyses and economic analyses

Recent systematic reviews and meta-analyses of anticoagulation clinics were reviewed and are presented here. As discussed in more detail in the following section, the components of each anticoagulation clinic vary considerably. It may therefore not be appropriate to draw conclusions about anticoagulation clinics as a model of care given the marked differences between the clinics described in these studies.

Van Walraven *et al* 2006 conducted a systematic review of the literature to determine the effect of study setting on INR. A total of 67 studies were identified, with 123 study arms. Of these, 68.3% were from anticoagulation clinics, 7.3% were from clinical trials, and 24.4% were from community practices. Differences in INR control between these three study settings was evaluated using a meta-regression model (see Table 9). Across all studies, the mean TTR was 64% (95% CI 62%, 66%). The TTR was highest in randomised clinical trials (66.4%, 95% CI 59.4%, 73.3%), and slightly lower for anticoagulation clinics (65.6%, 95% CI 63.7%, 67.7%). The mean TTR in the community was lower than for anticoagulation clinics (56.7%, 95% CI 51.5%, 62.0%). After adjusting for differences between studies, there was no significant difference in TTR between randomised controlled trials and anticoagulation clinics (3.9%, 95% CI 10.7%, 2.9%). There was a significant difference between

anticoagulation clinics and community practices (8.3%, 95% CI 4.4%, 12.1%). The meta-regression model showed that study setting was the most significant factor predicting INR control.

Table 9 Study setting and INR control

Study setting	No (%)	Unadjusted % mean TTR (95% CI)	Adjusted % effect TTR (95% CI)	P value
RCT	9 (7.3)	66.4 (59.4, 73.3)	Reference group	<0.0001
Anticoagulation clinic	84 (68.3)	65.6 (63.7, 67.7)	- 3.9 (-10.7, 2.9)	
Community	30 (24.4)	56.7 (51.5, 62.0)	-12.2 (-19.5,-4.8)	

Abbreviations: RCT:randomised controlled trial; TTR: time in therapeutic range

Connock *et al* 2007 conducted a systematic review to evaluate the clinical and cost effectiveness of patient self-testing and self-management of oral anticoagulation treatment. In patient self-testing the results of the test are relayed to a physician who then adjusts the patient's anticoagulant dose. In patient self-management, the patient adjusts the dose of anticoagulant themselves based on the test results. The literature search identified 15 articles, of which eight included specialised anticoagulation clinics as a comparator. The pooled estimates of INR time in range are shown in Table 10. When anticoagulation clinics were compared with either patients self-testing or self-management, the INR time in range was similar (66.3% vs. 67.1%). There was also no difference when anticoagulation clinics were compared with patient self-testing only (67.8% vs. 67.7%) or patient self-management only (66.2% vs. 67.0%). There was also no difference in the pooled estimates of INR time below, in and above the therapeutic range.

Table 10 Type of care and INR control

Type of care	Number of trials	% INR time in range, weighted by patient years	
		Anticoagulation clinic	PSM/PST
Anticoagulation clinic vs. PST or PSM	8	66.3	67.1
Anticoagulation clinic vs. PST	4	67.8	67.7
Anticoagulation clinic vs. PSM	5	66.2	67.0

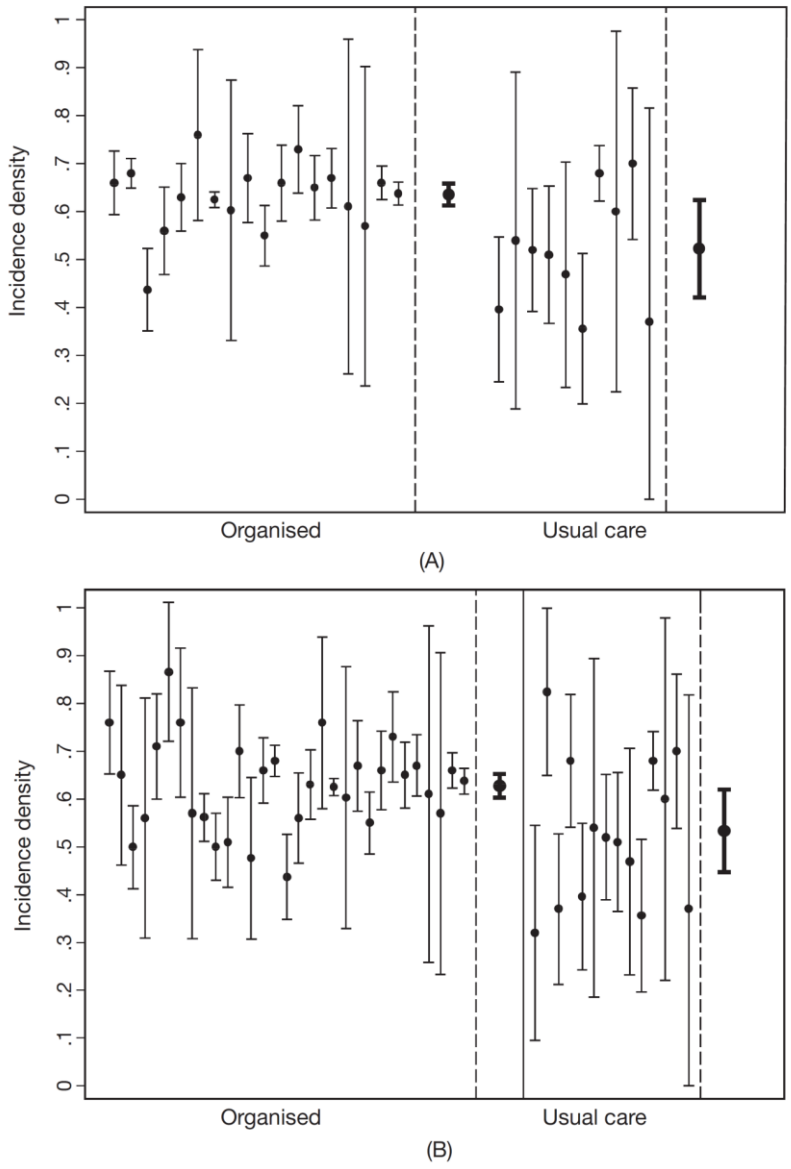
Abbreviations: INR: International normalised ratio, PSM=Patient self management, PST=Patient self testing

Dolan *et al* 2008 evaluated the relationship between different clinical settings and anticoagulation control. A systematic review identified 36 studies which met the inclusion criteria. The primary analysis included 22 studies which recruited patients with AF and had a target INR range of 2.0 – 3.0. The secondary analysis included an additional 14 studies which had a mixed patient population (i.e., AF and other conditions) and/or had a target INR range of 2.0 – 3.5. The paper defined studies as either organised care, which included

studies conducted in specialist anticoagulation clinics, or usual care, which was care delivered in non-specialist settings including family practice facilities.

The TTR for the individual studies is shown in Figure 7. Both the primary and secondary analysis showed a significantly higher TTR for organised care compared with usual care. TTR was 11.3% (95% CI 0.1%, 21.7%) higher in the primary analysis, and 9.4% (95% CI 0.5, 18.4%) higher in the secondary analyses.

Figure 7 Proportion of time spent in therapeutic INR range expressed as an incidence density with 95% confidence interval.

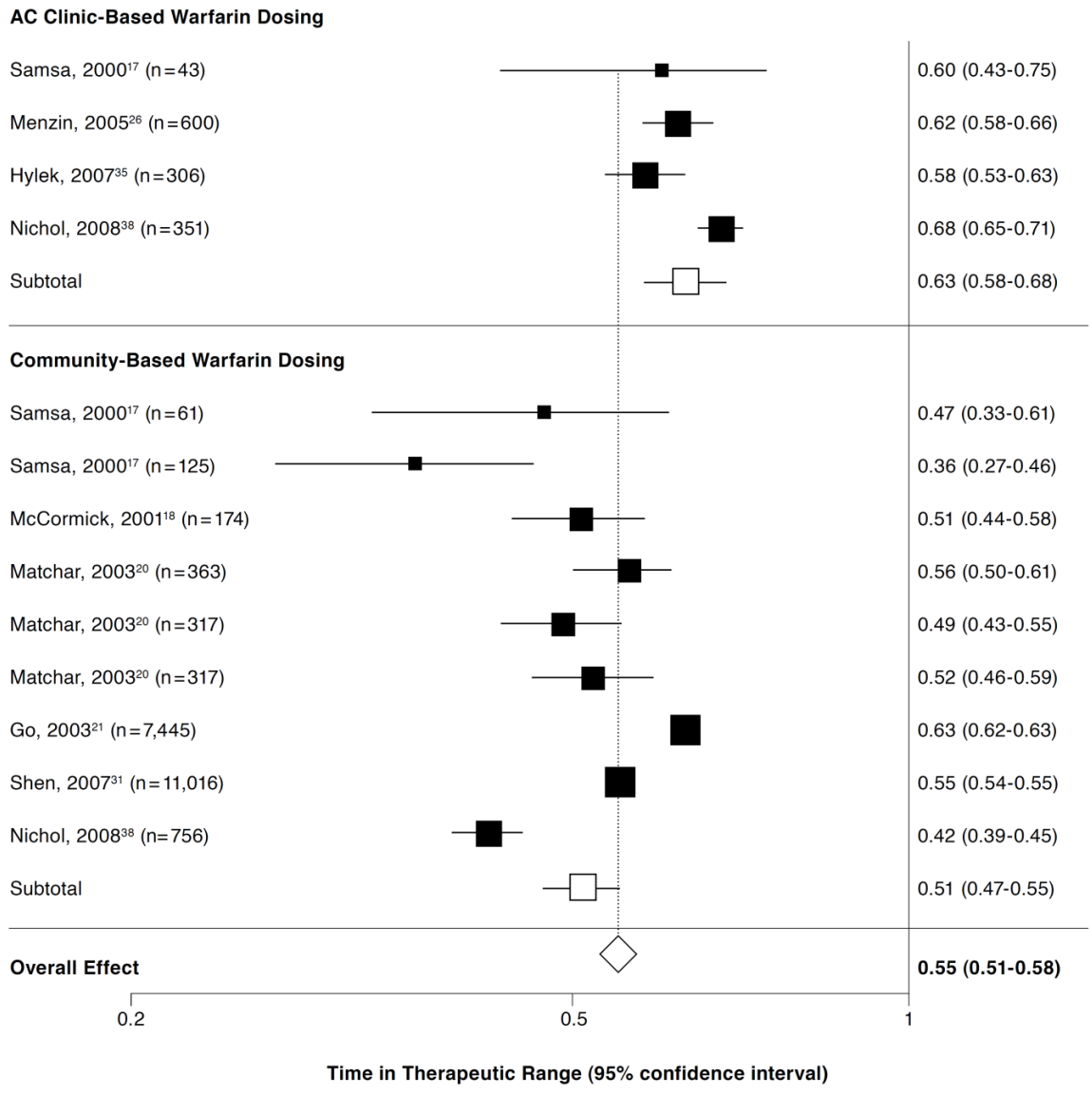


Abbreviations: INR: International normalised ratio
Notes: Pooled estimate for each category of monitoring organisation is shown in bold. (A) primary data set, (B) secondary data set

Baker *et al* 2009 conducted a systematic review and meta-regression of warfarin control and study setting. Studies must have been conducted in AF patients in the USA. The literature

search identified eight trials with 14 study arms. The TTR was higher in patients treated in an anticoagulation clinic (63%, 95% CI: 58%, 68%) compared with community practice (51%, 95% CI: 47%, 55%). This is shown in Figure 8. After controlling for covariates, meta-regression analyses showed that patients treated in a community setting spent 11% (95% CI: 2%, 20%) less time in therapeutic range compared with patient treated in an anticoagulation clinic. The authors noted that although anticoagulation clinics improved TTR, patients still spent over one-third of their time outside of the therapeutic range.

Figure 8 Study setting and INR control



Abbreviations: INR: International normalised ratio
Notes: The squares represent individual studies, and the size of the square represents the weight given to each study in the meta-analysis. Error bars represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending upwards from 1 is the null value.
Abbreviations: AC=anticoagulation.

Pengo *et al* 2006 described an observational, retrospective study of oral anticoagulation therapy in the US, Canada, France, Italy and Spain. Physicians were asked to participate in

the study if they used the model of care considered representative of the model of care predominately used in each country. This was routine medical care in the US, Canada and France and anticoagulation clinics in Spain and Italy. Physicians were asked to randomly select a cohort of patients with non-valvular atrial fibrillation to be included in the analysis. The results were not analysed statistically, however the proportion of patients with an INR of 2.0-3.0 was generally higher in the countries which used anticoagulation clinics (69.5% in Italy and 64.9% in Spain) when compared with the countries which used usual care (58.1% in the US, 62.8% in Canada and 59.3% in France). The mean time between INR tests was shortest in Italy (20.0 days) and highest in Spain (30.8 days). The publication did not explore the difference in usual care between the different countries, or the specific model of anticoagulation clinic used in Italy and Spain. The results show that anticoagulation clinics may be associated with a modest improvement in TTR, although the results are confounded by the different health care systems used in each country.

Table 11 Anticoagulation control and study setting

	US	Canada	France	Italy	Spain
Model of care	Usual care	Usual care	Usual care	Anticoagulation clinic	Anticoagulation clinic
Number of patients	638	148	264	177	218
Time in of INR 2.0-3.0 (%)	58.1	62.8	59.3	69.5	64.9
Mean INR test interval (days)	25.3	24.3	23.6	20.0	30.8

Abbreviations: INR: International normalised ratio

Lafata *et al* 2000 conducted an economic analysis of usual care compared with anticoagulation clinics and patient self-testing. The baseline model include INR time spent below and above therapeutic range, with data obtained by taking an average values reported by a number of large clinical trials. The publication did not describe the different types of anticoagulation clinics assessed in the trials and it is likely that there was a degree of heterogeneity between the studies used to calculate these values.

The frequency of INR testing was higher in anticoagulation clinics compared with usual care (23 vs. 14 tests per year), however these cost increases were offset with the savings due to avoided adverse events. In comparison patient self-testing was also associated with an increase in INR testing (52 tests per year) and there was an overall increase in medical care costs as the savings due to reduced adverse events were not offset by the increased costs of testing. The cost per QALY was calculated, and anticoagulation clinics were considered cost-saving when compared with usual care. Patient-self testing had an incremental cost-effectiveness ratio (ICER) of US$153,504 when compared with anticoagulation clinics. The

authors noted that the ICERs were markedly different if the costs incurrent by patients and their caregivers were included due to the increased frequency of testing and the associated time and travel costs. When these costs were also considered, anticoagulation clinics had an ICER of US$232,226 when compared with usual care, while patient self-testing was cost saving compared with anticoagulation clinics.

Structure of anticoagulation clinics

An anticoagulation clinic typically refers to a dedicated anticoagulation service run by staff members who are specifically trained in anticoagulation care. Globally, anticoagulation clinics vary in the level of service offered, the types of staff who offer the service and the patients who are able to access the service. The primary caregiver could be a clinician, nurse or pharmacist, with multidisciplinary support given by a team comprising of a variety of clinical staff such as haematologists, cardiologists and nutritionists. Some anticoagulation clinics are physician-led, where patients visit a clinician at the clinic to have INR testing performed and dose adjustments made as appropriate. Collaborative care is provided by nurses, pharmacists and/or other staff members. Lee *et al* 2011 describes a physician led clinic. In this study, the physician was responsible for developing the care plan, including interpretation of INR results, determination of warfarin dose adjustments, and timing of follow-up visits and frequency of INR monitoring. A clinical pharmacist provided a one-on-one educational session to the patients. Nurses were the liaison between the pathological laboratory and the physician, as well as being responsible for contacting patients to deliver physician instructors and organise appointments.

An alternative model of care is a pharmacist-led anticoagulation clinic. In most pharmacist-led clinics, pharmacists monitor INR and recommend dose adjustments in collaboration with a physician. Point-of-care testing is a common component of pharmacist-run anticoagulation clinics. The level of care provided can be more extensive, such as the anticoagulation clinic described in Witt *et al* 2005 where specifically trained pharmacists facilitate all aspects of anticoagulation therapy. This includes patient education, the ordering of relevant laboratory tests including INRs, the adjustment of anticoagulation medication doses, the planning for interruption of anticoagulation therapy during invasive procedures, and the management of adverse events.

One of the most comprehensive models of anticoagulation clinics has been established in the Netherlands. This is a nationally coordinated anticoagulation service. All patients receiving anticoagulation treatment are referred to a clinic in their region for anticoagulant monitoring (Rosendaal *et al* 1996). As reimbursement is based on participation in these clinics, very few patients receive treatment outside of a specialised clinic. The clinics are part

of the Federation of Dutch Thrombosis Services, which is an organisation that sets guidelines for treatment, facilitates laboratory quality control, organises conferences and postgraduate training and promotes research. Anticoagulation clinics may be associated with a hospital and some clinics also monitor inpatients. A nurse trained in anticoagulation services provides care for the patients, taking a medical history, conducting education and collecting blood samples. Medication dosage is monitored by a clinician, aided by a computerised algorithm.

The Department of Veterans Affairs (DVA) in the USA provides anticoagulation therapy through anticoagulation clinics. The DVA provides guidance on the structure of each anticoagulation clinic (DVA 2010), however there are variations between each clinic. The Veterans Health Administration manages 128 sites, each of which includes a hospital, an outpatient care centre, and several outlying community-based clinics (Rose *et al* 2011). Each site has a specialised anticoagulation clinic, which is usually run by clinical pharmacists under the supervision of a medical director. The clinics monitor INR and provide medical advice to patients, such as educating patients on dietary requirements, as well as providing training to staff members. Patients have the option of using self-testing devices where appropriate. A review of the anticoagulation clinics by Rose *et al* 2011 described the differences in clinic structure. Approximately 50% of clinics conducted visits face to face, while the remainder provided care by telephone or mail. There was also variation in the staff at the centre, degree of documentation and patient tracking, use of quality improvement programs and coordination of care. None of these differences was a statistically significant predictor of improved anticoagulation control.

Establishing anticoagulation clinics in Australia

Implementing a system of anticoagulation clinics in Australia would require a significant investment of resources. The first step in establishing anticoagulation clinics in Australia would be evaluating which model would be most appropriate in the Australian clinical setting. A key consideration is the type of clinical staff who will be the primary service provider. Generally, anticoagulation clinics are either physician or pharmacist run. Currently, Australian pharmacists are unable to perform certain clinical functions, such as ordering INR tests and undertaking warfarin dose adjustments. If these functions were to be a component of pharmacist-led anticoagulation clinics, significant and costly changes to current Australian clinical practice would be required, for example development of training programs for pharmacists in anticoagulation management, which would be associated with additional costs.

Burnett *et al* 2011 describe the challenges of setting up an anticoagulation clinic in a hospital in the USA. In addition to need to develop an appropriate service model with the resources available, protocols for monitoring and evaluation of anticoagulation dosing had to be established. Staff members received extensive training, with a focus on both inpatient and outpatient management. The clinic had to develop a range of tools such as anticoagulation alerts and monitoring alerts to ensure effective communication between members of the multidisciplinary team, as well as metrics to evaluate the effectiveness of the clinic. The authors note that there is no single anticoagulation clinic model that will be appropriate for all institutions and that hospital and clinic specific models must be developed. It is therefore important that the most appropriate model of anticoagulation clinics for the Australian healthcare setting be determined prior to multiple clinics being established. This would require a review of the international literature in the context of the existing Australian health care system, determining which components of international clinics are relevant and feasible and then running pilot studies to evaluate the clinical efficacy in Australian patients. As discussed in Section 5, anticoagulation clinics are expensive and it would be an inefficient use of resources to introduce anticoagulation clinics without Australian specific evidence.

The most successful models of anticoagulation clinics require almost universal coverage, ensuring that all patients have access to a clinic. As previously discussed, there is currently a shortage of GPs and pharmacists in Australia. The lack of available medical and pharmacy staff would be even more pronounced in rural and remote settings. Anticoagulation clinics are effective in small countries such as the Netherlands, but are a more challenging model of care in large, less densely populated countries such as Australia. There is some evidence that anticoagulation clinics could be used in rural and remote regions. Hodge et al 2008 described a study conducted in rural Victoria which included an anticoagulation clinic, point-of-care testing and patient education. The clinic employed a specially trained nurse, part-time pharmacist and part-time dietician at the local hospitals. Subsequently, it was expanded to four other towns in the region. The clinic conducted INR testing and a one-hour, one-on-one patient education program. All INR tests were forwarded to the patient's doctor, who managed warfarin dosing. The mean TTR was 68.6%, although there was no control arm. This model of rural anticoagulation clinic could be further evaluated with controlled trials.

Conclusions

Meta-analyses of anticoagulation clinics compared with usual care suggest that anticoagulation clinics are more effective at maintaining INR within a therapeutic range. The improvement in TTR was approximately 5% - 10%. No difference was found between anticoagulation clinics and patients self-testing and management. Care must be taken when interpreting the results of these studies due to the significant differences between individual

anticoagulation clinics and varying standards of usual care. It must be noted that although anticoagulation clinics are associated with more effective INR control, the meta-analysed TTRs were less than 70% in all publications. Even with specialised care patients were still out of the optimal INR range at least 30% of the time. Therefore, it may be appropriate to use other methods of improving warfarin control in addition to anticoagulation clinics. The effects of anticoagulation clinics on patient relevant outcomes, not just TTR, would need to be established.

There is significant variability in the structure of anticoagulation clinics. Prior to the introduction of anticoagulation clinics, the most appropriate model for the Australian setting would need to be researched, particularly in terms of physician-led versus pharmacist-led, and in the context of the current health care delivery system in Australia. All anticoagulation clinics are resource intensive, with the need for a specially trained, multidisciplinary team. There would be accessibility issues if some Australians were unable to access an anticoagulation clinic, therefore the location and number of clinics would need to be considered. Anticoagulation clinics could be used in Australia as an intervention for improving warfarin control, however further research would need to be undertaken in the Australian setting to establish the most appropriate structure and the cost-effectiveness.

Finally, the cost-effectiveness of establishing anticoagulation clinics compared with reimbursing the use of dabigatran would need to be demonstrated with the same rigour with which dabigatran was evaluated.

Pharmacogenetic testing

Recent research has shown that genetic variations in the CYP2C9 and VKORC1 genes are associated with differences in warfarin metabolism and sensitivity. CYP2C9 codes for the cytochrome P450 enzyme, which metabolises warfarin. Single nucleotide polymorphisms (SNPs) in this gene, such as CYP2C9*2 and CYP2C9*3, reduce the activity levels of this enzyme. This suggests that patients with these SNPs would require lower maintenance dosages of warfarin and may take a longer time to achieve steady-state plasma warfarin concentrations (Gulseth *et al* 2009). This could increase their risk of supratherapeutic INRs and subsequently lead to higher rates of bleeding events if standard warfarin dosing protocols were used. VKORC1 codes for the vitamin K epoxide reductase complex subunit 1 gene which is the enzymatic target of warfarin. Mutations in this gene have been associated with a deficiency in vitamin-K-dependent clotting factors, resulting in increased sensitivity to warfarin (Gulseth *et al* 2009). Multiple SNPs in this gene have been identified. The association between SNPs and warfarin insensitivity in VKORC1 is less well established

than for CYP2C9. It is postulated that the SNPs in VKORC1 produce higher or lower levels of VKOR enzyme, and are therefore associated with different warfarin dose requirements.

Although a link between specific genetic variations and warfarin metabolism and sensitivity has been established, the clinical relevance of pharmacogenetic testing remains unclear. It has been proposed that dosing algorithms based on pharmacogenetic information should allow clinicians to more accurately predict each patient's response to warfarin. However, the CYP2C9 and VKORC1 status predicts less than half of the variation in the response to warfarin (Martin 2009). Warfarin dose variability is associated with many factors, including age, height, body weight, race, dietary vitamin K intake, current illness, drug interactions as well as genetic variation. A review published in Australian Prescriber noted that current linear regression analyses which consider genetic polymorphisms of CYP2C9 and VKORC1, in addition to factors such as body weight, body surface area and height, have been able to capture only approximately half of the large inter-and intra-patient variation in dose requirements (Martin 2009). Other factors such as vitamin K status, alcohol intake and additional genetic factors are likely to account for some of the remaining difference in warfarin requirements. Although pharmacogenetic information improves the predictive ability of linear regression analyses, it is a single factor which must be considered in the context of other clinical indicators.

The clinical effectiveness of dosing algorithms which included pharmacogenetic information was evaluated in a systematic review and meta-analysis (Kangelaris *et al* 2009). To be eligible for inclusion, the trial must have been a randomised study comparing a pharmacokinetic algorithm with a standard algorithm. Three trials, evaluating three different algorithms, were identified (Hillman *et al* 2005, Caraco *et al* 2008 and Anderson *et al* 2007). There was no significant difference in the meta-analysed rate of major bleeding (RR 0.69, 95% CI 0.16, 2.91) when the pharmacogenetic algorithm was used. The percentage of time INR was in the therapeutic range could not be meta-analysed due to the significant heterogeneity between the trials. Although a significant difference was found in Caraco *et al* 2008 (SMD -0.57, 95% CI -0.86, -0.28), this study was considered to be of poor quality due to inadequate randomisation and blinding, lack of ITT analysis and inappropriate follow-up. In contrast, no significant difference was found in Hillman *et al* 2005 (SMD -0.01, 95% CI -0.64, 0.63) or Anderson *et al* 2007 (-0.05, 95% CI -0.32, 0.23), which were considered good quality and excellent quality respectively. Caraco *et al* 2008 reported a trend towards improvement in outcomes such as lower incidence of minor bleeding, decreased time to therapeutic INR, decreased time to stable warfarin dose and fewer days of INR >3. However, Hillman *et al* 2005 or Anderson *et al* 2007 found no difference in these outcomes.

Overall, the authors concluded that there was insufficient evidence to support the use of pharmacokinetic dosing to guide warfarin therapy. RCTs published after this systematic review supported this conclusion. Huang *et al* 2009 found that the pharmacogenetic algorithm was associated with a shorter time to achieving an INR of 1.8 – 3.0 (24 days vs. 35 days in the control arm, p=0.001). Patients treated using the pharmacogenetic algorithm also spent more time with an INR of 1.8 – 3.0 (28 days vs. 22 days, p=0.001) and were more likely to reach a stable dose (50% vs. 61.7%, p=0.013). However, there was no difference in the time of dose adjustments in the hospital (19 days vs. 20 days, p=0.300) or the rate of serious adverse events (11.5% vs. 13.3%, p=0.757). McMillin *et al* 2010 evaluated a pharmacogenetic dosing algorithm in patients receiving warfarin after joint replacement surgery. There was no significant difference in the mean number of doses to first therapeutic INR (3.9 doses for the pharmacogenetic algorithm vs. 3.4 doses for the control algorithm) or the mean number of doses before the first dose adjustment (3.1 doses for the pharmacogenetic algorithm vs. 3.6 doses for the control algorithm). There was also no significant difference in the incidence of adverse events, time to first supratherapeutic INR, and percent of INR determinations that fell below, within, and above the therapeutic range. Burmester *et al* 2011 reported that patients in the interventional arm did not achieve greater time in therapeutic range (30.8% vs. 29.1%, p=0.564). There was also no difference in time to stable therapeutic dose (31 days vs. 29 days, p=0.90). There was also no difference in time in INR >4 or the rate of adverse events between the two study arms. Overall, these studies found no significant improvement in clinical outcomes when pharmacogenetic algorithms were used.

The cost-effectiveness of pharmacogenetic screening has been explored in a number of publications. McWilliam *et al* 2008 published a cost-analysis of pharmacogenetic testing. However the analysis was not based on any clinical trial data, with assumptions made about the potential effectiveness of pharmacogenetic screening. The authors concluded that serious bleeding events could fall by 4,500 – 22,000 events per year if genetic-based dosing proved to be effective. The additional cost per patient could range from US$300 to cost saving. A number of publications have described economic models based on clinical trial data. Eckman *et al* 2009 evaluated pharmacogenetic screening in patients with atrial fibrillation newly initiated on warfarin. Screening was not found to be cost effective, with an ICER of US$171,800 per QALY. The model was sensitive to the cost of the screening test, time taken for results to be available and effectiveness of the algorithm in preventing major bleeding. You *et al* 2009 evaluated pharmacogenetic guided dosing on patients initiating warfarin therapy. The reported ICER was US$347,059 per QALY. The three most influential variables on the ICER were genotyping cost, relative percentage reduction in out-of-range

INRs in the genotype-guided dosing group and percentage of out-of-range INRs in the standard dosing group. Meckley *et al* 2010 evaluated the addition of pharmacogenetic screening for patients receiving warfarin. The ICER was US$60,725 per QALY. The largest influence on the ICER was the cost of the screening test. The number of screening tests must also be considered, with the total cost increasing when multiple alleles are tested (eg CYP2C9 alone compared with both CYP2C9 and VKORC1). The authors of all three papers concluded that there was considerable uncertainty in the economic value of pharmacogenetic testing, with the base case ICER being outside the range generally considered cost-effective.

The Australia and New Zealand Horizon Scanning Network (ANZHSN) evaluated the evidence for CYP2C9 testing in patients receiving warfarin (ANZHSN, 2010). The report noted that pharmacogenetic testing was not regularly used in Australia or internationally. A small number of laboratories in Australia perform CYP2C9 and VKORC1 testing, with costs ranging from $50 - $90. All commercial platforms and in-house assays assessed in the report were considered accurate in terms of identification of specific CYP2C9 and VKORC1 polymorphisms. The review noted the need for large clinical trials to determine the clinical utility of genotyping all patients prior to commencing warfarin therapy. A further limitation was the lack of Australian specific economic analyses. The report concluded that these issues should be considered before pharmacogenetic testing enters routine clinical practice in Australia.

Genetic testing for variations in the CYP2C9 or VKORC1 genes is currently not funded by Medicare. The test is available in some laboratories, with the full cost of the test paid borne by the patient. In order for these tests to be reimbursed they would need to be considered by the Medical Services Advisory Committee (MSAC), who would evaluate the strength of evidence relating to the safety, effectiveness and cost effectiveness of testing. As discussed above, there is limited evidence that pharmacogenetic testing is clinically effective or cost effective. Even if additional data were available, the average duration from lodgement to listing through the MSAC process is over 30 months (O'Malley 2010). Consequently, it is unlikely that pharmacogenetic testing will be reimbursed and made available to all Australians in the near future.

When all of the current data is considered, there is insufficient evidence to suggest that the use of pharmacogenetic information improves clinical outcomes in patients receiving warfarin. The results from three different economic models indicated that pharmacogenetic testing was not cost effective. This was supported by a recent publication (Johnson *et al* 2011) which reviewed the evidence for pharmacogenetic testing and concluded that *"routine application of this biotechnology to clinical medical care is not yet recognized to be cost*

effective or clinically useful." Given the lack of supportive clinical and economic data, pharmacogenetic testing is unlikely to be reimbursed by Medicare. Pharmacogenetic testing is therefore not a model of health system delivery which could currently be used to optimise the use of warfarin in Australia.

Pharmacist-led Anticoagulation Management

The final report of the New Zealand Community Pharmacist-led Anticoagulation Management Service (CPAMS) project has recently been published (Shaw *et al* 2011). It was an observational study describing the outcomes of a new model of care involving point of care testing performed by pharmacists. The subjects were patients taking warfarin. An online decision-support system provided dosing recommendations and allowed pharmacists to communicate with GPs. A total of 693 patients were referred to the service by their general practitioners, which was provided in 15 pharmacies across New Zealand. The majority of patients (74%) were taking warfarin for the prevention of ischaemic stroke associated with atrial fibrillation. The mean TTR in the 671 patients for whom data was available for evaluation (at least 2 INR results) was 78.6% within the 26-week evaluation period, although this data was uncontrolled. A total of 106 patients (15.3%) withdrew from the service. The number of minor adverse events reported in the trial was 436 were reported during the study period, with 10 major adverse events (seven major bleeds and three thromboembolic events).

Comparative data was only available for a subset of 154 patients. INR data for the 6-months preceding the implementation of the service was evaluated. In these patients, the mean TTR was 60.4% under standard care provided by GPs and 77.5% under the intervention ($p < 0.001$). This is the only comparative data available from the study report and it is therefore difficult to draw conclusions from the other outcomes presented in the report.

Patients were enrolled in the study based on the recommendation of their pharmacist, GP or practice nurse. They could also volunteer themselves for the trial. There is a selection bias towards more stable patients, as people with unstable INRs are not as likely to have been referred to the service. There was no apparent change in the testing interval in patients with pre-CPAMS INR data available. As there was no control group controlling for some of these variables, it is unknown how each factor contributed to the improvement in INR control compared to standard care. Adverse event data presented in the report were based on patient reporting, and were not verified using GP or hospital records, making the interpretation of these data difficult.

The CPAMS intervention is broadly similar to the PoCT trial (see Bubner 2009 page 45). The main difference between the trials was the use of a computerised decision-support tool. The

key limitations of this study are the lack of comparative data and selection bias. It is also a model of care which is not appropriate for all patients, particularly patients who require or prefer more regular interactions with their GP. This intervention would need to be tested in a controlled way in Australian to evaluate its effectiveness and costs prior to being introduced as a routine service. Long term health outcomes would also need to be assessed.

Canadian Agency for Drugs and Technologies in Health (CADTH) review of warfarin management

CADTH conducted a systematic review of the literature in order to compare the clinical effectiveness of different models of warfarin management. The report identified one HTA and eight systematic reviews or meta-analyses and 18 primary studies. They evaluated anticoagulation clinic care, different models of specialised care, self-testing or self-management computer-assisted anticoagulant dosing.

The key findings of the clinical systematic review were:

- Specialised anticoagulation services improve TTR compared with usual care.
- Improvement of TTR within the included studies did not necessarily translate into a reduction in haemorrhage, thromboembolism, or need for additional medical care.
- The evidence available that compares different specialised models of care or service components is limited in both quantity and quality.
- The effect of patient self-testing (PST) or patient self-management (PSM) on TTR was mixed, with studies showing either improved TTR with patient self-testing / patient self-management (patient self-testing alone or in combination with patient self-management) or no difference between models of care.
- Effects on clinical outcomes were also mixed, but patient self-testing / patient self-management generally resulted in lower mortality rates and reduced incidence of thromboembolism.
- Patient self-testing / patient self-management did not affect the rate of bleeding events. Patient self-testing / patient self-management may improve quality of life and patient satisfaction.

The systematic reviews indicated that specialised anticoagulation clinics were associated with higher TTR compared with usual care, but do not tend to result in significant differences in bleeding events, thromboembolism, or mortality. There was a difference between RCT evidence and non-randomised trials, which may be more reflective of actual practice. The results of the systematic reviews were supported by findings from five additional trials.

Systematic reviews comparing patient self-testing or self-management with other models of anticoagulation care showed that PST/PSM resulted in lower mortality rates and lower incidence of thromboembolic events, but there was no significant difference in the rates of bleeding events where reported. TTR was similar between PST/PSM patients and those receiving care in anticoagulation clinics, but self-testing or management resulted in better TTR than usual care in one HTA. One meta-analysis showed that use of point-of-care monitoring devices in any setting improved INR control. In contrast to the systematic reviews, results from additional primary studies indicated an increase in TTR with PST/PSM compared with specialised anticoagulation clinic care, but no difference compared with usual care. One study found, when patients were stratified based on quality of INR control (TTR above or below 60%), that patients with poor control had a significant improvement in TTR when switched to PSM. One of the primary studies showed a trend toward fewer bleeds or thromboembolisms with self-testing, but no statistical analysis was provided.

Four articles compared the use of computer dosing algorithms with manual dosing by medical staff. These studies found an increase in TTR with computer-assisted dosing, but reported no significant difference in thromboembolism, bleeding, or mortality rates. One study compared different models of specialised care and found nurse-managed and pharmacist-managed services to result in a statistically significant increase in TTR compared with usual care. When compared with nurse-managed care, pharmacist-managed services were associated with a significantly higher TTR. However, nurse-managed care was not statistically different from usual in the number of hospitalisations or ER visits; both resulted in a significant increase in hospital or ER visits compared with pharmacist-managed services.

The reported noted that the patients who participated in studies examining patient self-testing or self-management may not be representative of the general population. They are typically self-selected, and other eligibility criteria, such as the ability to use a computer and internet-based dosing programs, may select for a particular demographic that is not indicative of the suitability of self-testing or self-management for all patients receiving anticoagulation therapy.

CADTH also conducted an economic evaluation and concluded that the cost of specialised anticoagulation services in Canada were uncertain. The key were:

- The incremental cost-effectiveness ratio of patient self-management compared with physician management of anticoagulation was C$14,000 over a five-year time horizon and from a health payer perspective.

- Hospital-based physician- or pharmacist-managed anticoagulation services were associated with lower costs than community physician-managed care in two costing studies and with higher costs in a third study.
- The three-month Ministry of Health costs of anticoagulation were C$108, C$145, and C$199 for hospital-based physician-managed care, hospital-based pharmacist-managed care, and community physician anticoagulation management, respectively.
- The cost-utility estimate was limited by uncertainty in the clinical data. Two costing studies had methodological weaknesses that may limit the validity of the findings. In the third costing study, there were differences in the characteristics of patients treated in the hospital compared with the community, which may have affected the costs. The duration of two costing studies was insufficient to capture differences between comparators on the costs related to bleeding or thromboembolic events.

An expert review committee considered the evidence and concluded that specialised anticoagulation services do not consistently reduce haemorrhages, thromboembolism, or the need for additional medical care. Specialised anticoagulation services improve time in TTR compared with usual care by a modest amount. The available evidence comparing different specialised models of care or service cCanomponents is limited in both quantity and, in particular, quality. The committee also noted that there is a need to look beyond TTR and include hard outcomes such as bleeding and frequency of emergency room visits. Their recommendation was that *"patients with non-valvular atrial fibrillation requiring warfarin be managed by a well-coordinated, structured approach dedicated to their anticoagulation therapy. This does not need to be restricted to specialised anticoagulation clinics."*

5. INCREMENTAL COSTS OF INTERVENTIONS PER PATIENT

The systematic review of the literature identified numerous studies aimed at improving warfarin use in the Australian clinical setting. In this section an approximate cost per patient was estimated for each study by category of intervention (i.e., Point-of-Care, Home Medication Reviews and Prescriber Training and Education). The studies in the category Hospital based interventions were not costed as there was no evidence of long-term outcomes and the proposed use of dabigatran is primarily for patients in the community treatment setting.

Some of the programs presented in this section appear to have a relatively low cost. When viewing these costs however, one must remain cognisant of the evidence of effectiveness presented in the previous section. A smaller amount of money poorly spent is still an inefficient use of scarce health resources and the opportunity cost of such wasteful spending should also be considered.

To truly examine whether the programs discussed here represent a worthwhile investment of public money, a detailed cost-effectiveness analysis is required. Interestingly, the only program to have such an assessment by the Medical Services Advisory Committee (MSAC) is Point-of-Care Testing, which was ultimately found not to be cost-effective. It is highly doubtful given the limited evidence of long-term effectiveness that any of the other programs discussed here would represent value for money.

The program costs presented in this analysis are conservative in that many costs associated with the implementation of the programs are not accounted for (e.g., costs of pilot programs, administrative costs, costs of reviews). It should also be pointed out that all costs per patient are reported as incremental costs; any costs shown here are in addition to any existing drug and monitoring costs. It is important to note that this is simplistic since the comparative effectiveness of the interventions is not considered here. To truly examine whether an intervention represents value for money a detailed cost-effectiveness analysis is required, which is beyond the scope of this submission.

Some programs, such as the introduction of specialised anticoagulation clinics would need to be trialled in Australia before being adopted given the significant differences in Australian treatment practices and geography compared to the overseas environments in which they have previously been operated.

Approach

The analyses presented in this section are based on the resource items use reported in the identified studies. The costs of the resource items have been modified to be consistent across all studies and more accurately reflect the real financial cost of the proposed programs. Where costs of resource items were modified, a justification is provided.

Many studies which were reviewed did not include any financial analysis. In this case an attempt was made to estimate the costs of the program based on costs provided for similar programs. Each of these assumptions is clearly described.

A key consideration in determining the cost per patient for each of the identified categories of interventions to improve warfarin use in Australia is the uptake of the program by patients, pharmacists and general practitioners. To enable appropriate comparisons between programs the same uptake rates were used.

Finally, the estimated cost per patient for each program represents an approximate value only. This is because many costs associated with setting up and running a program were excluded. For example, the cost to the Department of Health to administer the program and costs associated with the promotion of the program to patients and health care providers were not included.

Community Prescriber Training

The literature search identified three trials evaluating community prescriber training: Crotty *et al* 2004, Jackson *et al* 2004a and Mandryk *et al* 2008. Crotty 2004 described a physician and nurse training program at a residential care facility, while Jackson 2004a and Mandryk 2008 evaluated two different models of GP education programs.

The clinical effectiveness of these interventions was discussed in detail in Section 4.1. There was insufficient evidence to conclude that community prescriber training would significantly improve warfarin use in Australia. Crotty *et al* 2004 found no difference in the proportion of patients prescribed warfarin when residential care staff were trained. Mandryk *et al* 2008 concluded that there was no change in prescribing behaviour as a result of GP training. Jackson *et al* 2004a reported a significant increase in warfarin use over a 12 month period. However, the study did not assess the effectiveness of warfarin treatment eg an assessment of INR control or bleeding events. In order for this type of education to beneficial over the longer term, the educational messages would need to be regularly reinforced, and potentially changed over time to ensure it remains effective. These factors were not explored in the trial. The cost-effectiveness of community prescriber training was not evaluated.

Despite the limited evidence for the clinical effectiveness of these interventions, and lack of evidence for the cost effectiveness of these interventions, the cost per patient associated with each of these PoCT models is described in more detail below.

Training program at a residential care facility – Crotty et al 2004

The costs involved in a training program conducted at a residential care facility are based on Crotty *et al* 2004. This study evaluated an outreach program in which physicians at residential care facilities received two visits by a pharmacist as well as a presentation to staff of the facility. An audit of was conducted at each facility and the information fed back to the physician. One nurse per facility was also given training in change management.

No estimate of the cost of delivering this service is provided in the study. The utilisation estimates used in the cost analysis are, where possible, estimated from the description of the services provided in this study. Due to the limited information reported in the paper and general lack of information on the cost of educational programs, not all items of resource could be attributed a cost. Nonetheless, the items of resource use and associated cost included in the analysis are presented in Table 12.

In order to estimate the cost of this community education program, an estimate of the total number of general practitioners and residential facilities who would participate in the program is required. No such estimates are reported in the study or reported elsewhere at the time of this submission. However, the study by Mandryk *et al* 2008, reports an NPS study which at its peak involved 33% of all GPs in Australia. It is therefore assumed that this level of participation would also be achieved by residential facilities. Tannous and Luo 2005 report that there are approximately 3,000 residential facilities in Australia. The total number of participating residential facilities is therefore estimated as 990. Since a total of six physicians per facility were recruited, the total number of GP participating in the program is 5,940 (990 x 6 = 5,940).

Each of the estimated total number of physicians received two 30 minute visits from the pharmacist. The total number of visits by pharmacists is therefore 11,880. The corresponding cost of these visits is based on the pharmacist hourly rate of $52.53 per hour as reported by Peterson *et al* 2010.

The pharmacist also visited each facility to present to staff on reducing the use of medications. The study did not report the duration of this visit and for the purpose of this cost analysis it is assumed that this visit was of one hour duration.

One nurse in each facility underwent four two hour sessions in change management, management of behavioural symptoms, medication management and falls prevention

techniques. The nurse's time is costed at the hourly rate of $29.90 per hour as reported by Peterson *et al* 2010.

Due to the lack of information provided by Crotty *et al* 2004, it was not possible to attribute a cost to the pharmacist education, facility audit or the cost of developing the training program.

Unlike the analysis conducted for the Point of Care Testing Programs, educational programs are assumed to represent an incremental cost. As such the community education program would be over and above that currently offered in clinical practice.

In order to enable comparisons with the other warfarin interventions presented, the total cost of the community education program must be converted to a cost per patient. At the time of this submission, there are no estimates available on the total number of patients in residential facilities who could potentially benefit from this program. Therefore it is assumed that approximately 60,027 patient would benefit from this program. This figure was chosen to maintain consistency with the patient estimates used for the other warfarin intervention programs.

Table 12 Training program at a residential care facility: Resource utilisation and cost assumptions

Resource Item	Cost/Item	Source
Remuneration		
Pharmacist remuneration	$52.53/hour	Peterson *et al* 2010
Nurse remuneration	$29.90/hour	Peterson *et al* 2010
Program Uptake		
Number of patients per annum	60,027	Based on Peterson *et al* 2010
GP's Participating (6 x 990)	5,940	Crotty *et al* 2004
Residential Care Facilities (33% of all facilities)	990	NPS, Tannous & Luo 2005
Utilisation		
GP education visit (30 min pharmacist)	2	Crotty *et al* 2004
Facility education sessions (1 hour pharmacist)	1	Crotty *et al* 2004
Nurse education (2 hours – 1 per facility)	4	Crotty *et al* 2004

The total cost of the program is estimated at $600,000 per year which on a per patient basis translates to approximately $10.01 per patient per year (Table 13).

Table 13 Training program at a residential care facility: Total Cost per Patient

Resource Item	Cost/Unit	Units	Total Cost
Community Education			
Cost per patient			
Pharmacist remuneration GP visits	$52.53	5,940	$321,028.20
Pharmacist remuneration Facility	$52.53	990	$52,004.70
Nurse Education (8 hours at $29.90/hour)	$239.20	990	$236,808.00
Total Cost Community Education			$600,840.90
Total Cost per Patient Community Education			**$10.01**

GP education 1 – Jackson et al 2004a

The costs involved in a GP education program are based on Jackson *et al* 2004a. A second type of GP education program was described by Mandryk *et al* 2008 and is costed in the following section. Jackson *et al* 2004a study described a comprehensive GP education program where GPs mailed stroke prevention guidelines and received an educational visit by a pharmacist. The study does not provide an estimate of the cost of delivering this education program. As such the resource utilisation was estimated from the description provided in the study.

As was the case for Crotty *et al* 2004, in order to estimate the cost of this warfarin intervention program, an estimate of the total number of general practitioners participating in the education program is required. Again it was assumed that the uptake rate of 33% reported by Mandryk *et al* 2008 would be achieved. Thus, approximately 6,600 GPs would participate in this program (20,000 GPs x 33% = 6,600).

The total number of pharmacies that would participate in this program is based on the maximum participation rate reported in the Pharmacy Guild of Australia study by Peterson *et al* 2010 of 1,700 pharmacies nationally.

The pharmacist visit to the GP was estimated to take approximately an hour of the pharmacist time.

Several items of resource are not included in the cost analysis due to the lack of information. For example, it is not clear whether the treatment guidelines were newly developed or whether existing guidelines were reproduced and provided to the GPs. Similarly, in order for the GP to agree to participate in this program GP compensation would be required. This analysis is therefore restricted solely to the time of the pharmacist to deliver the service which is costed at the hourly rate. As evidenced by the HMR program currently in existence, pharmacist and GP alike would require compensation far in excess of the estimates provided

in this analysis. Despite the potential shortcomings of this analysis, the items of resource use and associated cost included in the analysis are presented in Table 14.

Table 14 GP education 1: Resource utilisation and cost assumptions

Resource Item	Cost/Item	Source
Remuneration		
Pharmacist remuneration	$52.53/hour	Peterson *et al* 2010
Program Uptake		
Number of patients per annum	60,027	Based on Peterson *et al* 2010
GP's Participating (33% of all GPs)	6,600	Crotty *et al* 2004
Pharmacies participating	1,700	Peterson *et al* 2010 (p161)
Utilisation		
Pharmacist visit (1 hour pharmacist)	1	Crotty *et al* 2004

As was the case in earlier analyses it was assumed that approximately 60,027 patients would benefit from this intervention.

Based on the above-mentioned assumptions, including the uptake rate, the annual cost for Community Education Programs would be approximately $347,000 or on a per patient basis $5.78 per patient per year (Table 15).

Table 15 GP education 1: Community Education Program

Resource Item	Cost/Unit	Units	Total Cost
Community Education			
Cost per patient			
Pharmacist remuneration GP visits	$52.53	6,600	$346,698.00
Total Cost Community Education			$346,698.00
Total Cost per Patient Community Education			**$5.78**

GP education 2 – Mandryk et al 2008

Mandryk *et al* 2008 described a different GP education program to that presented in Jackson *et al* 2004a. The costs of this program are presented here. Mandryk *et al* 2008 evaluated the impact of educational activities run by the National Prescribing Service (NPS) including mail outs to all GPs in Australia and one-on-one or small group educational sessions.

This publication did not report a financial analysis but it does report the total number of visits to GPs, small group meetings, clinical audits/case studies conducted and the total number of participating GPs. For each of these items assumptions were made with regard to the cost associated with these activities (Table 16).

Table 16 GP education 2: Resource utilisation and cost assumptions

Resource Item	Cost/Item	Source
Remuneration		
Pharmacist remuneration	$52.53/hour	Peterson *et al* 2010
Nurse Remuneration	$29.90/hour	Peterson *et al* 2010
Program Uptake		
Number of patients per annum	60,027	Based on Peterson *et al* 2010
GP's Participating (33% of all GPs)	7,000	Mandryk *et al* 2008
Educational visits to GPs	5,103	Mandryk *et al* 2008
Small group meetings	1,974	Mandryk *et al* 2008
Clinical Audits/Case Studies	1,175	Mandryk *et al* 2008
Utilisation		
Pharmacist visit (1 hour pharmacist)	1	Crotty *et al* 2004
Small Group Meeting (Venue hire/day)	$320.00	MGSM Rates 2011
Clinical Audits/Case Studies (Nurse 8 hours)	$239.20	Assumption

Cost estimates for the GP education by pharmacists were costed at the pharmacist hourly rate reported by Peterson *et al* 2010.

Each of the reported small group meetings were costed at $320.00. This is the current day rate for meeting room hire at Macquarie Graduate School of Management (MGSM) conference centre and although the small group meetings did not last an entire day, some time and effort would have been required by the staff of the NPS to organise the meeting and prepare the materials for the education session.

Clinical audits and case studies are part of standard practice by the NPS and as such do not represent an incremental cost. However, it is assumed that if this program was to be implemented on an ongoing basis, these costs would be incurred on an ongoing basis. The tasks associated with these clinical audits and case studies are assumed to be undertaken by nurses currently employed by the NPS and take approximately 8 hours to complete.

Some resource items are not included in the cost analysis due to a lack of detail in the Mandryk *et al* 2008 report. For example, it is not clear whether the mail out was newly developed and what, if any, costs were incurred during the development of the materials (e.g. expert panel meetings, graphic design agency fees, material fees, printing).

Nonetheless, based on the above-described assumptions the annual cost per patient for Community Education Programs would be approximately $1.2 million or $19.67 per patient per year assuming that approximately 60,027 patients would receive benefit from this service (Table 17).

Table 17 GP education 2: Total Cost per Patient

Resource Item	Cost/Unit	Units	Total Cost
Community Education			
Cost per patient			
Pharmacist remuneration GP visits	$52.53	5,103	$268,060.59
Small group meetings	$320.00	1,974	$631,680.00
Clinical audits and case studies	$239.20	1,175	$281,060.00
Mail out costs			
Total Cost Community Education			$1,180,800.59
Total Cost per Patient Community Education			**$19.67**

Point-of-Care Testing (PoCT)

The literature search identified three trials evaluating point-of-care testing: Bereznicki *et al* 2010, Bubner *et al* 2009 and McLachlan *et al* 2005. The three studies described different type of point-of-care testing. Bereznicki *et al* 2010 and McLachlan *et al* 2005 evaluated point-of-care testing in the pharmacy setting, working in collaboration with GPs to adjust dosing. The INR testing was performed by patients (self-monitoring) in Bereznicki *et al* 2010 and pharmacists in McLachlan *et al* 2005. Bubner *et al* 2009 evaluated point-of-care testing conducted by GPs.

The clinical effectiveness of these interventions was discussed in detail in Section 4.1. Overall, there was limited evidence that point-of-care testing was effective. The intervention was not associated with improved quality of life. Bereznicki *et al* 2011 reported a non-significant increase in the mean TTR and a significant increase in the mean proportion of tests in range for each patient, although this was based on a very small sample of patients (N=28). Eligible patients in Bereznicki *et al* 2010 were selected by pharmacists, with the report noting that this is not a model of warfarin management suitable for all patients. McLachlan *et al* 2005 recruited a larger patient population (N=53) and found no difference in the length of time INR readings were 2-3. The most rigorous study was conducted by Bubner *et al* 2009, recruiting 944 patients from 53 practices around Australia, including urban, rural and remote locations. It was a cluster randomised trial conducted over an 18 month period. Point-of-care testing was associated with a lower proportion of patients with an INR of 2-3 and a significantly lower proportion of tests with an INR of 2-3. The authors concluded that point-of-care testing was less effective than laboratory testing. Bubner *et al* 2009 conducted a cost effectiveness analysis and concluded that point-of-care testing was not cost-effective. McLachlan *et al* 2005 found point-of-care testing to be more expensive than usual care in the first year, but less expensive in subsequent years.

Despite the lack of evidence for the clinical effectiveness and cost effectiveness of these interventions, the cost per patient associated with each of these PoCT models is described in more detail below.

Patient self-monitoring of INR- Bereznicki et al 2010

The costs involved in patient's self-monitoring their INR through point-of-care testing are based on Bereznicki *et al* 2010. This study provided an education session to pharmacists. The program covered helping pharmacists to identify patients who would be suitable for self-monitoring and providing patients with training in the use of point-of-care testing. Pharmacists referred eligible patients to their GP along with a recommendation to set up a home medicine review.

This study did not include a financial analysis of the cost of the program. To derive an approximate estimate of the cost per patient, assumptions on resource utilisation were made. Each assumption is presented in Table 18.

Table 18 Patient self-monitoring of INR: Resource utilisation and cost assumptions

Resource Item	Cost/Item	Source
Remuneration		
Pharmacy initial training cost	$500.00	Peterson *et al* 2010
Pharmacist remuneration per HMR	$194.07	Medicare Australia
GP HMR	$148.90	MBS item 900
GP remuneration per patient	$16.30	MBS item 3
Ongoing incentive scheme per pharmacy	$300.00	Peterson *et al* 2010
Program Uptake		
Number of patients per annum	60,027	Peterson *et al* 2010
Number of pharmacies per annum	1,700	Peterson *et al* 2010
Utilisation		
Cost of INR Testing Device	$649.95	www.chemistaustralia.com.au
Cost per Device INR Test (incl. Disposables)	$5.95	
Cost/Lancet	$0.16	www.chemistaustralia.com.au
Cost/Strip	$5.79	www.chemistaustralia.com.au
INR pathology test	$19.80	
MBS Pathology	$13.80	MBS Item 65120
Patient Initiation Episode Fee	$6.00	MBS item 73928
GP consultation	$16.30	MBS item 3
INR Tests/Year without program (14.4)	20.4	Bereznicki *et al* 2010 - adjusted
INR Tests/Year with program (32.4)	32.4	Bereznicki *et al* 2010 - unadjusted

As shown in Table 18 above, it is assumed that in order to successfully implement this program in Australia, both the pharmacist and the general practitioner must be remunerated.

In addition, an ongoing incentive scheme is required to keep pharmacists participating in the program.

In the absence of existing government funded remuneration for Point of Care testing, the estimates reported in the Peterson *et al* 2010 study were used. Peterson *et al* 2010 (Pharmacy Guild of Australia) study investigated home medication review together with point-of-care testing. Therefore, it is assumed that the same remuneration would apply for point-of-care testing in order for both pharmacists and general practitioners to participate. The figures reported in Peterson *et al* 2010 were updated to reflect the current cost. Consistent with the study, only one HMR is performed (i.e. pharmacist HMR: $194.07, GP HMR: $148.90, Annual pharmacy incentive: $300.00, Pharmacy Training: $500.00). These assumptions are reasonable because eligible patients would receive an HMR from the pharmacist for training with the INR testing device. In addition, the pharmacist would conduct an HMR in consultation with the GP annually.

In current clinical practice where INR test are conducted through laboratories a short consultation with a GP is required for every six INR tests. It is assumed that if this point-of-care testing program is implemented, a short consultation with a GP is required. Consistent with the INR Point of Care Testing in General Practice Report (MSAC 2005) a short consultation is costed at one sixth of $16.30 per INR test (MBS Item 3 - Level A consultation).

The cost per year is also influenced by the rate of uptake of the proposed program. Bereznicki *et al* 2010 do not provide an estimate of the rate of uptake of the point-of-care testing program. However Peterson *et al* 2010 reported an estimate rate of uptake for improving warfarin use programs for patients recently discharged from hospital. Although the Peterson *et al* 2010 study evaluates the use of HMRs, it does provide insight into the estimated uptake of these types of programs for patients recently discharged from hospital. Peterson *et al* 2010 estimates that, despite remuneration and ongoing incentive schemes, only one-third of pharmacies would participate (approximately 1,700 pharmacies) and that these pharmacies would treat approximately 20,000 of the total estimated 73,300 patients who are discharged on warfarin each year. Thus, the uptake rate is 27.3%. Applying this per cent to the reported total number of patients treated with warfarin each year (i.e. current warfarin use and new initiations) of 220,000 (of which approximately half would be AF patients), the maximum total number of patients who would be willing to participate in the point-of-care program in Australia is 60,027.

The cost of the INR testing at the Point of Care is estimated based on the current retail price of the device of $649.95 and the associated consumables of $5.95 per INR test (i.e. test

strips: $5.79, lancets: $0.16). Since all patients entering the program require an INR testing device and associated consumables, it is assumed that these costs are funded by the Commonwealth.

By implementing this point-of-care program, it would replace current practice which involves a patient visiting the GP for a blood sample and INR testing through the pathology laboratories. To estimate the cost of current practice, the existing MBS items for INR pathology testing and a GP consultation is applied to the total number of INR tests conducted per patient per year multiplied by the total number of patients who would use point-of-care testing instead of visiting their GP (i.e. 60,027 patients per year).

Bereznicki *et al* 2010 reports that 14.4 INR tests were conducted prior to intervention (i.e. PoCT). However, General Practice Research Network (GPRN) (Appendix M – Commercial in Confidence) data indicates that in current clinical practice patients receive on average 20.4. This estimate has been used in the cost analysis.

During the Point of Care program, patients were tested 32.4 times. Although it is possible to adjust the number of INR tests at the Point of Care Testing using the ratio of current clinical practice over pre-intervention (i.e. 20.4/14.4 = 1.41), for the purpose of the cost analysis the number of INR test for PoCT is maintained at the 32.4 observed during the trial. This is because adjusting the total number of INR tests performed with point-of-care testing using the above-mentioned method this would generate a total of 45.9 tests per year. This may be considered too high and therefore potentially lead to an overestimation of the cost of the program.

The cost of implementing this point-of-care program is estimated as the difference between the cost of the proposed program and current clinical practice. On a per patient basis, the cost of this program is $837 in the first year (Table 19). The total cost of the program is estimated at $77.8 million in the first year but with cost off-sets of $27.6 million, the net total cost of this program is $50.2 million. A substantial proportion of the cost is associated with the purchase of the INR point-of-care testing device for patients participating in the program.

Table 19 Patient self-monitoring of INR: Total Cost per Patient

Resource Item	Cost/Unit	Units	Total Cost
Patients self-monitoring of INR			
Cost per patient			
Pharmacist remuneration (HMR)	$194.07	60,027	$11,649,495.23
GP Remuneration HMR	$148.90	60,027	$8,938,062.76
GP remuneration per test	$2.72	1,944,884	$5,283,601.64
INR testing Device	$649.95	60,027	$39,014,733.97
$/INR test	$5.95	1,944,884	$11,569,304.77
Cost per pharmacy			
Pharmacy training	$500.00	1,700	$850,000.00
Ongoing incentive program	$300.00	1,700	$510,000.00
Patient self-monitoring of INR			$77,815,198.36
Current Practice			
Cost per patient			
GP remuneration per test (1/6th)	$2.72	1,224,556.62	$3,326,712.14
INR Tests	$19.80	1,224,556.62	$24,246,221.01
Total Current Practice			$27,572,933.15
Net Total Cost of Proposed Program			
Total Cost of Proposed Program			$50,242,265.21
Total Cost per Patient for self-monitoring of INR			**$836.99**

GP point-of-care testing – Bubner et al 2009

The costs involved in GP point-of-care monitoring of INR are based on Bubner et al 2009. This Department of Health funded study compared point-of-care testing in general practices with laboratory testing and included a full cost-effectiveness analysis and importantly, the final recommendations to the Department of Health and Ageing also included an estimate of the appropriate MBS item fee[2].

This program proposes that patients would continue to visit their GP but that instead of having INR testing done by pathology laboratories, the GP uses an INR testing device at the point of consultation and advises the patient of the result immediately. Hence, the cost analysis was adjusted from that reported in the study to consider only:

- GP consultation (MBS Item 3);
- INR pathology testing (MBS Item 65120 for an INR test & MBS Item 73928 for a patient episode initiation fee); and

[2] (http://www.health.gov.au/internet/main/publishing.nsf/Content/poctgenpract-report-execsum~keyfindgs~poctgenpract-report-execsum-mbsfee).

- INR point of Care Testing (MBS item fee estimate of $24.12).

The total number of INR tests conducted per patient per year was initially derived from the Bubner *et al* 2009 study (Laurence *et al* 2010).

Although the number of INR tests is reported in the study, it is inconsistent and substantially less than that reported for the majority of studies. Indeed, most studies report that in current clinical practice patients receive an average 20 INR tests per year. This is confirmed by the GPRN data which demonstrate that the total number of INR tests in current clinical practice is 20.4.

For the purpose of this analysis, the number of tests reported in the study for current clinical practice is replaced by the original estimates reported in the dabigatran submission to the PBAC of 20.4. To account for the increase number of INR tests at the Point of Care Testing, the ratio of point-of-care testing over current practice testing is used to determine a more realistic estimate of the number of INR test that would be performed in clinical practice if the Point of Care program is implemented (i.e. 26.3 tests per year). This is shown in Table 20.

Table 20 GP point-of-care testing: Resource utilisation and cost assumptions

Resource Item	Cost/Item	Source
Remuneration		
GP Consultation	$16.30	MBS Item 3
Program Uptake		
Number of patients per annum	60,027	Peterson *et al* 2010 (p149)
Number of pharmacies per annum	1,700	Peterson *et al* 2010 (p161)
Utilisation		
INR pathology test	$19.80	
MBS Pathology	$13.80	MBS Item 65120
Patient Initiation Episode Fee	$6.00	MBS item 73928
INR point of Care testing	$24.12	Department of Health
INR Tests/Year without PoCT program	20.4	GPRN audit
INR Tests/Year with PoCT program	26.3	Assumption

PoCT = Point of Care Testing

As shown in Table 21, the cost of the acquisition of the INR testing device and associated consumables are not included in the analysis. This is because it is assumed that the device and consumables are purchased by the GP and that the MBS item fee for point-of-care testing includes a consumables and device depreciation component.

The rate of uptake of the point-of-care program was assumed to be the same as that used for Bereznicki *et al* 2010 (Section 4.1).

The implementation of this Point-of-Care Testing program would replace INR laboratory testing in a proportion of patients and therefore the cost of this program is best estimated as the difference between the cost of the program and current clinical practice.

In current clinical practice where INR test are conducted through laboratories a short consultation with a GP is required for every six INR tests. Consistent with the INR Point of Care Testing in General Practice Report (MSAC 2005) a short consultation is costed at one sixth of $16.30 per INR test (MBS Item 3 - Level A consultation)

The results of this analysis shows that the annual cost per patient for INR testing at the point-of-care would be approximately $175 per patient per year. The total cost of the program is estimated at $38.1 million per year but with cost off-sets of $27.6 million, the net total cost of this program is $10.5 million.

Table 21 GP point-of-care testing: Total Cost per Patient

Resource Item	Cost/Unit	Units	Total Cost
GP Point of Care Testing			
Cost per patient			
INR Tests including GP remuneration	$24.12	1,578,718	$38,078,668.49
Total Cost GP Point of Care Testing			$38,078,668.49
Current Practice			
Cost per patient			
GP remuneration per patient per test	$2.72	1,224,557	$3,326,712.14
INR Tests	$19.80	1,224,557	$24,246,221.01
Total Current Practice			$27,572,933.15
Net Total Cost of Proposed Program			
Total Cost of Proposed Program			$10,505,735.33
Total Cost per Patient GP Point Of Care Testing			**$175.02**

Pharmacist point-of-care testing – McLachlan et al 2005

The costs involved in pharmacist point-of-care monitoring of INR are based on McLachlan et al 2005. This study evaluated the use of point-of-care testing in the pharmacy setting where pharmacists provided patient education, support and INR monitoring. Results of the INR tests conducted by the pharmacist were discussed with the patient's GP.

The study reports the results of an economic comparison of delivering this service versus current clinical practice. The utilisation estimates reported in this study were used in the cost analysis (Table 23). However, some of the cost estimates provided in the study report were adjusted to provide a more accurate assessment of the cost associated with this point-of-care testing program.

Each of the items of resource use are presented in Table 22. Cost estimates were adjusted for the following items of resource:

- **INR testing device:** This was reported as $1,200 per device. However, the current retail price for a device is $649.95. Hence the current retail price is used in the cost analysis.
- **Pharmacist Hourly Rate:** An hourly rate of $65.00 was reported for a pharmacist. The more recent study by Peterson *et al* 2010, reports an hourly rate of $52.53. For consistency of reporting across all studies, the value of $52.53 is used in the cost analysis.
- **GP MBS Item Fee:** The MBS item was updated from $30.85 to $16.30 to reflect the current fee (MBS Schedule November 2011)
- **INR Pathology Testing:** The study utilises the MBS items for collection and analysis of the INR testing at a pathology laboratory. As above, based on the 2005 MSAC review of INR PoCT, the MBS item codes for pathology testing (MBS Item 65120) and a patient episode initiation fee (MBS Item 73928) were used.
- **INR Tests:** The study reports that pre-intervention, a total of 7 INR tests were performed over an average follow-up of 4.7 months. This translates to approximately 18 INR tests per year. During the intervention, the total number of tests was 13 over a follow-up period of 8.8 months. The total number of INR tests per year with the intervention is therefore also approximately 18. Since both the total pre- and post-intervention INR tests are the same, for the purpose of the cost analysis it is assumed that the number of INR tests performed is the same.

  The observed numbers of INR tests have been updated with the GPRN data which shows that the total number of INR tests in current clinical practice is 20.4.

The study reports cost of the point-of-care testing program for both “pharmacist” and “pharmacists in charge”. It is assumed that if this program were to be implemented in Australian clinical practice, that the INR testing would be conducted by the “pharmacist” rather than the “pharmacist in charge”.

Table 22 Pharmacist point-of-care testing: Resource utilisation and cost assumptions

Resource Item	Cost/Item	Source
Remuneration		
Pharmacist remuneration per patient	$52.53/hour	Peterson *et al* 2010
GP remuneration per patient	$16.30	MBS Item 3
Program Uptake		
Number of patients per annum	60,027	Peterson *et al* 2010
Number of pharmacies per annum	1,700	Peterson *et al* 2010
Utilisation		
Cost of INR Testing Device	$649.95	www.chemistaustralia.com.au
Cost per Device INR Test (incl. Disposables)	$5.95	
Cost/Lancet	$0.16	www.chemistaustralia.com.au
Cost/Strip	$5.79	www.chemistaustralia.com.au
Quality Control	$500.00	McLachlan *et al* 2005
GP Consultation/Patient/Year without PoCT	4	McLachlan *et al* 2005
GP Consultation/Patient/Year with PoCT	2	McLachlan *et al* 2005
INR pathology test	$19.80	
MBS Pathology	$13.80	MBS Item 65120
Patient Initiation Episode Fee	$6.00	MBS Item 73928
INR Tests/Year without PoCT program	20.4	GPRN survey
INR Tests/Year with PoCT program (1.6 * 12)	20.4	GPRN survey

The assumptions on uptake of the program as previously described for Bereznicki *et al* 2010 were used in this cost analysis.

The implementation of this Point of Care Testing program would replace INR laboratory testing and therefore the cost of this program is best estimated as the difference between the cost of the program and current clinical practice.

The results of this analysis show that the annual cost per patient for INR testing at the point-of-care would be approximately $253 per patient in the first year of the program (Table 23). In the subsequent year, the cost is reduced to $234.80 per patient per year due to the exclusion of the cost of the INR testing device. The total cost of the program is estimated at $43.3 million in the first year but with cost off-sets of $28.6 million, the net total cost of this program is $15.2 million.

Table 23 Pharmacist point-of-care testing: Total Cost per Patient

Resource Item	Cost/Unit	Units	Total Cost
Pharmacist Point of Care Testing			
Cost per patient			
Pharmacist remuneration per patient	$52.53	1,224,557	$32,162,979.54
GP remuneration per patient	$16.30	120,055	$1,956,889.50
INR testing Device	$649.95	1,700	$1,104,915.00
Quality Control	$500.00	1,700	$850,000.00
$/INR test	$5.95	1,224,557	$7,284,377.08
Total Cost Pharmacist Point of Care Testing			$43,359,161.11
Current Practice			
Cost per patient			
GP remuneration per patient	$16.30	240,109	$3,913,778.99
INR Tests	$19.80	1,224,557	$24,246,221.01
Total Current Practice			$28,160,000.00
Net Total Cost of Proposed Program			
Total Cost of Proposed Program			$15,199,161.11
Total Cost per Patient Pharmacist Point Of Care Testing			**$253.20**

Home Medication Reviews

Four trials identified in the literature search involved a pharmacist reviewing patient's medications in the home: Peterson *et al* 2010, Peterson *et al* 2006, Roughead *et al* 2011 and Mullan *et al* 2005. Peterson *et al* 2006 evaluated the effectiveness of home based educational visits for patients newly initiated on warfarin. Peterson *et al* 2010 describes an expanded program evaluating the same intervention. Mullan *et al* 2005 describes a warfarin management program which included patient education and a medication review. Roughead *et al* 2011 evaluates the effectiveness of Government funded home medication reviews.

The clinical effectiveness of these interventions was discussed in detail in Section 4.1. There was some evidence that expanded home medicine reviews, including warfarin education and point-of-care testing, can be effective in reducing bleeding events in the short term. A significant improvement in the proportion of patients with a therapeutic INR eight days after discharge was reported in Peterson 2006, but not Peterson 2010. There was no significant difference in INR control at day 90. However, both Peterson 2006 and Peterson 2010 reported a significantly lower rate of bleeding events although there was no improvement in quality of life. In contrast, Mullan 2005 found no difference in INR control, hospitalisations or emergency room visits. The main limitation of these studies is the short duration of follow-up. Roughead 2011 reported a significant reduction in hospitalisations for bleeding at 2-6 months post intervention, however there was a significantly higher rate of hospitalisations for

bleeding after 12 months. Given that most patients would be prescribed warfarin for more than 12 months, establishing the long term efficacy of these interventions is critical. Peterson 2006 and Peterson 2010 concluded that home medicine reviews were cost saving due to the reduction in bleeding events. However Peterson 2010 found that the intervention was more expensive than the control arm when all healthcare costs were considered.

Despite the mixed evidence for the clinical effectiveness and cost effectiveness of these interventions, the cost per patient associated with each of these PoCT models is described in more detail below.

HMR, education and INR testing 1 – Peterson et al 2010

The costs involved in an HMR, with warfarin specific patient education and INR testing are based on Peterson *et al* 2010 study. This study evaluated a program where trained pharmacists make 2 to 3 visits to the homes of patients who have been discharged from hospital and had been initiated on warfarin therapy. Patients were provided point-of-care INR testing, warfarin education and a Home Medication Review. This study included an analysis of the cost of the proposed intervention and included suggested payments to pharmacies and GPs for participation in the program.

This cost analysis is largely based on the resource utilisation and cost estimates reported in the Peterson *et al* 2010 study (Table 24).

Peterson *et al* 2010 suggested that the appropriate compensation for a pharmacist for the first visit is $175.00 and $75.00 for every subsequent visit. With 64.8% of patients receiving two visits and the remainder three visits, the average compensation for the pharmacist under this program is $276.40 per patient.

For the GP the remuneration would be in accordance with the current MBS item 900 for home medication reviews. At the time of this submission, the value of MBS item 900 is $148.90.

Additional compensation would be required to cover training of pharmacy staff of $500 and on-going incentive for continued participation of $300 per pharmacy per year.

Under the proposed program, patients would receive two to three INR tests in the first ten days after discharge. 64.8% of patients received two INR tests and the remainder received three INR test. On average therefore, the total number of tests under the proposed program is 2.35. In current practice, it was assumed patients would only receive one INR test during this period. Hence this cost analysis assumes that if this program is implemented, that it would replace 1.35 INR test for each patient participating in the program.

Current practice is costed using the methods previously described (refer Point of Care Testing). That is, INR test are conducted through laboratories and a short consultation with a GP is required for every six INR tests. Consistent with the INR Point of Care Testing in General Practice Report (MSAC 2005) a short consultation is costed at one sixth of $16.30 per INR test (MBS Item 3 - Level A consultation)

The study concludes that if this program is implemented in Australian clinical practice, a maximum total of 20,000 patients would participate.

Table 24 HMR, education and INR testing 1: Resource utilisation and cost assumptions

Resource Item	Cost/Item	Source
Remuneration		
Pharmacist remuneration/patient	$276.40	Peterson *et al* 2010
GP Remuneration/patient	$148.90	MBS Item 900
GP Consultation	$16.30	MBS Item 3
Pharmacy Training	$500.00	Peterson *et al* 2010
INR test pathology laboratory	$19.80	
MBS Pathology	$13.80	MBS Item 65120
Patient Initiation Episode Fee	$6.00	MBS item 73928
Pharmacy On-going incentive/year	$300.00	Peterson *et al* 2010
Program Uptake		
Number of patients per annum	20,000	Peterson *et al* 2010
Pharmacies participating	1,700	Peterson *et al* 2010
Utilisation		
INR test with Program	2.35	Peterson *et al* 2010
INR tests without program	1	Assumption

Based on the assumptions described above, the total cost per patient of the new Home Medication Review program is approximately $516 (shown in Table 25).

Implementing this program in Australian clinical practice would cost $10.8 million with the majority of the costs related to the payments to pharmacists (i.e. $5.6 million) and to GPs ($2.9 million). A total of $0.45 million can be achieved as a result of reduced INR testing at pathology laboratories, resulting in a net cost to the Commonwealth of $10.3 million for this program.

Table 25 HMR, education and INR testing 1: Total Cost per Patient

Resource Item	Cost/Unit	Units	Total Cost
HMR Program			
Cost per patient			
Payments to pharmacy per patient managed	$281.04	20,000	$5,620,800.00
GP payments per patient managed	$148.90	20,000	$2,868,000.00
INR Tests	$19.80	47,040	$931,392.00
Cost per pharmacy			
Pharmacy training	$500.00	1,700	$850,000.00
Ongoing incentive program	$300.00	1,700	$510,000.00
Total cost of HMR Program			**$10,780,192.00**
Current Practice			
Cost per patient			
INR testing	$19.80	20,000	$396,000.00
INR tests replaced by the program	$2.72	20,000	$54,333.33
Total Current Practice			**$450,333.33**
Total Net Cost of HMR Program			**$10,329,858.67**
Total Cost per patient HMR			**$516.49**

HMR, education and INR testing 2 – Peterson et al 2006

An alternative model of HMR was described by Peterson *et al* 2006, and it costed here. As discussed previously, it was a pilot study which was expanded into a larger trial published as Peterson *et al* 2010. The previous section describes the costs associated with this expanded trial. Peterson *et al* 2006 studied patients discharged from hospital with warfarin therapy who received home visits from a pharmacist on day 2, day 4, day 6 and day 8 following discharge or were treated according to usual care. Those patients in the intervention group were provided education and advice by the pharmacist and also had their INR tested. The result of each Point of Care INR test conducted by the pharmacist was discussed with the GP.

This study did not report a financial analysis. However, the study by Peterson *et al* 2010 was very similar since Peterson *et al* 2010 is the expanded trial of the Peterson *et al* 2006 pilot program. Most of the resource utilisation and associated costs in this cost analysis is therefore derived from the Peterson *et al* 2010 study.

The total number of INR tests conducted per patient per year is derived directly from the study. A total of four INR tests were conducted for those tested at the point-of-care while those following current clinical practice received two INR tests.

Pharmacist remuneration for the first visit is reported at $175.00. However, for every subsequent visit, the pharmacist is remunerated $75.00. Therefore, pharmacist remuneration for four visits is $400.00 per patient.

The compensation for a GP is based on MBS item 900 with a value of $148.90 for each HMR conducted. Peterson *et al* 2010 further suggests that additional compensation would be required to cover pharmacy staff training equivalent to $500 and on-going incentive for continued participation of $300 per pharmacy per year. This is shown in Table 26.

Table 26 HMR, education and INR testing 2: Resource utilisation and cost assumptions

Resource Item	Cost/Item	Source
Remuneration		
Pharmacist remuneration/patient (4 visits)	$400.00	Peterson *et al* 2010
GP Remuneration/patient	$148.90	MBS item 900
GP Consultation	$16.30	MBS item 3
Pharmacy Training	$500.00	Peterson *et al* 2010
INR test pathology laboratory	$19.80	
MBS Pathology	$13.80	MBS Item 65120
Patient Initiation Episode Fee	$6.00	MBS item 73928
Pharmacy On-going incentive/year	$300.00	Peterson *et al* 2010
Program Uptake		
Number of patients per annum	20,000	Peterson *et al* 2010
Pharmacies participating	1,700	Peterson *et al* 2010
Utilisation		
INR test with Program	4	Jackson *et al* 2004a
INR tests without program	2	Jackson *et al* 2004a

The total estimated cost per patient of the new program is $651.07 in the first year. As is the case for the Peterson program, this would treat 20,000 patients per annum. It would replace 40,000 existing pathology based INR tests. The overall cost of the program is again driven by payments to pharmacists of approximately $8.0 million and to GPs of $3.0 million. The total program would cost $13.9 million. With the $0.9 million from the reduction in pathology based INR testing, the net cost to the Commonwealth of the scheme would be $13.0 million in the first year. This is shown in Table 27.

Table 27 HMR, education and INR testing 2: Total Cost per Patient

Resource Item	Cost/Unit	Units	Total Cost
Community Pharmacy home follow-up of warfarin initiation			
Cost per patient			
Payments to pharmacy per patient managed	$475.00	20,000	$8,000,000.00
GP payments per patient managed	$148.90	20,000	$2,978,000.00
INR tests	$19.80	80,000	$1,584,000.00
Cost per pharmacy			
Pharmacy training	$500.00	1,700	$850,000.00
Ongoing incentive program	$300.00	1,700	$510,000.00
Total cost of HMR Program			**$13,922,000.00**
Current Practice			
Cost per patient			
INR testing	$19.80	40,000	$792,000.00
GP payments	$2.72	40,000	$108,666.67
Total Current Practice			**$900,666.67**
Net Total Cost of HMR			
Total Net Cost of HMR Program			**$13,021,333.33**
Total Cost per patient of HMR Program			**$651.07**

Government funded HMRs – Roughead et al 2011

The costs involved in GP point-of-care monitoring of INR are based on Roughead *et al* 2011. This study undertook a retrospective cohort study using administrative claims data for veterans who had received an HMR and compared this group with those not receiving an HMR. While under the current arrangements patients are only eligible for one review every 12 months, it was suggested that a second review within 12 months may be necessary to provide patients with a sustained therapeutic benefit.

The study did not present a cost analysis of the program. Nevertheless, the study examines an existing Home Medication Review program to determine the effect on patients treated with warfarin who receive an HMR.

This cost analysis uses the existing HMR MBS fees paid by Medicare Australia to community pharmacists. Since it was suggested that a second HMR within 12 months would likely offer a sustained benefit, a second scenario where patients receive two HMRs is also presented. The resource utilisation and associated cost used in the analysis are shown in Table 28.

Table 28 Government funded HMRs: Resource utilisation and cost assumptions

Resource Item	Cost/Item	Source
Remuneration		
Pharmacist remuneration/patient	$194.07	Medicare Australia
GP Remuneration/patient	$148.90	MBS Item 900
Program Uptake		
Number of patients per annum	20,000	Peterson *et al* 2010 (p161)
Pharmacies participating	1,700	Peterson *et al* 2010 (p161)
Utilisation		
HMRs	1	Roughead *et al* 2011

The cost per patient in the first year would be $343 with 1 HMR and $687 with 2 HMRs. As for the other cost analyses, it was assumed that 20,000 patients would participate in the program. The overall cost of the program would $6.9 million for the 1 HMR and $13.7 million for 2 HMRs per patient. This is shown in Table 29.

Table 29 Government funded HMRs: Total Cost per Patient

Resource Item	Cost/Unit	Units	Total Cost
HMR for patients treated with Warfarin			
Cost per patient			
Payments to pharmacy per patient managed	$194.07	20,000	$3,881,400.00
GP payments per patient managed	$148.90	20,000	$2,978,000.00
Total Net Cost of Proposed Program 1 HMR			**$6,859,400.00**
Total Net Cost of Proposed Program 2 HMRs			**$13,718,800.00**
Total Cost per patient HMR for Warfarin patients - 1 HMR			**$342.97**
Total Cost per patient HMR for Warfarin patients - 2 HMR			**$685.94**

HMR and collaborative care – Mullan et al 2005

The costs involved in a HMR and improved collaborative care between the hospital and community setting are based on Mullan *et al* 2005. This trial evaluates a program that aimed to improve communication and increase compliance with warfarin by providing easy to read information, improving continuity of care between home and hospital, and better ensuring follow up. This study did not include an analysis of the cost of the program.

The study methods are not well described but appear to propose three main elements:

1. Pharmacists delivering the educational material, helping patients with testing and monitoring and undertaking a complete medication review. These cost associated with these activities are costed at the current MBS item fee for an HMR conducted by the pharmacist.

2. Pharmacist follow-up with the patient (approx. 30 minutes duration). This is included in the cost analysis at the hourly rate for an accredited pharmacist of $52.53 which was derived from the study by Peterson *et al* 2010.
3. Finally, the program involved leaving fridge magnets. These were costed at $200 for 1000 fridge magnets. Assuming that 20,000 patients would participate in the program, the total cost would be $4000.

Due to the limited information reported in the paper and general lack of information on the cost of educational programs, not all items of resource reported in the study can be attributed a cost including the development and printing of the material, the running of the program or any additional incentives for pharmacists. This is shown in Table 30.

Table 30 HMR and collaborative care: Resource utilisation and cost assumptions

Resource Item	Cost/Item	Source
Remuneration		
Pharmacist HMR remuneration/patient	$194.07	Medicare Australia
Pharmacist Follow-up remuneration/hour	$52.53	Peterson *et al* 2010 (p149)
Program Uptake		
Number of patients per annum	20,000	Peterson *et al* 2010 (p161)
Pharmacies participating	1,700	Peterson *et al* 2010 (p161)
Utilisation		
Pharmacist follow-up (hours)	0.5	Mullan *et al* 2005
Fridge magnets ($200/1000 magnets)	1	www.magnetexpress.com.au

The total cost per patient of the new program is $221. As with all the pharmacy intervention programs it is assumed this would treat 20,000 patients per annum. The total estimated cost of the program would is $4.4 million which is almost entirely driven by the payments to pharmacists. This is shown in Table 31.

Table 31 HMR and collaborative care: Total Cost per Patient

Resource Item	Cost/Unit	Units	Total Cost
Pharmacists Warfarin education program			
Cost per patient			
Initial payments to pharmacy per patient managed	$194.07	20,000	$3,881,400.00
Pharmacist follow up after 1 week	$26.27	20,000	$525,300.00
Fixed costs pharmacy			
Fridge magnets	$4,000.00	1	$4,000.00
Net Total Cost of HMR Program			
Total Net Cost of HMR program			**$4,410,700.00**
Total Cost per patient HMR Program			**$220.54**

Anticoagulation clinics

The clinical effectiveness of anticoagulation clinics are described in detail in Section 4.1. Meta-analyses of anticoagulation clinics compared with usual care suggest that anticoagulation clinics are more effective at maintaining INR within a therapeutic range. The improvement in TTR was approximately 5% - 10%. Care must be taken when interpreting the results of these studies due to the significant differences between individual anticoagulation clinics and varying standards of usual care. There is significant variability in the structure of anticoagulation clinics. Prior to the introduction of anticoagulation clinics, the most appropriate model for the Australian setting would need to be established and tested, particularly in terms of physician-led versus pharmacist-led clinics. Longer term outcomes would need to be evaluated. All anticoagulation clinics are resource intensive, with the need for a specially trained, multidisciplinary team. There would be accessibility issues if all Australians were not able to access an anticoagulation clinic, therefore the location and number of clinics would need to be considered. While anticoagulation clinics could be used in Australia as an effective intervention for improving warfarin control, however further research would need to be undertaken in the Australian setting to establish the most appropriate structure and the cost-effectiveness of this intervention. The cost per patient for anticoagulation clinics is described in more detail below.

The Rose 2011 and US Medicine 2011 publications discuss the Department of Veteran Affairs (DVA) anticoagulation clinics program. An outline of the staffing of these clinics is provided in Ansell *et al* 2010 and this was based as the basis for staff costs included below.

The Ansell paper listed the required staff complement for clinics run within a hospital. To cover the management overhead a manager has been added for this costing exercise. Each of the staff full time equivalents (FTEs) were multiplied by Australian costs for those staff positions (i.e., 2 pharmacy FTEs x cost of a pharmacy FTE). For general expenses the cost of running a General Practice clinic was used as a proxy. PricewaterhouseCoopers (PwC) had been engaged by the Commonwealth to cost the running of GP practices. Costs were reported as at 1999. We took the costs from a 3 GP clinic and extrapolated them to 2011 costs by using the Health deflator published by the Australian Institute of Health and Welfare (AIHW). Once the staff and overhead costs were added together the costs of running a Warfarin clinic were calculated at $661,000 per annum (see Table 32). If the program was to be provided by private operators an extra cost for return on investment would need to be included. This was not included in our calculations.

Based on Ansell *et al* 2010, each clinic would treat 450 patients per annum. It was assumed that somewhere between 60,000 and 220,000 patients on warfarin therapy would attend a clinic.

Table 32 Ansell *et al* 2010 resource utilisation and cost assumptions

Resource Item	Cost/Item	Source
Staff costs		
Unit Director (FTE)	1.0	Ansell et al p11 Unit Director added to account for stand alone clinic
Pharmacists (FTE)	1.5	Ansell et al p11
Administration (FTE)	1.0	Ansell et al p11
Medical Technician (FTE)	1.5	Ansell et al p11
Medical Director (FTE)	0.2	Ansell et al p11
Unit Director	$106,321	Peterson et al 2010 (p161) hourly rate $52.53 x 40hours x 46 weeks plus 10%
Pharmacists	$96,655	Peterson et al 2010 (p161) hourly rate $52.53 x 40hours x 46 weeks
Administration	$42,713	http://www.payscale.com/research/AU/Job=Ward_Clerk/Hourly_Rate
Medical Technician	$63,220	http://www.smh.com.au/lifestyle/diet-and-fitness/red-cross-to-use-nursing-assistants-on-blood-donors-20101219-191yi.html
Medical Director	$115,000	http://www.imrmedical.com/australiasalaries.htm
Total staff costs	$411,847	
General Expenses		
Costs at 1999 levels		
Occupancy costs	$47,151	PwC A resourced-based model of private medical practice in Australia Vol 1 2000 3 GP clinic used as approx
Office Expense	$41,865	PwC A resourced-based model of private medical practice in Australia Vol 1 2000 3 GP clinic used as approx
Other costs	$22,176	PwC A resourced-based model of private medical practice in Australia Vol 1 2000 3 GP clinic used as approx
Professional costs	$16,704	PwC A resourced-based model of private medical practice in Australia Vol 1 2000 3 GP clinic used as approx
Transport	$25,734	PwC A resourced-based model of private medical practice in Australia Vol 1 2000 3 GP clinic used as approx
Capital	$15,093	PwC A resourced-based model of private medical practice in Australia Vol 1 2000 3 GP clinic used as approx
Cost per clinic	$168,723	
Costs at 2011 level		
Occupancy costs	$69,614	Costs as at 2011 using health deflator AIHW
Office Expense	$61,809	Costs as at 2011 using health deflator AIHW
Other costs	$32,741	Costs as at 2011 using health deflator AIHW
Professional costs	$24,662	Costs as at 2011 using health deflator AIHW
Transport	$37,994	Costs as at 2011 using health deflator AIHW
Capital	$22,283	Costs as at 2011 using health deflator AIHW
Cost per clinic	$249,103	
Costs at 2011 level	0.033	Health and Welfare Expenditure Series Number 42 Australian Institute of Health and Welfare Cat. no. HWE 51 Health Expenditure Aust 2008-2009 p13
Total cost per clinic	$660,949	
Program Uptake		
Number of pts per clinic	450	Ansell et al p11
Program Uptake		
Lower est. pts per yr	60,027	Peterson et al 2010 (p161)
Upper est. pts per yr	220,000	Peterson et al 2010 all patients attend clinics

From the assumptions described above, the total cost per patient of the anticoagulation clinics program is estimated to be approximately $1,469 (see Table 33).

Implementing this program in Australian clinical practice would cost between $88.2m and $323.1m per annum. Most of the costs would be comprised of labour costs required for the running of the anticoagulation clinics.

Table 33 Total cost per patient and total program costs – anticoagulation clinics

Resource Item	Cost/patient	Patients	Total Cost
Total cost anticoagulation clinic lower est.	$1,469	60,027	$88,166,616
Total cost anticoagulation clinic upper est.	$1,469	220,000	$323,130,649

Pharmacogenetic testing

The clinical effectiveness of pharmacogenetic testing is described in detail in Section 4.1. There is insufficient evidence to suggest that the use of pharmacogenetic information improves clinical outcomes in patients receiving warfarin. The results from three different economic models indicated that pharmacogenetic testing was not cost effective. Given the lack of supportive clinical and economic data, pharmacogenetic testing is unlikely to be reimbursed by Medicare. Pharmacogenetic testing is therefore not a model of health system delivery which could currently be used to optimise the use of warfarin in Australia.

Despite the lack of evidence for the clinical effectiveness of pharmacogenetic testing, the cost per patient is described in more detail below.

Several studies have looked at the cost and cost effectiveness of pharmacogenetic testing ANZHSN 2010, Meckley *et al* 2010 and McWilliam *et al* 2008. The ANZHSN report provided estimates of pharmacogenetic testing in Australia, whereas McWilliam *et al* 2008 reported costs for the US.

The main costs associated with this testing were assumed to be a GP visit and costs of the test. Costs published from the US showed a figure of around $250 for the Pharmacogenetic test. Reported costs from Australia were much lower than this figure.

The Horizon scanning report, prepared for the Australian Government, stated that the single base extension assay from private pathologist Gribbles Pathology test identifying mutations in CYP2C9 and VKORC1 genes, costs $90. On the other hand the RFLP–PCR based genotyping method offered by public pathology, the Diversity Health Institute, for the CYP2C9*2 and *3 polymorphisms cost $50. For this analysis we chose the mid point between these two figures - $70.

As in the other costing analysis undertaken in this report, GP consultation was valued at $16.30. The total cost per patient was therefore estimated at $86.30 ($70.00 + $16.30). This is shown in Table 34.

Table 34 Pharmacogenetic testing: Resource utilisation and cost assumptions

Resource Item	Cost/Item	Source
Utilisation		
Pharmacogenetic testing	$70.00	ANZHSN 2010 p7
GP remuneration per patient	$16.30	MBS item 3
Total cost per patient	$86.30	
Program Uptake		
Number of patients per annum	60,027	Peterson et al 2010 (p161)

The overall cost of the program was calculated at $5.2million (see Table 35).

Table 35 Pharmacogenetic testing: Total Cost per Patient and total program costs

Resource Item	Cost/patient	Patients	Total Cost
Pharmacogenetic testing	$86.30	60,027	$5,180,355

Conclusion and discussion

This section estimated the approximate cost of implementing point-of-care testing, community education programs, Home Medication Reviews, anticoagulation clinics and pharmacogenetic testing to improve the use of warfarin in Australian clinical practice. The majority of the studies did not report a cost analysis and provided limited details on the resource utilisation associated with the program. Nonetheless, the results of the preliminary costing analyses for each of these programs show that there is considerable variability in the cost per patient per year. The range of costs per patient derived for the different types of programs were estimated at:

- Community Education:$5 – $20
- Point-of-Care Testing: $175 – $837
- Home Medication Reviews: $220 – $686
- Anticoagulation Clinics: $1,469
- Pharmacogenetic testing: $86

As discussed earlier not all potential costs such as setup costs, and educational material costs are considered. For both the PoCT and Home Medication Reviews, the main cost drivers are the payments to pharmacists and GPs. As mentioned above, very few studies

provided adequate detail on the resource utilisation associated with the program but importantly, were focussed solely from the perspective of the authors and consequently excluded resource utilisation and costs that would be incurred by other health care professionals. For example, the majority of the studies that were undertaken by pharmacists were focused on payments to pharmacy. Consequently, the role of the general practitioner was not always considered and the need for compensation ignored. Some others considered point-of-care devices in the study but did not provide details on how the devices would be funded.

It is important to note that The Medical Services Advisory Committee (MSAC) has reviewed the use of INR PoCT in the general practice in 2005. Although MSAC agreed with the sponsor on the estimated MBS fee for PoCT (i.e. approx. $25.00), it determined that there was little data on the use of INR PoCT in general practice, with only two studies identified. The MSAC also raised concerns about the uncertainty about the diagnostic performance of PoCT device. The MSAC concluded that if additional studies demonstrate superior effectiveness for PoCT that there may be potential for a favourable cost-effectiveness ratio. However, given the lack of data, especially in the longer term, it recommended not to support the use of INR PoCT in general practice. Hence in considering point-of-care testing, it is important to consider both the cost and effectiveness of such a program to improve the use of warfarin in Australian clinical practice.

The cost analysis of the HMR programs must be considered in conjunction with the findings of the report commissioned by the Department of Health on Home Medication Reviews (Campbell Research & Consulting 2008). Some of the key conclusions include:

- "…*five years of implementation, less than 10% of GPs are participating in the HMR Program*"
- "…*the existing model is not focused on ensuring access by those consumers who could benefit most from the HMR Program*"
- ‘‘…*at best, GPs are ambivalent about the HMR Program, with very few GPs actively supporting the Program and many considering it a waste of time and Government resources"*

Although there are many other conclusions, there are none that are favourable for the current HMRs program. Instead, the report concludes that without substantial changes in the way the program is delivered, the HMR Program is unlikely to meet its objectives.

In terms of Community Education programs, none of the studies provided an adequate description of the resource utilisation associated with the design of the program which

complicates any cost analysis. The calculations reported for these programs are therefore provided as a simple guide.

Overseas evidence suggests that anticoagulation clinics are able to offer modest improvements in TTR compared to usual care. Such clinics are resource intensive, the improvements in TTR have not been conclusively linked to better health outcomes, and their effectiveness in the Australian health care setting is unproven.

The clinical effectiveness of pharmacogenetic testing for warfarin treatment remains uncertain. Economic modelling of the impact of pharmacogenetic testing consistently results in ICERs that are not conventionally thought to be cost-effective.

It is important to note that the preliminary analyses presented in this submission are primarily based on the resource utilisation reported in studies. Given the lack of detailed reporting, a full, rigorous analysis of each of the programs would most likely result in higher and more accurate estimates than reported here.

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