Technology Assessment Report No. 165

Indicative Economic Analysis on Dabigatran Etexilate for the Prevention of Stroke, Systemic Embolism and Reduction of Vascular Mortality in Patients with Atrial Fibrillation

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Subject:	Indicative Economic Analysis of Dabigatran Etexilate for the prevention of Stroke, Systemic Embolism and Reduction of Vascular Mortality in Patients with Atrial Fibrillation.

Summary of Proposal

Pharmaceutical Dabigatran Etexilate (Pradaxa®)
Supplier Boehringer Ingelheim NZ ltd
Proposed Indication Prevention of Stroke, Systemic Embolism and Reduction of Vascular Mortality in Patient with Atrial Fibrillation
Dosing Recommended dose of 150mg twice daily. With a lower dose for patients with renal impairment
Pharmaceutical Price [redacted]
Current Treatment Warfarin or aspirin

Executive Summary

Objective

The objective was to assess the cost-effectiveness of dabigatran compared with either warfarin or aspirin for the prevention of ischemic stroke in patients with atrial fibrillation. It is assumed dabigatran will be used in patients who are at moderate to high risk of stroke, i.e. $CHAD_S \geq 2$.

Clinical Effectiveness Review

The key evidence for dabigatran is the phase III non-inferiority trial, RE-LY. The RE-LY trial was designed to show non-inferiority of dabigatran compared with warfarin. The trial reported that dabigatran 300mg daily was superior to dose-adjusted warfarin; however PTAC and the Cardiovascular Subcommittee considered that, until further evidence becomes available, dabigatran should be considered therapeutically equivalent to warfarin.

There was no evidence identified that compared dabigatran to aspirin, therefore an indirect comparison of the clinical evidence was made. The BAFTA trial that compares aspirin to warfarin was used.

Cost-Utility Analysis

A Markov model was constructed to simulate the different treatment strategies. The analysis was based on the methods described in version 2 of the Prescription for Pharmacoeconomic Analysis (PFPA).

Key inputs in the model included the reduction in ischemic stroke derived from the BAFTA trial. Key uncertainties in the CUA included the proportion of patients switching from warfarin or aspirin (with the majority of patients switching from warfarin); the reduction in overall mortality (and whether a reduction in risk of stroke is directly correlated with reduced mortality); and the efficacy of dabigatran compared with warfarin (where it is assumed that dabigatran is not associated with any QALY gain compared to warfarin). Costs were estimated from the perspective of the funder and included cost of treatments and costs of events such as ischemic stroke. Quality of life scores were estimated by mapping of heath states to the EQ-5D. Costs and benefits were discounted using a discount rate of 3.5%.

The incremental cost per quality-adjusted life year (QALY) of a dabigatran compared to warfarin or aspirin for the prevention of ischemic stroke in atrial fibrillation was estimated to [redacted] QALYs gained per $1 million invested). This assumes a daily cost of dabigatran of [redacted], and that a reduction in ischemic strokes will result in a reduction in overall mortality.

Breakdown of base case results for both comparators

Weight	Model	Incr Cost	Incr Gain	Cost Per QALY	QALY gained per $1 million invested
25%	Aspirin	[redacted]	0.224	[redacted]	[redacted]
75%	Warfarin	[redacted]	0.000	[redacted]	[redacted]
	Average	[redacted]	**0.056**	[redacted]	[redacted]

The results of the CUA are sensitive to changes in the proportion of patients switching from warfarin or aspirin; the reduction in overall mortality; whether dabigatran is associated with any QALY gain compared to warfarin; the reduction in risk of ischemic strokes; and the cost of dabigatran.

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1 Context

1.1 Proposal under Assessment

An application for the funding of dabigatran for the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation (AF) was received from Boehringer Ingelheim NZ ltd in May 2010. The application included an economic analysis, which was reviewed by PHARMAC staff.

Dabigatran was not registered by Medsafe for use in patients with AF upon application for funding to PHARMAC. As at December 2010 dabigatran is still awaiting registration. The FDA is the first and only organisation to date to register dabigatran for atrial fibrillation.

The application was reviewed by the Pharmacology and Therapeutic Advisory Committee (PTAC) in November 2010 and by the Cardiovascular Subcommittee in October 2010. The relevant minutes of these meetings are included below.

PTAC November 2010

Application

The Committee considered an Application from Boehringer Ingelheim NZ Limited to fund dabigatran for prevention of stroke, systemic embolism and reduction of vascular mortality in patients in atrial fibrillation.

Recommendation

The Committee **recommended** that dabigatran be funded with low priority for prevention of stroke, systemic embolism and reduction of vascular mortality in atrial fibrillation.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Māori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

The Committee noted that dabigatran is registered in New Zealand, and was previously reviewed by PTAC in November 2008 for the prevention of venous thromboembolism (VTE) following total hip and knee replacement, but is not currently registered for use in atrial fibrillation. The Committee noted that dabigatran was recently reviewed by the Cardiovascular Subcommittee for this indication, but the minutes were not yet available.

The Committee noted the pivotal study for dabigatran in atrial fibrillation, the RE-LY study (Connolly et al NEJM 2009; 361: 1139-1151), which was a randomised trial comparing two fixed doses of dabigatran, 110mg or 150mg twice daily administered in a blinded manner, and open label warfarin in patients with atrial fibrillation. The Committee noted that in the warfarin group, the mean percentage of the study period during which the International Normalised Ratio (INR) was within the therapeutic range was 64%. The Committee noted the rates of stroke or systemic embolism, which was the primary outcome, were 1.69% per year in the warfarin group compared with 1.53% per year in the 110mg dabigatran group and 1.11% per year in the 150mg dabigatran group. Both doses of dabigatran were non-inferior to warfarin ($p<0.001$), and the 150mg dose of dabigatran was superior to warfarin with an absolute risk reduction (ARR) of 0.58% and number-needed-to-treat (NNT) of 172.

The Committee noted that the primary safety outcome of major bleeding in the RE-LY trial was lower with both dosages of dabigatran and was statistically significant for the 110mg dose (2.71% versus 3.36% per year, p=0.003, ARR 0.65%, NNT 154). The Committee noted that

the rate of gastrointestinal bleeding was significantly higher with the 150mg dabigatran dose than warfarin (1.51% versus 1.02% per year, ARR 0.49%, NNT 204), but intracranial haemorrhage was significantly lower with both dosages of dabigatran. The incidence of haemorrhagic stroke was significantly lower for both dosages of dabigatran when compared with warfarin, but the incidence of myocardial infarction was higher in the dabigatran groups (p=0.048). The Committee noted that the mortality rate from any cause was not statistically different between the three treatment arms. The Committee noted that the net clinical benefit outcome, which was a composite measure of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death or major bleeding, was better with both dosages of dabigatran but that this was only statistically significant for the 150mg dabigatran dose (p=0.04). The Committee noted that unlike ximelagatran, which was withdrawn from the market because of hepatotoxicity, no signal of hepatotoxicity was detected with dabigatran. The Committee considered that dyspepsia was however more common with dabigatran when compared with warfarin (p<0.001).

The Committee considered that based on the RE-LY trial, the absolute risk reduction with dabigatran when compared with warfarin, although statistically significant, was very small (ARR 0.58%). Therefore, the Committee considered that dabigatran should be considered therapeutically equivalent to warfarin. The Committee also considered that the evidence for increased safety of the 110mg twice daily dose of dabigatran for patients aged >75 years of age, or with creatinine clearance 30-50ml/min, with concomitant p-glycoprotein inhibitors or previous gastrointestinal haemorrhage, is inadequate.

The Committee also considered that the inability to monitor dabigatran therapy could mean that the first sign of over anticoagulation could be a major haemorrhage, especially in the elderly and those with renal impairment. There is also currently no antidote for dabigatran in the event of haemorrhage. The Committee noted that patients with a creatinine clearance of <30ml/min were excluded from the RE-LY trial. The Committee also considered that there are potentially significant drug interactions between dabigatran and p-glycoprotein inhibitors, with a risk of severe bleeding, and that possible interacting drugs are likely to include more than just verapamil, amiodarone and quinidine.

The Committee considered that although one of the advantages of dabigatran is its ease of use, it is noteworthy that the rates of discontinuation in the RE-LY trial were about 5% higher with dabigatran when compared with warfarin. Dyspeptic symptoms may also be a significant issue in real life practice. The Committee also considered that, due to its short half-life (unlike warfarin), missing a dose of dabigatran could be associated with an increased risk of stroke.

The Committee noted that there was no direct head-to-head trial comparing dabigatran with aspirin. The Committee noted the meta-analysis by Hart et al (Ann Intern Med 1999; 134:492-501) and the BAFTA study (Mant et al Lancet 2007; 370:493-503), which compared the efficacy of warfarin versus aspirin in atrial fibrillation. The BAFTA study indicated that warfarin resulted in an absolute risk reduction of 2.0% when compared with aspirin. The Committee was however concerned about making an indirect comparison and considered that evidence for dabigatran was currently lacking in patients who currently use aspirin because warfarin is contraindicated or maintaining INRs within the therapeutic range is difficult. This patient group was not included in the RE-LY trial. The Committee considered that although clinical evidence is currently lacking, this patient group would possibly benefit most from dabigatran.

The Committee noted that dabigatran was significantly more expensive than warfarin even after taking into account the cost of warfarin monitoring. The Committee considered that on average, patients stable on warfarin are tested every four to six weeks.

The Committee noted the supplier's recommendation to limit dabigatran to patients with $CHADS_2$ score ≥ 2 and who were contraindicated to warfarin or had trialled warfarin but INR levels failed to be maintained within the therapeutic range. The Committee considered that it would be difficult to restrict dabigatran use to certain subgroups of patients with atrial fibrillation without a significant risk of other patients with atrial fibrillation gaining access.

The Committee noted that although there are potential advantages of an oral anticoagulant like dabigatran that does not require regular monitoring, the main issue with dabigatran is its high cost and the risk of it being used in other patient groups beyond the funded indications. The Committee also considered that home INR testing of warfarin is currently being trialled and could reduce some of the burden of warfarin monitoring. The Committee noted that there are a number of other similar oral anticoagulants, namely rivaroxaban and apixaban, which may present for funding, and resulting competition may result in price reductions.

Cardiovascular Subcommittee October 2010

The Subcommittee reviewed an application from Boehringer Ingelheim for the listing of dabigatran etexilate (Pradaxa) on the Pharmaceutical Schedule for the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation (AF). The Subcommittee noted that dabigatran is currently registered in New Zealand for venous thromboembolism (VTE) prophylaxis post-orthopaedic surgery and registration for the use in AF is expected by the end of 2010.

The Subcommittee noted that the pivotal trial in the application was the RELY trial (Connolly SJ, et al. N Engl J Med 2009; 361: 1139-51) which was a large multi-centre, multi-national, randomised non-inferiority trial comparing open label warfarin and two doses of dabigatran (220 or 300mg/day in 2 divided doses) in 18,113 patients with AF. The median duration of follow-up was 2 years and the primary outcome was stroke or systemic embolism. The Subcommittee considered that the trial showed that both doses of dabigatran were non-inferior to warfarin for the primary outcome with little difference in major bleeding. The Subcommittee noted that although the trial was a non-inferiority trial, the 300mg dabigatran dose was superior to warfarin for the primary outcome with an ARR of 0.58% (relative risk 0.66; NNT 172; 95% CI 0.53-0.82; p<0.001). The Subcommittee noted that there was no difference in hepatic adverse events between any of the three treatment arms but dabigatran was associated with a higher rate of dyspepsia. The Subcommittee considered that this trial was of good quality and grade 1+ level on the SIGN (Scottish Intercollegiate Guidelines Network) rating scheme.

The Subcommittee noted that there were no comparative studies between dabigatran and aspirin currently available. The Subcommittee noted that a meta-analysis (Hart RG, et al. Ann Intern Med 1999; 134: 492-501) showed that warfarin reduced the absolute risk of stroke by 0.7% compared to aspirin. However, the Subcommittee considered that the results of the BAFTA trial (Mant J, et al. Lancet 2007; 370: 493-503) involving 973 patients which showed an ARR of 2% for warfarin versus aspirin, was more accurate as it was a head-to-head trial directly comparing warfarin and aspirin. From the RELY and BAFTA trials, the Subcommittee considered that dabigatran would probably result in an ARR of 2% for stroke when compared to aspirin. When compared to aspirin, dabigatran would likely be associated with an increased risk of bleeding with an absolute risk increase of 0.9% per year based on the difference in the warfarin arm and aspirin only arm in the ACTIVE-W and ACTIVE-A trials.

The Subcommittee noted the ACTIVE-W trial (The Active Writing Group. Lancet 2006; 367:1903-12) which was a large multicentre parallel groups study of clopidogrel plus aspirin versus oral anticoagulation for AF. The primary outcome was the first occurrence of stroke, systemic embolism, myocardial infarction or vascular death. The Subcommittee noted that the median follow up was 1.28 years and the study was discontinued because interim analysis showed superiority of anti-coagulation. The Subcommittee considered that the conclusions from this trial are that the combination of clopidogrel plus aspirin is inferior to oral anticoagulation and possibly results in increased bleeding. The Subcommittee also considered the ACTIVE-A trial (The Active Investigators. N Engl J Med 2009; 360: 2066-78) which was a large multicentre parallel groups study of clopidogrel plus aspirin versus aspirin alone. The primary outcome variable was time to first stroke, myocardial infarction, vascular death or non-CNS metabolism with a median follow up of 3.6 years. The Subcommittee considered that combination clopidogrel and aspirin was superior to aspirin alone with an ARR of 0.8% (NNT 125; 95% CI 0.81-0.98; p=0.01) but with an increased risk or major bleeding (absolute risk increase 0.7%; NNH 142; 95% CI 1.29-1.92; p<0.001). Based on both ACTIVE trials, the Subcommittee considered that clopidogrel in combination with aspirin was inferior to anticoagulation and although evidence suggests it is better than aspirin alone, it is associated with an increased risk of bleeding.

The Subcommittee concluded that the most appropriate comparators to dabigatran were warfarin and aspirin monotherapies. While the Subcommittee also considered that there would be a group of patients on neither warfarin nor aspirin it concluded that these patients would be unlikely candidates for dabigatran and this patient group was not included in the clinical trials.

The Subcommittee considered that there is no publication with robust NZ data to estimate the prevalence of AF or the use of warfarin or aspirin as a treatment. The Subcommittee considered that the NZ Guidelines Group estimate that there are approximately 30,000 to 100,000 New Zealanders living with AF (New Zealand Guidelines Group 2005.*The*

management of people with atrial fibrillation and flutter; xxxi-xxxii). The Subcommittee noted the supplier estimate of 65,000 patients based on a general practice database *HealthStat*. The Subcommittee considered that there was a higher prevalence of AF among the older population and Maori. as well as Pacific peoples. The Subcommittee considered that approximately 25-40% of patients with AF are using warfarin and most of the remaining patients are using aspirin (30-60%) based on several trials (Burgess C, et al. Ther Clin Risk Manag. 2007 Jun; 3(3): 491-8 and Somerfield J, et al. Stroke 2006; 37: 1217-20). The Subcommittee considered that 10-20% of AF patients may not be on any anti-thrombotic therapy. The Subcommittee considered that it is likely that <1% of AF patients are using dipyridamole or clopidogrel with or without aspirin and likely only in special circumstances.

The Subcommittee noted the suppliers proposed Special Authority criteria to limit dabigatran to patients with a $CHADS_2$ score of ≥2 and who have trialled warfarin but INR levels failed to be maintained within the therapeutic range or who are contraindicated to warfarin therapy. The Subcommittee considered that the New Zealand Guidelines Group risk assessment tool based on the Framingham study was more commonly used here. Although it was appropriate to limit patients through risk stratification, the Subcommittee considered that it would be very difficult to restrict its use via Special Authority without a significant risk of slippage.

The Subcommittee noted that while most guidelines do not recommend warfarin for those at very low risk of stroke, the majority of people with AF fall within the intermediate or high risk category and would be candidates for dabigatran. The Subcommittee considered that it is very likely that all patients using warfarin would switch to dabigatran except those with severe renal impairment (GFR <30ml/min) and those allergic or intolerant of it. The Subcommittee also considered that dabigatran would replace aspirin in patients who are taking aspirin because they have a higher risk of an adverse event with warfarin i.e. those intolerant or allergic to warfarin, those with dementia, the very elderly and those on multiple medications. The Subcommittee considered that approximately 30-60% of AF patients currently on aspirin would switch to dabigatran.

The Subcommittee considered that dabigatran would remove the need for regular venepunctures and the difficulty with drug as well as food interactions with warfarin. The Subcommittee considered that the ease of use of dabigatran would increase the use of anticoagulation and probably reduce the burden of stroke to the health system in those poorly controlled on warfarin or on aspirin. However, the Subcommittee noted that there are risks with dabigatran therapy including a lack of long term outcome and adverse effect data, and no antidote for bleeding from dabigatran, unlike Vitamin K for warfarin. The Subcommittee considered that there would need to be some guidance provided to clinicians to mitigate and manage the bleeding risk if dabigatran is listed.

The Subcommittee considered that while dabigatran and warfarin were clinically equivalent dabigatran would make management of patients easier and would be an advantage for patients contraindicated or difficult to control with warfarin and are therefore on aspirin. The Subcommittee however noted that it had a much higher cost.

The Subcommittee **recommended** that dabigatran be listed on the Pharmaceutical Schedule with a medium priority. The Subcommittee considered that listing both strengths of dabigatran would be appropriate to allow for dose-adjustment in certain patient groups including those with renal impairment.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iv) The clinical benefits and risks of pharmaceuticals and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule*

This assessment considers the cost-effectiveness of dabigatran for the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation who are at a moderate to high risk of ischemic stroke (e.g. $CHADS_2$≥2).

1.2 Disease and Patient Population

Atrial Fibrillation (AF) is a tachyarrhythmia characterised by predominantly uncoordinated atrial activation with consequent deterioration of mechanical function. AF may occur as a result of numerous cardiovascular (for e.g. ischemic heart disease or hypertension) and non-cardiovascular conditions (for e.g. thyrotoxicosis). Different types of AF have been defined according to the timing and duration of arrhythmia i.e. paroxysmal, persistent or permanent. Chronic (permanent or persistent) AF is more likely to be observed in older patients and those with additional cardiovascular problems.

Patient management, regardless of the pattern of AF, includes strategies of rate or rhythm control to address the underlying arrhythmia. Stroke prevention with antithrombotic therapy also forms a key part of management of patients with AF. AF is associated with a hypercoagulable state and a predisposition to thrombus formation. The presence of AF is associated with an almost 5-fold excess of stroke compared with its absence. Framingham data suggest that patients with atrial fibrillation have a 1.5-1.9 fold increase in mortality rate when compared with the general population.

Incidence of atrial fibrillation is significantly higher in men than in women in all age groups. AF is strongly age-dependent (and in those with additional cardiovascular problems), affecting 4% of individuals older than 60 years and 8% of persons older than 80 years. AF is the most common cardiac arrhythmia in clinical practice and as a consequence of the ageing population; AF is becoming an increasingly important public health burden[1].

1.3 Current Treatments in New Zealand

One of the major management decisions in atrial fibrillation is determining the risk of stroke and appropriate anticoagulation regimen for low, intermediate, and high-risk patients. For each anticoagulant, the benefit in terms of stroke reduction must be weighed against the risk of serious bleeding.

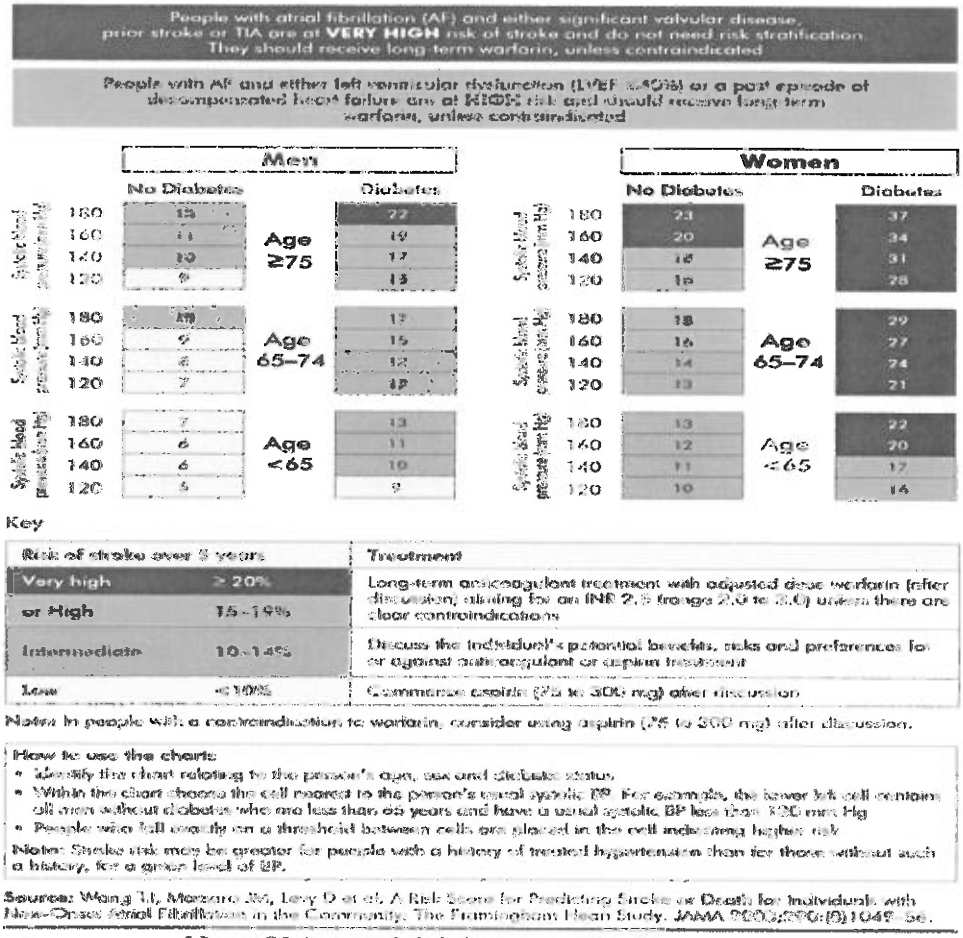
Current treatment options in New Zealand for patients with AF include aspirin, warfarin, no anticoagulation treatment, clopidogrel, or clopidogrel plus aspirin. The Cardiovascular Subcommittee of PTAC advised PHARMAC that the most common treatments for patients with AF are either warfarin or aspirin.

One of the most important considerations in the management of AF is the need for anticoagulation to reduce the risk of thromboembolism. Oral anticoagulation is currently the treatment of choice for patients at high risk of stroke.

Risk Factor Assessment Algorithms

A number of risk factor classification schemes have been developed to group patients into high, intermediate and low risk categories. The New Zealand Best Practice guidelines developed by the New Zealand Guidelines Group recommend warfarin for intermediate to high risk of stroke, while aspirin is suggested for those at low risk. The following figure presents the baseline risk of stroke in people with new-onset atrial fibrillation from Framingham Data (5-year stroke risk in %) sourced from the New Zealand Cardiovascular Guidelines Handbook[2].

Figure 1. Baseline risk of stroke in people with new-onset atrial fibrillation (and without prior TIA or stroke) from Framingham Data (5-year stroke risk in %)



Another risk classification system is the $CHADS_2$ index (Cardiac failure, Diabetes, Stroke [or S2 = TIA]). The $CHADS_2$ index uses a point system to determine yearly thromboembolic risk. Two points are assigned for a history of stroke or TIA, and one point is given for age over 75 or a history of hypertension, diabetes, or heart failure. The predictive value of this scoring system was evaluated in 1733 elderly patients with nonvalvular atrial fibrillation aged 65-95 who were not given warfarin at hospital discharge. Although high scores were associated with an increased rate of stroke, few patients had a score greater than 5 or a score of 0.

The following table presents the adjusted stroke rate in patients with nonvalvular AF not treated with anticoagulation.

CHADS2 Score	Adjusted Stroke Rate (%/y)[1]
0	1.9
1	2.8
2	4.0
3	5.9
5	8.5
5	12.5
6	18.2

Warfarin

The vitamin K antagonists (VKAs), typified by warfarin, are the most widely prescribed oral anticoagulants. VKAs have a slow onset and offset of action, high inter- and intra-individual variability in their effective plasma concentrations, and have a high potential for food and drug interactions, and require regular monitoring on the level of anticoagulation. This class of drugs when used in patients with AF also has shown to have a higher risk of bleeding at therapeutic doses than aspirin alone. Some estimate that under half of potentially eligible patients receive oral anticoagulants therapy[3].

In general it is considered that the risk-benefit ratio of warfarin therapy in low-risk patients with AF is not advantageous (due to the increased risk of a significant bleed vs. the risk of stroke in low-risk patients). However, warfarin therapy has been shown to be beneficial in higher-risk patients with AF. A target international normalised ratio (INR) of 2-3 is traditionally used in this cohort as this limits the risk of haemorrhage, while providing protection against thrombus formation. Many practices have developed specialised anticoagulation monitoring services to closely monitor INR values.

Monitoring is required for the duration of therapy to ensure that the anticoagulant effect is maintained within the recommended target therapeutic range (TTR). Evidence suggests that testing more frequently than every 4 weeks may lead to greater time in the therapeutic range. However, even in a well-controlled population monitored at a university teaching hospital, where patients had INR tests 23 times a year on average, AF patients treated with warfarin were outside the INR target range 32.1% of the time[4]

Aspirin

The antiplatelet agent aspirin (acetylsalicylic acid; ASA) is recommended for patients at low risk of stroke and for those in the moderate-to-high risk category who refuse or cannot tolerate warfarin or for whom warfarin are contraindicated.

The appropriate treatment regimen for patients with AF at intermediate risk is controversial. In this population, the clinician is likely to assess risk factors for thromboembolic disease, patient preference, risk of bleeding, risk of falls or trauma, and likelihood of medication adherence.

The following table presents the benefits and harms of treatment with warfarin compared to aspirin sourced from the NZ Cardiovascular Guidelines Handbook. Note that a risk of major bleeding with aspirin is not reported in the table; however the same meta-analysis as used for the table below reported the relative risk of major bleeding with aspirin is 0.58 compared to warfarin[5].

Table 1. Benefits and harms of treatment with warfarin compared to aspirin[2].

Benefit of warfarin*			Benefit of aspirin†		Bleeding with warfarin‡		Intracranial haemorrhage with aspirin
5 year stroke risk %	Strokes prevented per 1000 people treated for 5 years	NNT for 5 years to prevent one stroke	Strokes prevented per 1000 people treated for 5 years	NNT for 5 years to prevent one stroke	Major bleeding with warfarin per 1000 people treated for 5 years	Intracranial haemorrhage per 1000 people treated with warfarin for 5 years	Intracranial haemorrhage per 1000 people treated with aspirin for 5 years
30	20	5	6	17	10	3.5	1.5
20	13	8	4	25	10	2.5	1.5
15	10	10	3	33	10	2.5	1.5
10	7	15	2	50	10	2.5	1.5
3	3	30	1	100	10	2.5	1.5

Note Major bleeding is that which requires hospital admission, transfusion or new medicine. Definition includes prolonged, recurrent or abdominal bleed. The risk of intracranial haemorrhage is 0.5 per 1000 patients per year on warfarin and 0.3 per 1000 patients per year on aspirin.

NNT = Number needed to treat

Estimates:

* based on the estimate that warfarin reduces strokes in people with AF by 65%

† based on the estimate that aspirin reduces strokes in people with AF by 22%

‡ based on the estimate that the incidence of major bleeding with warfarin is 2% per year.

Source data analysis from van Walraven C, Hart R, Singer D, et al. JAMA 2002 [illegible]

1.4 Pharmaceutical under Assessment

Dabigatran is an anticoagulant from the class of the direct thrombin inhibitors. Dabigatran is being studied for various clinical indications and may replace warfarin (known as a 'warfarin alternative drug') as the preferred anticoagulant in many cases.

Dabigatran is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

In-vivo and ex-vivo animal studies have demonstrated antithrombotic efficacy and anticoagulant activity of dabigatran after intravenous administration and of dabigatran after oral administration in various animal models of thrombosis.

Dabigatran is registered for use in the United States of America for the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation who are at a moderate to high risk of ischemic stroke (e.g. $CHADS_2 \geq 2$). The approved doses were 150mg and 75mg both to be taken twice daily.

The recommended daily dosage of dabigatran for AF is 300 mg, given orally as 150 mg twice daily. Therapy should be continued life-long. For patients with a potentially higher risk of major bleeding, e.g. age ≥75 years, a $CHADS_2$ score of ≥3, moderate renal impairment (CrCL 30-50 mL/min), concomitant treatment with strong P-gp inhibitors (e.g. amiodarone, quinidine or verapamil), or previous gastrointestinal bleeding, a reduced daily dose may be considered. A reduced daily dose of 110mg twice daily was used in the RE-LY trial[6], however when the American FDA[7] approved dabigatran at the lower dose of 75mg twice daily (this was in addition to standard dose of 150mg twice daily). Therefore, it is uncertain what the lower dose of dabigatran would be if used in New Zealand.

Like other anticoagulants, an important safety concern with the use of dabigatran is bleeding. Bleeding was the most common and important safety concern identified in RE-LY[6]. Assessments of bleeding should take into consideration the severity/reversibility of the bleeding event. An overdose would be expected to result in hemorrhagic complications. There is no established antidote to dabigatran-induced haemorrhage and in RE-LY, investigators were told to give consideration to the following therapies in subjects with major bleeding on dabigatran: packed cells, fresh frozen plasma (FFP), prothrombin complex concentrates, and recombinant factor VIIa. Haemodialysis could also be considered[8].

2 Clinical Effectiveness Review

2.1 Dabigatran vs. warfarin

The pivotal RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study published in 2009[6] was a large, multicentre, prospective, randomised trial that compared the efficacy and safety of two fixed dosages of dabigatran (110 mg twice daily and 150 mg twice daily) with open-label adjusted-dose warfarin therapy over a period of 2 years in a total of 18,113 AF patients at risk of stroke. Patients enrolled in the study had a mean age of 71.5 years and a diagnosis of persistent, paroxysmal or permanent AF with at least one of the following characteristics:

- previous stroke or transient ischemic attack (IA);
- left ventricular ejection fraction (LVEF) <40%;
- New York Heart Association (NYHA) class II or higher heart failure symptoms within 6 months of screening and;
- age at least 75 years or age 65 to 74 years plus diabetes mellitus, hypertension or coronary artery disease.

The primary efficacy outcome was stroke or systemic embolism, while the primary safety outcome was major bleeding. Secondary outcomes included stroke (ischemic/unspecified, haemorrhagic, non-disabling or disabling/fatal), myocardial infarction, pulmonary embolism, Transient Ischemic Attack (TIA), hospitalisation, and death. The net clinical benefit of the treatments was defined as a composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding. The primary analysis was designed to test whether either dose of dabigatran was non-inferior to warfarin, as evaluated with Cox proportional-hazards modelling; after non-inferiority of the dabigatran had been established, all subsequent p-values were determined by two-tailed tests of superiority.

The results of the primary outcome (stroke or systemic embolism) of RELY study showed that both dosages of dabigatran were non-inferior to warfarin (p<0.001). Rates of the primary outcome were 1.69% per year in the warfarin group, as compared to 1.53% per year in the group that received 110mg of dabigatran (relative risk with dabigatran, 0.91; 95% CI, .74-1.11; P<0.001 for non-inferiority). The 150 mg bd dosage had a statistically significant reduction in the rate of stroke or systemic embolism compared to warfarin (relative risk 0.66; 95% CI 0.53 – 0.82; p < 0.001 for superiority). The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with 110mg bd of dabigatran (p=0.13) and 3.64 per year with 150mg bd of dabigatran (p=0.051).

The rate of haemorrhagic stroke with warfarin was 0.38% per year, while with dabigatran 110 mg bd it was 0.12% per year (relative risk 0.31; 95% CI 0.17 - 0.56; p < 0.001), and with dabigatran 150 mg bd it was 0.10% per year (relative risk 0.26; 95% CI 0.14 - 0.49; p < 0.001). The 150 mg bd dosage of dabigatran was statistically significantly superior to warfarin (relative risk 0.76; 95% CI 0.60 - 0.98; p = 0.03) for this endpoint.

Major bleeding events were lower with both dosages of dabigatran compared with dose-adjusted warfarin. The difference vs. warfarin was statistically significant for the 110 mg bd dosage (2.71% vs. 3.36% per year; relative risk 0.80; 95% CI 0.69 - 0.93; p = 0.003). With the 150 mg bd dosage, the rate of major bleeding events was marginally lower than with warfarin (3.11% vs. 3.36% per year; relative risk 0.93; 95% CI 0.81 - 1.07; p = 0.31). However, the rate of gastrointestinal bleeding (which was a subcategory of major bleeding) was significantly higher with dabigatran at the 150-mg dose than with warfarin (1.51% vs. 1.02% per year; relative risk 1.50; 95% CI 1.10-1.89; p<0.001).

Intracranial haemorrhage was significantly lower with both dosages of dabigatran than with warfarin (110 mg bd dosage: 0.23% vs. 0.74% per year; relative risk 0.31; 95% CI 0.20 – 0.47; p < 0.001; 150 mg bd dosage: 0.30% vs. 0.74% per year; relative risk 0.40; 95% CI 0.27 – 0.60; p < 0.001).

Hospitalisations were similar between dabigatran and warfarin (110 mg bd dosage: 19.4% vs. 20.8% per year; relative risk 0.92; 95% CI 0.87 – 0.97; p < 0.003; 150 mg bd dosage: 20.2% vs. 20.8% per year; relative risk 0.97; 95% CI 0.92 – 1.03; p =0.34).

From the RELY study, there was no evidence of hepatotoxicity from the serial measurements of liver function undertaken in patients receiving dabigatran. Dyspepsia was significantly more common with dabigatran, which occurred in 11.8% and 11.3% of patients in the 110 mg bd and 150 mg bd dosage groups, respectively, as compared with 5.8% of patients in the adjusted-dose warfarin group (p < 0.001 for the comparison of either dose of dabigatran with warfarin).

INR monitoring

Patients on warfarin are monitored in order to keep their international ratio (INR) in the therapeutic range of 2-3; the greater the time in therapeutic range (TTR) the greater the efficacy. Therefore, theoretically dabigatran may have less benefit over warfarin in patients with a greater TTR. Several reports in the literature show a trend towards less benefit with dabigatran when the TTR is greater in warfarin use[8,9,10].

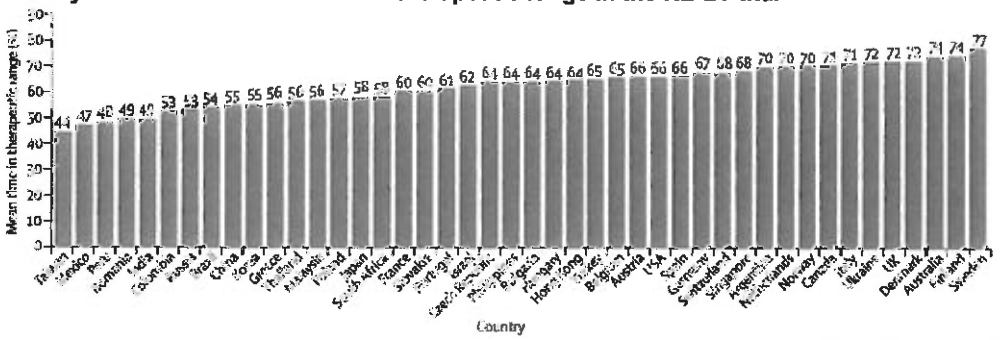
Three reports of relative efficacy of time in TTR were identified - one journal article and two FDA documents. The analyses are based on the average TTR of each of the 951 sites in the study.

Relative efficacy, measured by number of stroke and systemic embolism, of dabigatran 150mg BD compared to warfarin by TTR, Various reporting of the RE-LY trial

Source	TTR grouping. Hazard Ratio, 95% CI and number of patients (warfarin and dabigatran)	Comment
FDA[9]	TTR by quartiles <58.5% 0.60 (0.39-0.94) n~2,800 58.5 - 66.8% 0.53 (0.35-0.81) n~3,100 66.7 - 74.2% 0.65 (0.42-1.02) n~3,200 >74.2% 0.90 (0.57-1.41) n~3,000	Authors comment that there is not a clear graded relationship, and that the results suggest the relative benefit of dabigatran is somewhat dependant on INR control achieved with warfarin.
Wallentin et al[10]	TTR by quartiles <57.1% 0.57 (0.37-0.88) n=3,013 57.1 – 65.5% 0.50 (0.33-0.77) n=3,040 65.5 – 72.6 % 0.69 (0.44-1.09) n=2,971 >72.6 0.95 (0.61-1.48) n=3,023	P value for interaction was 0.2. When haemorrhagic strokes were excluded the HR's ranged from 0.54 to 1.21 and the P value for interaction was 0.076
Boehringer Ingelheim[8]	TTR by groups ≥65% (mean 78%) 0.68 (0.50-0.92) ≥68% (mean 80%) 0.70 (0.51-0.96)	The analysis controlled for $CHADS_2$ score

Results from the RE-LY trial suggest there is a significant difference in the TTR of patients treated with warfarin between countries. This can be seen in the chart below. The range reported is 44% (Taiwan) and 77% (Sweden). New Zealand was not included in the RE-LY study.

Country distribution of mean time in therapeutic range in the RE-LY trial[10]



The effect that TTR for warfarin use has on the relative efficacy of dabigatran is uncertain. However, it is plausible that the greater the TTR, the lesser the relative efficacy of dabigatran.

2.2 Warfarin vs. aspirin

As at December 2010 there are no direct comparator trials between dabigatran and aspirin in the prevention of stroke and systemic embolism in people with AF. Therefore, indirect comparisons are made using a comparison of warfarin vs. aspirin.

A key trial identified by the Cardiovascular Subcommittee was BAFTA trial. This is discussed below. Two key meta-analyses were also identified and are summarised below.

BAFTA trial

Mant et al (2007)[11] evaluated whether warfarin reduced the risk of major stroke, arterial embolism, or other intracranial haemorrhage compared with aspirin in elderly patients. The BAFTA trial was a prospective randomised open-label trial with blind assessment of endpoints. 973 patients aged 75 years or over (mean age 81.5 years) with AF were recruited from primary care and randomly assigned to warfarin (target INR ratio 2-3) or aspirin (75mg per day). The follow up period was for a mean of 2.7 years. Frequency of INR testing ranged from once per week or less if control needed to be established, to every 12 weeks if the INR were stable. A stroke that led to a hospital admission of 30 days or more was classified as disabling. The proportion of patients with previous stroke or TIA was 13% and 12% of warfarin and aspirin patients, respectively. The primary analysis was an intention-to-treat (ITT) comparison of warfarin vs. aspirin for prevention of the primary endpoint and of the secondary outcome measures, including major haemorrhage.

The primary endpoint was fatal or disabling stroke (ischemic or haemorrhagic), intracranial haemorrhagic, or clinically significant arterial embolism. Secondary endpoints included frequency of major haemorrhage, other vascular events, and all cause mortality.

The Mant et al study reported that there were 24 primary events (21 strokes, two other intracranial haemorrhagic, and one systemic embolism) in patients assigned warfarin and 48 primary events (44 strokes, one other intracranial haemorrhage, and three systemic emboli) in people assigned to aspirin;

- Yearly risk of primary events1.8% vs. 3.8%, relative risk 0.48, 95% CI 0.28-0.80, P=0.003; absolute year risk reduction 2%, 95% CI, 0.7-3.2; and
- Yearly risk of extracranial haemorrhage was 1.4% warfarin vs. 1.6% aspirin, relative risk 0.87, 0.43-1.73; absolute risk reduction 0.2% -0.7 to 1.2.

The following table presents the results from the primary outcomes.

BAFTA Primary Results

	Warfarin (n=488)	Aspirin (n=485)	Warfarin vs. aspirin		
	Risk per year (n)	Risk per year (n)	RR (95% CI)	ARR	P-value
Stroke	1.6% (21)	3.4% (44)	0.46 (0.26-0.79)	1.8%	0.003
Fatal	1.0% (13)	1.6% (21)	0.59 (0.27-1.24)	0.6%	0.14
Disabling non-fatal	0.6% (8)	1.8% (23)	0.33 (0.13-0.77)	1.2%	0.005
Type of Stroke					
Ischemic	0.8% (10)	2.5% (32)	0.30 (0.13-0.63)	1.7%	0.0004
Haemorrhagic	0.5% (6)	0.4% (5)	1.15 (0.29-4.77)	-0.1%	0.83
Unknown	0.4% (5)	0.5% (7)	0.69 (0.17-2.51)	0.1%	0.53
Other intracranial haemorrhage	0.2% (2)	0.1% (1)	1.92 (0.10-113.3)	0.1%	0.65
Systemic Embolism	0.1% (1)	0.2% (3)	0.32 (0.01-3.99)	0.1%	0.36
Total number of events	1.8% (24)	3.8% (48)	0.48 (0.28-0.80)	2.0%	0.0027

Patients on warfarin had INR values in the therapeutic range (2-3) 67% of the time, and were below range 19% and above range 14% of the time.

The following table shows the results from secondary outcomes.

BAFTA Secondary Results

	Warfarin (n=488)	Aspirin (n=485)	Warfarin vs. aspirin		
	Risk per year (n)	Risk per year (n)	RR (95% CI)	ARR	P-value
Death	8% (107)	8.4% (108)	0.95 (0.72-1.26)	0.4%	0.73
Haemorrhage (fatal and non fatal)					
Major extracranial haemorrhage	1.4% (18)	1.6% (20)	0.87 (0.43-1.73)	0.2%	0.67
Other hospital admission for haemorrhage	1.8% (24)	1.5% (19)	1.22 (0.64-2.36)	-0.58%	0.52
All major haemorrhages (including intracranial and haemorrhagic stroke)	1.9% (25)	2.0% (25)	0.96 (0.53-1.75)	0.1%	0.90

The overall mortality rates were similar in both groups. Yearly risk of haemorrhage did not differ between people assigned to warfarin who were on anticoagulant treatment.

The authors concluded that the data supported the use of anticoagulation treatment for patients aged over 75 years who have AF, unless they are contraindicated or the patients decides that the benefits are not worth the inconvenience.

Meta-analyses

Two key meta-analyses were identified that compared warfarin to aspirin - Hart et al[12] and Walraven et at[5]. Given the small number of patients in the individual trials who have events such as haemorrhagic stroke, myocardial infarction, systemic embolism, intracranial haemorrhage extracranial bleed, transient ischemic attack and minor bleed,, it was considered that a meta-analysis would provide better estimates for these outcomes than a single trial.

There is significant overlap of trials included in the meta-analyses. About three quarters of patients (approximately 3,000) in each of meta-analyses are included in both meta-analyses. Both are used as some of the outcomes reported differ.

The results of the meta-analyses are summarised alongside the BAFTA under probabilities in the modelling section. The absolute reductions in stroke were similar to BAFTA.

2.3 Dabigatran vs. aspirin

Given the absence of evidence directly comparing the efficacy and safety of dabigatran with aspirin in patients with AF, an indirect comparison of these treatments was undertaken.

It is assumed that dabigatran has the same efficacy as warfarin, based on advice from PTAC and the Cardiovascular Subcommittee. Therefore, when comparing dabigatran with aspirin, evidence comparing warfarin with aspirin is used to model event rates, as discussed in the section above. For example the model rates of ischemic stroke are 2.5 per annum and 0.8% per annum for aspirin and dabigatran respectively.

3 International Recommendations

No international economic evaluations were indentified from the Scottish Medicines Consortium (SMC), or the Pharmaceutical Benefits Advisory Committee (PBAC) of Australia for the use of dabigatran in the prevention of stroke and systemic embolism in people with atrial fibrillation.

NICE is currently appraising the clinical and cost-effectiveness of dabigatran within its licensed indication for the prevention of stroke and systemic embolism in people with atrial fibrillation. NICE anticipates these results will be published August 2011[13].

The Canadian Agency for Drugs and Technologies in Health (CADTH) has published an emerging health technology report assessing the new anticoagulants dabigatran and rivaroxaban for the prevention of stroke in patients with atrial fibrillation. The health technology assessment (HTA) concludes: "patients with excellent INR control on warfarin may not benefit from a change in therapy, but vitamin K antagonist alternatives could have a role when warfarin is not an option or when the international normalised ratio (INR) cannot be stabilised"[14]. CADTH has previously rejected dabigatran for stroke prevention but is now assessing it again.

4 Review of Supplier Economic Analysis

A cost-utility analysis (CUA) was received from Boehringer Ingelheim NZ ltd. A review of this model, undertaken by PHARMAC staff, is included in Appendix 1. Subsequent to the review, PHARMAC staff constructed a new model with a number of amended inputs and assumptions.

The PHARMAC model is detailed in the following section.

5 Economic Analysis

This section outlines the cost-utility analysis undertaken by PHARMAC staff.

5.1 Scope of Analysis

An indicative cost-utility analysis was undertaken to estimate the cost per QALY of dabigatran for the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation. The target population for this analysis was defined as patients with AF who are at moderate to high risk of stroke or systemic embolism. The comparators used in the analysis were aspirin and warfarin.

It is assumed that 25% of patients are likely to switch from aspirin to dabigatran, and 75% switch from warfarin. This is based on [redacted] indicating that 2.6% of aspirin use is for atrial fibrillation/flutter (approx 400,000 aspirin patients) and 57% of warfarin use is for atrial fibrillation (approx 40,000 warfarin patients), and also PTAC advice that 25-40% of patients with AF are using warfarin and most of the remaining patients are using aspirin (30-60%). The rate of warfarin use is likely to be higher in patients who are at a moderate to high risk of ischemic stroke, as per the prescribing guidelines discussed in section 1.3 above. This key assumption is varied in the sensitivity analysis.

5.2 Economic Model

A Markov model was constructed to model the different treatment strategies. This model uses data derived from the BAFTA trial and two meta-analyses that compared the efficacy of aspirin to warfarin. These meta-analyses and trial reported that patients administered warfarin had a reduced risk of ischemic stroke compared with patients administered aspirin.

Based on the recommendation of the Cardiovascular Subcommittee and PTAC, it is assumed that dabigatran will have the same efficacy as warfarin. Therefore dabigatran is assumed to have the same health outcomes as warfarin and improved health outcomes compared to aspirin (to the same degree as warfarin improves health outcomes compared to aspirin).

Time Horizon

The time-horizon of the CUA was a lifetime (median survival approximately 8 years). Each Markov cycle was one year. All costs and benefits were discounted at 3.5% per annum.

The average age of patients was estimated to be 78. This is based on information from HealthStat[i] for the average age of AF patients with a CHADS≥2 in New Zealand. The average age in the RE-LY trial and in the meta-analyses (Hart et al and Walraven et al) was approximately 71 years. This is lower than the average age of patients in New Zealand (based on the HealthStat data), as the patient eligibility criteria in the trials restricted participants to healthier patients who tend to be younger. The average age in the BAFTA trial was 81.5 years, but older patients were specifically recruited to study the effect of warfarin in elderly patients.

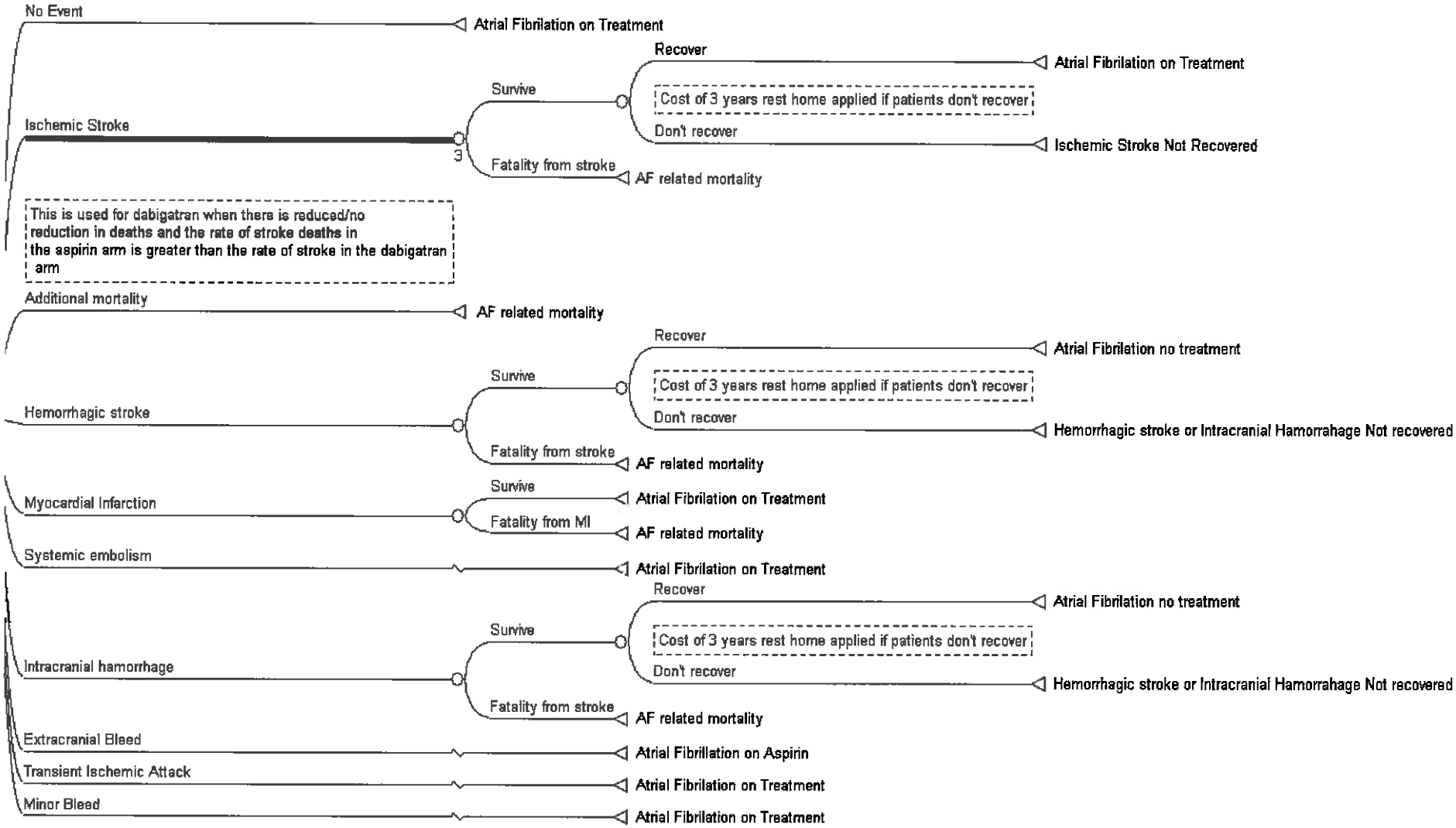
[i] HealthStat is a database of sample information of General Practitioners in New Zealand. Data was provided by the supplier.

Model Structure
The Markov model included the following health states:

- AF – receiving dabigatran;
- Ischemic stroke – not recovered;
- Haemorrhagic stroke or intracranial haemorrhage – not recovered;
- AF – no treatment;
- AF – on aspirin;
- Background mortality;
- AF-related death.

The probability of patients having an event is conditional on what treatment they are receiving at the time. It is assumed that patients who have a haemorrhagic stroke or intracranial haemorrhage will not be on treatment in order to reduce the risk of a subsequent event. If a patient has an extra cranial bleed it is assumed they will switch to aspirin (if they are not already on aspirin) in order to reduce the risk of further bleeding.

A branch of the Markov model is included on the following page.


No Event
Atrial Fibrilation on Treatment
Recover
Atrial Fibrilation on Treatment
Survive
Cost of 3 years rest home applied if patients don't recover
Ischemic Stroke
Don't recover
Ischemic Stroke Not Recovered
3
Fatality from stroke
AF related mortality
This is used for dabigatran when there is reduced/no reduction in deaths and the rate of stroke deaths in the aspirin arm is greater than the rate of stroke in the dabigatran arm
Additional mortality
AF related mortality
Recover
Atrial Fibrilation no treatment
Survive
Cost of 3 years rest home applied if patients don't recover
Hemorrhagic stroke
Don't recover
Hemorrhagic stroke or Intracranial Hamorrahage Not recovered
Fatality from stroke
AF related mortality
Survive
Myocardial Infarction
Atrial Fibrilation on Treatment
Fatality from MI
AF related mortality
Systemic embolism
Atrial Fibrilation on Treatment
Recover
Atrial Fibrilation no treatment
Survive
Cost of 3 years rest home applied if patients don't recover
Intracranial hamorrhage
Don't recover
Hemorrhagic stroke or Intracranial Hamorrahage Not recovered
Fatality from stroke
AF related mortality
Extracranial Bleed
Atrial Fibrillation on Aspirin
Transient Ischemic Attack
Atrial Fibrilation on Treatment
Minor Bleed
Atrial Fibrilation on Treatment

5.3 Key Assumptions and Inputs

The key assumptions regarding efficacy of dabigatran include:

- Superior to aspirin, annual ARR of 1.8% for ischemic stroke
- Equal to warfarin.

The key assumptions regarding the safety of dabigatran include:

- Increased risk of bleeding compared to aspirin
- Equal to warfarin

Other key assumptions include:

- Reductions in overall survival are based on reductions in events. There is a correlation of 0.8 between reduction in the risk a stroke and reduction in stroke/overall deaths
- 75% of patients switch from warfarin and 25% switch from aspirin.
- No difference in compliance
- Three outcomes from stroke;
  - Stroke death (above background mortality - 37%)
  - Long term reduction in QoL and enter rest homes 3 years earlier than those not having a stroke (27%)
  - Recover after 1 year and have no ongoing costs or reduction in QoL (36%)

Background mortality

At each point of time patients are at risk of non-AF related death. The rate of background mortality included in the model is based on the age-related life expectancy of the New Zealand population. The annual rate of background mortality for a 78 year old (average age of patient population) is estimated to be 4.5%. This rate subsequently increases as the patient population age.

Probabilities

The annual risks of AF-related events are shown in the table below. PTAC and the Cardiovascular Subcommittee recommended using the BAFTA[11] trial to compare efficacy of dabigatran and aspirin. As discussed above, meta-analyses (Hart et al[12] and Walraven et al[5]) have been used to determine the relative differences in haemorrhagic stroke, myocardial infarction, systemic embolism, intracranial haemorrhage extracranial bleed, transient ischemic attack and minor bleed.

None of the studies identified reported on rates of minor bleeding for aspirin. Therefore the estimates included in the supplier CUA were used. These were based on an unpublished mixed treatment comparison done by the supplier.

The analysis assumes that the probability of having an ischemic stroke is the same even if the patient had experienced a previous stroke or any other event. The evidence used included some patients who had had previous events; in addition some patients in the trials experienced an event more than once. Therefore the probabilities used reflect an 'average' patient and take in to account the probability of an event given past events.

Annual risks reported and those used in the cost-utility analysis

Outcome	Model	Annual Risk		Relative Risk	Reported RR 95% CI	Absolute risk reduction
		Aspirin	Warfarin			
Ischemic Stroke	BAFTA	2.5%	0.8%	0.30	0.13 - 0.63	1.8%
	Hart[i]					
	Walraven	4.2%	2.0%	0.48	0.37 - 0.63	2.2%
	Modelled	**2.5%**	**0.8%**	**0.30**	**0.13 - 0.63**	**1.8%**
Haemorrhagic Stoke	BAFTA	0.4%	0.5%	1.15	0.29 - 4.77	-0.1%
	Hart					
	Walraven	0.3%	0.5%	1.84	0.87 - 3.87	-0.2%
	Modelled	**0.3%**	**0.5%**	**1.84**	**0.87 - 3.87**	**-0.2%**
Myocardial Infarction	BAFTA	1.2%	1.1%	0.96	0.44 - 2.11	0.0%
	Hart					
	Walraven	1.1%	0.7%	0.63	0.39 - 1.04	0.4%
	Modelled	**1.1%**	**0.7%**	**0.63**	**0.39 - 1.04**	**0.4%**
Systemic Embolism	BAFTA	0.2%	0.1%	0.32	0.01 - 3.99	0.2%
	Hart					
	Walraven	0.3%	0.2%	0.71	0.29 - 1.74	0.1%
	Modelled	**0.3%**	**0.2%**	**0.71**	**0.29 - 1.74**	**0.1%**
Intracranial haemorrhage	BAFTA	0.1%	0.2%	1.92	0.1 - 113.3	-0.1%
	HART			2.28	1.04 - 4.99	-0.2%
	Walraven					
	Modelled	**0.1%**	**0.2%**	**2.28**	**1.04 - 4.99**	**-0.1%**
Extracranial Bleed	BAFTA	1.6%	1.4%	0.87	0.43 - 1.73	0.2%
	Hart			1.70	0.86-3.34	-0.2%
	Walraven					
	Modelled	**1.6%**	**2.7%**	**1.70**	**0.86-3.34**	**-1.1%**
Transient Ischemic attack	BAFTA	0.7%	0.5%	0.77		0.2%
	Hart					
	Walraven					
	Modelled	**0.7%**	**0.5%**	**0.77**	**0.29–2.06[ii]**	**0.2%**
Minor Bleed	BAFTA					
	Hart					
	Walraven					
	Modelled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[i] Relative efficacy of Ischemic stroke on it's own was not reported
[ii] Not reported, calculated by PHARMAC staff

The relative risk of events for patients not receiving any treatment (due to having an intracranial haemorrhage or haemorrhagic stroke) compared to aspirin are based on supplier estimates. These were based on an unpublished mixed treatment comparison undertaken by the supplier. These were used because they were readily available. They have a small impact on the result as less than one percent of patients do not receive treatment in the model. The relative risks are shown in the table below.

Relative risk of events for no treatment compared to aspirin

Outcome	Relative risk
Ischemic stroke	
Haemorrhagic stoke	
Myocardial Infarction	
Systemic embolism	
Intracranial haemorrhage	
Extracranial bleed	
TIA	
Minor Bleed	

5.4 Transformation and Extrapolations

Reduction in mortality following stroke

The base case assumes a correlation of 0.8 between reduction in the risk of stroke and reduction in stroke deaths. That is, a 70% reduction in strokes results in a 56% reduction in stroke mortality.

It is uncertain whether a reduction in the risk of stroke is directly correlated with reduced stroke mortality. PHARMAC received expert advice that there is likely to be a correlation between these variables, therefore this has been incorporated in the analysis. However, due to the lack of evidence a correlation rate of 0.8 was used in the base-case analysis.

Identified trials have not shown, with statistical significance, that dabigatran or warfarin reduces overall mortality. This is likely due to the trials not being sufficiently powered to detect a difference in mortality. However, given the estimated reduction in ischemic strokes it seems plausible this would in turn reduce mortality from strokes; which in turn would reduce all cause mortality.

In comparisons of aspirin with warfarin, ARR for death from all causes were reported to be 0.3% (P-value 0.32, meta-analysis)[5], 0.4% (p-value 0.73)[11]; and 0.5% (p-value not reported but stated not statistically significant, meta-analysis) [12]. In the meta-analysis by Walraven[5], six of the seven trials showed a non-statistically significant reduction in mortality.

In RE-LY the ARR for all cause mortality for dabigatran 150mg bd compared to warfarin was 0.49% (p-value 0.051).

As stated in PHARMACs Prescription for Pharmacoeconomic Analysis, 'For clinical events with a p value close to (but still larger than) 0.05 (i.e. the event is close to but does not reach statistical significance), the following should be considered

- Magnitude of effect
- Clinical significance
- Independent study
- Composite events'[15]

In the case of dabigatran, stroke mortality is considered to be clinically significant and the majority of independent studies identified indicate a trend that dabigatran and warfarin

reduce mortality. Therefore, the base case assumes a reduction in mortality, although the full effect is not modelled.

Death following an event

Death following a stroke

The rate of death following stoke is estimated to be 37%. This is the risk after an event with no ongoing increased risk of death. The fatality rate is based on the 5 year rates of a New Zealand cohort of 1744 stroke patients aged 75-84[16], adjusted to take account of background mortality.

Follow-up data looking at fatalities of patients with strokes found that between 21% and 43% of patients die from the stroke. Difference in fatality rates may be due to age of the population, duration of follow up and when the observation was made.

Based on the ARCOS[17] study it seems that fatality rates from stroke are lower than they were historically. The 28 day fatality rate fell 12% ($p<0.001$) between 1981 and 2002/03. It is assumed that the higher historical rates no longer apply.

The results of the 1995 Auckland cohort were 21% - 25% 28 day stroke fatality rates, and 34% - 37% 5 year stroke fatality rates. These were for patients aged 65-74 and 75-84 respectively. This showed that after adjusting for background mortality the difference in fatality from stroke due to age is relatively small.

The fatality rates from trials are unlikely to give a representative average rate due to the relatively low number of strokes. This illustrated by the variance in cause fatality in trials that were set up to identify the efficacy of warfarin compared to aspirin. The BAFTA[11] trial reported a 52% case fatality rate while the SPAF II[19] trial reported a case fatality rates of 6% and 10% (depending on age group).

Fatality rates following stroke

Patient population	Events (n) Population (N) Fatality rate	Incremental fatality compared to average population [i]	Time period [ii]
New Zealand cohort (1995)[16]			
Age 65-74	613/1374 45%	32%	5 Years
Age75-84	1166/1744 68%	37%	
Age 65-74	289/1374 21%[iii]	21%	28 days
Age75-84	610/1744 35%[iii]	25%	
Auckland cohort (ARCOS)			
1981 Mean age 71	306/680[18] 45%[iii]	43%	1 year
	450/1360[17] 33%	33%	28 days
2002/03 Mean age 73	407/1938[17] 21%	21%	
England 2001 - 2004[11]			
Average age 81.5	34/65 52%	52%	2.7 years (mean) follow up. Mortality was restricted to where stroke was the cause of death.
USA 1987 -1992[19]			
Patients ≤ 75	2/32 6%	6%	2.3 years (mean) follow up. Mortality was restricted to where stroke was the cause of death.
Patients > 75	3/31 10%	10%	

[i] Average mortality based on the mortality table for the New Zealand population, based on the median age for the age group
[ii] Includes deaths pre hospitalisation
[iii] Percentages taken from graphs, number of events inferred from percentages

The rate of death in the dabigatran arm is set so the relative risk reduction (RRR) is 80% of the RRR of the event, e.g. RRR of 0.56 ischemic stroke mortality compared to a RRR of 0.7 for ischemic stroke.

The table below reports the differences in stroke fatality used in the model.

Rates of fatal strokes used in the cost-utility analysis

Death from	Risk per year		Dabigatran vs. aspirin	
	Aspirin	Warfarin/ dabigatran	RR	ARR
Ischemic Stroke	0.94%	0.41%	0.44	0.52%
Hemorrhagic stoke	0.10%	0.17%	1.67	-0.07%
Total	1.04%	0.58%	0.56	0.46%

Applying the same rates of death following a stroke for both warfarin and aspirin results in a similar rate of fatal strokes than reported in the BAFTA trial[11]. The reported ARR was 0.6 while the modelled ARR is 0.46.

Death following intracranial haemorrhage

The rate of death following intracranial haemorrhage was assumed to be the same as the rate of death following a stroke. An intracranial haemorrhage is assumed to have a similar fatality rate as a haemorrhage stoke.

The rate of death following an intracranial haemorrhage was not reported for the BAFTA trial.

The resulting annual rates of fatal intracranial haemorrhage used in the updated model are 0.03% for aspirin and 0.07% for dabigatran. As with strokes, this assumes 37% risk of death following an event with no ongoing risk.

Death following a MI

The rate of death following myocardial infarction (MI) is estimated to be 49%. This is the immediate risk with no ongoing risk of death. The fatality rate is based on a New Zealand cohort of 1371 MI patients aged 75-84[16].

The 5 year and 28 day fatality rates for patients were reported. After adjusting the 5 year rate for background mortality, the fatality rate (41%) is less than the 28 day fatality rate (49%). An explanation for this is that patients who do not have MI will have a greater than average life expectancy. Therefore, it is considered that the 28 day rate is the most appropriate rate to use.

Patient population	Events (n) Population (N) Fatality rate	Incremental fatality compared to average population [1]	Time period [1]
New Zealand cohort (1995)[16]			
Age 65-74	695/1499 46%	34%	5 Years
Age75-84	980/1371 71%	41%	
Age 65-74	465/1499 31%[1]	31%	28 days
Age75-84	672/1371 49%[1]	49%	

[1] Percentages taken from graphs, number of events inferred from percentages

The rate of death following MI was not reported for the BAFTA trial.

The resulting annual rates of fatal MI used in the updated model are 0.54% for aspirin and 0.38% for dabigatran.

Recovery following an event

Recovery following a stroke
It is assumed that some patients have a temporary reduction in quality of life of one year, then return to the quality of life they had prior to the stroke; assumed to apply to 36% of patients. This is based on the results of the RE-LY trial where 173 out of 483 strokes were classed as non-disabling.

Stroke severity	Total events for all treatments[1]	Percentage
Non-disabling stroke	173	36%
Disabling or fatal	310	64%

[1] Treatments were dabigatran and warfarin

The modified rankin score was used to determine if a stroke was non-disabling, where a score of 0-2 was classed as non-disabling. The scale is as follows:

0 - No symptoms.
1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3 - Moderate disability. Requires some help, but able to walk unassisted.
4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6 - Dead.

Recovery following an intracranial haemorrhage
This is assumed to be the same as for stroke.

Recovery following a myocardial infarction
It is assumed that all patients who survive a MI will recover to their prior-MI health state.

5.5 Health-Related Quality of Life

The utility values included in the analysis were obtained using the New Zealand EQ-5D. Health state descriptions were informed by literature search and PHARMAC staff. NZ Tariff-2 EQ-5D weights were then applied to the generic health states to derive quality of life scores. These are outlined in the table below. These were then validated by comparing to previous PHARAMC analyses, GBD weight, the supplier analysis and another analysis.

There is assumed to be no difference in HR-QoL based on what treatment patients are receiving.

Although there is some uncertainty regarding the quality of life values, their impact on the results of the analysis is relatively small as the majority (84%) of QALY gains is from increased life expectancy.

Utility values used in the cost-utility analysis

Health state	QoL	Disutility compared to base line
Atrial Fibrillation (AF)	0.891	
Ischemic/Hemorrhagic Stroke, Intracranial Haemorrhage – First 3 months	0.275	-0.616
Ischemic/Hemorrhagic Stroke, Intracranial Haemorrhage– 4 - 12 months	0.636	-0.257
Ischemic/Hemorrhagic Stroke, Intracranial Haemorrhage – Recovered after 1 year	0.891	0
Ischemic/Hemorrhagic Stroke, Intracranial Haemorrhage – Not Recovered after 1 year	0.634	-0.257
Myocardial Infarction - First month	0.275	-0.616
Myocardial Infarction – After 1 month	0.891	0
Systemic Embolism - 1 month post event	0.636	-0.255
Extracranial Bleed – 1 month post event	0.627	-0.264
Transient Ischemic Attack	0.891	0
Minor Bleed	0.891	0

Health states used in the model and their corresponding EQ-5D descriptions

Health state	EQ-5D	EQ5D description
Atrial Fibrillation (AF)	11(1-2)11	No problems walking around, No problems with self care, Some problem with performing usual activities, No pain or discomfort, No anxiety or depression.
Ischemic Stroke – First 3 months	(2-3)(2-3)(2-3)22	Between some problems walking about and confined to a bed, between some problems and unable to wash and dress, between some problems and unable to perform usual activities. Moderate pain or discomfort. Moderately anxious or depressed
Ischemic Stroke – 4-12 months	(1-2)22(1-2)1	Some problems walking about, some problems washing or dressing self, some problems with performing usual activities, some pain or discomfort, not anxious or depressed.
Post Ischemic Stroke – Recovered after 1 year	Same as Atrial Fibrillation	
Post Ischemic Stroke – Not Recovered after 1 year	(1-2)22(1-2)1	Some problems walking about, some problems washing or dressing self, some problems with performing usual activities, some pain or discomfort, not anxious or depressed.
Post Haemorrhagic Stroke	Same as Ischemic Stroke	
Myocardial Infarction – First Month	(2-3)(2-3)(2-3)22	Between some problems walking about and confined to a bed, between some problems and unable to wash and dress, between some problems and unable to perform usual activities. Moderate pain or discomfort. Moderately anxious or depressed
Myocardial Infarction – After 1 month	Same as Atrial Fibrillation	
Post Systemic Embolism	22211	Some problems walking about, some problems washing or dressing self, some problems with performing usual activities, no pain or discomfort, not anxious or depressed.
Post Intracranial Haemorrhage	Same as Ischemic Stroke	
Extracranial Bleed – 1 month post event	21221	Some problems walking about, no problems with self care, some problems with performing usual activities, moderate pain or discomfort, not anxious or depressed.
Transient Ischemic Attack	Considered very short term, so no change in QoL is modelled	

Atrial Fibrillation

Patients with moderate to high risk of stroke, i.e. $CHADS_2$ score ≥2, could have a variety of co-morbidities. The $CHADS_2$ scoring mechanism is as follows

- Diagnosed heart failure, past or current (1 point)
- Hypertension treated or untreated (1 point)
- Age >= 75 years (1 point)
- Diabetes Mellitus (1 point)
- Secondary prevention in patients with prior ischemic stroke, TIA or thromboembolism (2 points)

The supplier estimates that the distribution of $CHADS_2$ scores for patients with AF is 47% ≤1, 31% = 2 and 22% ≥ 3.

A quality of life study looking at many chronic health states in patients in the United States, reported that patients with cardiac dysrthythmias (which AF is a subset) have a mean age of 68 (the average age of patients in this analysis is 78) and a median of 5 chronic co-morbidities (Sullivan P et al)[20].

It is assumed that the average patient will have some reduction in quality of life, compared to no health problems. Although it will differ between patients, especially given differences in co-morbidities, it is expected the 'average' patient will be somewhat restricted in their usual activities.

Stroke and Intracranial Haemorrhage
Ischemic stroke, haemorrhagic stroke and intracranial haemorrhage are modelled to have the same utility values; although the probabilities of the events differ. The first 3 months are assumed to be associated with the lowest quality of life. In this time it is expected that patients will first be in hospital (on average for one month) and then may leave hospital but still need to rest.

In 3 to 12 months post event it is expected that mobility, ability to perform usual activities and pain will improve although will still affect the patient.

After 12 months some patients (approx half of survivors) are expected to recover from the stroke and have the quality of life they had before the stroke. However, if patients don't recover after 12 months they are expected to have a continual reduction in quality of life.

Myocardial infarction
Patients are expected to be initially admitted to hospital. If patients survive it is expected they will return to the quality of life prior to the myocardial infarction. The disutility is expected to last a month

In a six month follow up of patients post MI it was reported 'Quality of life six months after myocardial infarction is generally high, and most patients are able to return to normal activities.' It was noted that in a small group of patients quality of life was significantly impaired.[21]

Post Systemic Embolism
A systemic embolism is assumed to reduce a patient's quality of life for one month. It is assumed there will be no long term effects. Long term effects from emboli are taken in to account by the ischemic stroke and myocardial infarction health states.

Extracranial Bleed
It is assumed the reduction in quality of life will last a month after an extracranial bleed (includes gastrointestinal bleeding). It is expected that patients will have some pain which may impact their mobility and ability to perform usual activities.

Transient Ischemic attack
There is no disutility modelled for a transient ischemic attack (TIA). Given by definition they resolve in 24 hours; the impact of including a quality of life adjustment would be negligible.

Minor Bleed
It is assumed that a minor bleed has no disutility associated with it.

A comparison of utility scores from various sources is included in the table below. One source indentified is a cost-utility analysis for dabigatran for prevention of ischemic stroke in patients with atrial fibrillation; this was done by Freeman et al[22], in the US setting with a societal perspective.

Heath States and corresponding utility values based on different sources

Health State	NZ EQ-5D	Utility	GBD	Previous PHARMAC Analyses	Freeman et al[22]	Sullivan et al[20] [redacted]
Atrial Fibrillation (AF)	*11(1-2)11*	0.891	N/A	N/A	Base line health state was termed 'Healthy with AF' 0.998(Aspirin) 0.987 (Warfarin) 0.994 (Dabigatran)	The supplier quoted two values 0.81 (Sullivan et al) and 0.82 (Gage et al[23])
Ischemic/Hemorrhagic Stroke + Intracranial Haemorrhage – First 3 months	(2-3)(2-3)(2-3)22	0.275	No distinction made between short and long term QoL			
Ischemic/Hemorrhagic Stroke + Intracranial Haemorrhage – 4 - 12 months	(1-2)22(1-2)1	0.634				
Ischemic/Hemorrhagic Stroke + Intracranial Haemorrhage – Recovered after 1 year	*11(1-2)11*	0.891	N/A			
Ischemic/Hemorrhagic Stroke + Intracranial Haemorrhage – Not Recovered after 1 year	(1-2)22(1-2)1	0.634	Permanent impairments Mild 0.64 Moderate 0.37 Severe 0.08	Used GBD weights	Mild: 0.75 Moderate – severe: 0.37 Over all: 0.53 Of the strokes with long term neurological sequelae 43% were mild and 57% were moderate to severe.	0.6715

Myocardial Infarction – First month	(2-3)(2-3)(2-3)22	0.275	No distinction made between short and long term QoL	0.464[ii], 0.58[iii],0.61[v] 0.92[iv]	No distinction made between short and long term QoL	
Myocardial Infarction – After 1 month	*11(1-2)11*	0.891	0.605	0.73[iii] , 0.92[iv], 0.464- 1 (Disutility only **Applied for 1** year)[ii], 0.75 (Disutility only Applied for 3 months)[v]	0.84	0.6853
Systemic Embolism	22211	0.636	N/A	N/A	N/A	0.6901 Ongoing
Extracranial Bleed (Major) – Applied for 1 month	21221	0.627	N/A	N/A	0.8 For 2 weeks	0.6286 Ongoing
Transient Ischemic Attack	No change		N/A	N/A	N/A	0.7068 Ongoing
Minor Bleed	No Change		N/A	N/A	N/A	No Change

[i] HRT analysis, weightings not stated. TAR 54
[ii] Glitazones analysis TAR 57 and clopidogrel TAR 46
[iii] **Abciximab and eptifibatide for PCI TAR 64**
[iv] **Statins analysis TAR 1**
[v] **Celecoxib and rofecoxib TAR 55**

5.6 Costs

Pharmaceutical Costs

The following pharmaceutical costs were included in the analysis:

Pharmaceutical	Dose per tablet	Cost ($) per tablet	Cost ($) per year (daily dose)
Dabigatran	150mg	[redacted]	[redacted]
Warfarin	1mg 2mg 3mg 5mg	$0.06 $0.09 $0.08 $0.11	$45 Range of $30-$60 (2-6mg)
Aspirin	100mg	$0.014	$5.16 (100mg)

The price of dabigatran [redacted]

There can be large variations in the prescribed doses of warfarin. However, the cost of each warfarin tablet ranges from $0.06-$0.11 (1mg-5mg) per tablet. Therefore, this does not impact on the overall cost of warfarin substantially. Between the warfarin doses of 2-6mg per day the year cost ranges from approximately $30-$60; the base case assumes $45.

No dispensing fees or pharmacy mark-ups have been included in the analysis. If more than one dose of warfarin tablets was dispensed, then there could be an additional cost of $5.30 for dispensing warfarin tablets. However, this would not have a substantial impact the overall result.

Health Sector Costs

INR monitoring

The cost of INR monitoring was included for patients receiving warfarin. The cost of INR monitoring is estimated to be $15 per INR test, $10 for the lab test and $5 for 10 minutes of nurse time. It is assumed that patients receive an average of 17 tests per year. This is based on average INR testing for New Zealand patients aged 65 and over between March 2009 and May 2010 that were receiving warfarin (excluding initial period on warfarin)[24]. The cost per year is estimated to be $255.

The Best Practice Journal states that once patients are stable, testing for most patients can be done every 4 – 6 weeks (9-13 times a year). However if patients become unstable then they will require more frequent testing[25]. The number of tests patients on warfarin receive is varied in the sensitivity analysis.

Cost Offsets

The table below reports the cost-offsets included in the model.

Cost-offsets included in the cost-utility model

Event	Cost
Stroke (ischemic or haemorrhagic)	$34,400 for all patients who survive (consisting of hospital and outpatient costs in year 1) . An additional cost of $35,800 per year for 3 years (patients not recovering (21%))
Intracranial Haemorrhage	
Fatal stroke or intracranial haemorrhage	$1,200
Myocardial infarction	$5,600[i]
Fatal Myocardial Infarction	$825
Systemic Embolism	$5,300
Extracranial Bleed	$3,100
Transient Ischemic Attack	$1,500
Minor Bleed	$240

[i] Applied to patients who survive

Stroke (Ischemic or Haemorrhagic)
The first year cost of a stroke for those who survive is estimated to be $34,400. In addition some patients (21%) are expected to enter rest home care 3 years earlier than if they didn't have a stroke; the estimated cost for this is $35,800 per year.

The first year cost can be divided in to inpatient and outpatients costs. The inpatient cost for patients with an ischemic stoke is $24,000. This includes 6.7 days of treatment on the medical wards and 24.2 days of rehabilitation. The out-patient cost for patients is estimated to be $10,400. This includes the cost of moving into a rest home for some patients and in-home rehabilitation and nurse help. The table on the next page provides a further break down of this cost.

The amount of inpatient care following a stroke is based on the McNaughton et al study that followed 181 stroke patients for a year. These were patients admitted to Wellington hospital in 1997[26]. The diagnostic-related group (DRG) codes for stroke excluding fatal cases (B70 A,B,C) were used to calculate the cost of time on the medical ward. For rehabilitation, the DRGs for rehabilitation (Z60A,B) were used, but the length of stay was adjusted to 24.2 days in order to make it consistent with the in the length of stay for stroke patients[26].

The cost of rehabilitation used in the model is higher than the case weight price provided by the ministry of health; This is due to using a length of stay of 24.7 days rather than 8.3. The length of stay used by MoH is probably shorter because it is based on a small subset of data that excludes rehab funded through a variety of funding streams[27].

The amount of outpatient care was also based on the study that followed NZ stroke patients[26]. The following costs were applied to usage of health care service. The cost of rest home care (21% of patients) was estimated to be $35,800 per year[ii] and includes the government contribution as well as patient contribution. The cost of at-home rehabilitation care is approximately $70 per[26] hour (average of 9 hours). Home help was estimated to cost $23.50 an hour (average of 95 hours).

The cost of private hospital care was not included as it is not subsidised by the health sector.

[ii] Based on personal communication with the Ministry of Health

Cost for ischemic stroke

Type of cost	Amount	Avg cost per patient
First year		
In-patient costs		
Medical Ward	6.7 days	$6,400
Rehabilitation	24.2 days	$17,600
Sub total	*30.9 days*	*$24,000*
Out-patient		
Private hospital	4%	$0[i]
Rest home	21%	$7,500
At home Rehab	9 hours per year	$600
Home help	95 hours per year	$2,200
Sub total		*$10,400*
Total first year cost		**$34,400**
Ongoing – for patients not recovering		
Rest home		**$35,800**[ii]

[i] No cost for private hospital has been included as it is not subsidised by the health sector
[ii] Included for 3 years

Ongoing costs – for patients not recovering
No information was found that compared healthcare resource for those who had experienced a stroke to those who had not. In this patient population (average age 78) it is assumed that a proportion of these patients would be in a rest home prior to a stroke and that many patients would become users of these services as they get older. Therefore it is assumed that rest home costs would only be included for 3 years as it assumes these are only delayed costs not avoided for the rest of a patient's life. This was tested in the sensitivity analysis.

Fatal stroke or intracranial haemorrhage

About half of fatal strokes occur prior to hospital admission[16] (adjusting for background mortality). It is assumed that these will not incur any health care costs. For the rest of fatal stroke cases a cost of hospitalisation prior to death was included, this is estimated to be $2,400 with an average length of stay of 1.8 days, based on DRG B70D. Therefore, the average cost per fatal stroke (with 50% of patients hospitalised prior to death) is estimated to be $1,200

Intracranial Haemorrhage
The costs of Intracranial Haemorrhage are the same as for stroke.

Myocardial Infarction
The cost used for a myocardial infarction is $5,600. This is only applied to patients who survive. This is based on a weighted average of the DRG costs for myocardial infarction, using NZ volumes (F41A,B F60A,B) The average length of hospital stay is estimated to be 5.0 days.

Fatal Myocardial Infarction
About three quarters of fatal MI's occur prior to hospitalisation[16] (adjusting for background mortality). For the quarter of patients who die from MI whilst in hospital, the cost of hospitalisation is estimated to be $3,300 with an average length of stay of 2.8 days (DRG F60C). Therefore, the average cost of hospitalisation for patients who have a fatal MI is estimated to be $825.

Systemic embolism
The estimated cost for a systemic embolism is $5,300. This is based on the DRGs for 'Peripheral Vascular Disorders' (F65 A,B) and 'Amputation for Circ System Except Upper Limb and Toe' (F11 A,B). The weightings are 93% and 7% respectively, based on NZ discharge volumes. The average length of stay is estimated to be 4.3 days.

Extracranial Bleed
The cost estimated for extracranial bleed is $3,100. This is based on the DRG 'GI Haemorrhage Age >64 or W (Catastrophic or Severe CC)' (G61A). The average length of hospital stay is estimated to be 2.8 days.

Transient Ischemic Attack
The cost estimated for a transient ischemic attack (TIA) is $1,500. It is assumed patients will be seen in the emergency department, with approximately half of patients being admitted to hospital. The inpatient cost following a TIA is estimated to be $2,700 and is based on the DRG's for TIA and Precerebral Occlusion with (17%) and without (83%) catastrophic or severe complications (B69A,B). The average length of hospital stay is 2.4 days. For patient not admitted into a hospital ward, it is assumed that they will be treated in the emergency department, at a cost of $300. Due to the uncertainty of this cost, it is varied over a wider range in the sensitivity analysis.

Minor Bleed
The estimated cost of a minor bleed is estimated to be $240. This is based on the majority of patients seeing their GP (75% at $65 per visit) and some patients going to the emergency department (25% at $300 per visit). Due to the uncertainty of this cost, it is varied over a wide range in the sensitivity analysis.

6 Results of Economic Analysis

The results of the analysis indicate that the cost per QALY of dabigatran for the prevention of stroke and stoke embolism in patients with atrial fibrillation is estimated to be [redacted] QALYs gained per $1 million invested). This assumes the daily cost of dabigatran is [redacted] that dabigatran has the same efficacy as warfarin; and that a reduction in ischemic strokes will result in a reduction in overall mortality.

The incremental costs and QALY gains in base-case analysis are included in the table below.

Incremental costs and benefits in the base case

Pharmaceutical	Cost[iii]	Incr Cost	QALY	Incr QALY	Cost per QALY	QALYs gained per $million
Aspirin/Warfarin	[redacted]		6.89			
Dabigatran	[redacted]	[redacted]	6.95	0.06	[redacted]	[redacted]

Breakdown of base case results for both comparators

Weight	Model	Incr Cost	Incr Gain	Cost Per QALY	QALY gained per $1 million invested
25%	Aspirin	[redacted]	0.224	[redacted]	[redacted]
75%	Warfarin	[redacted]	0.000	[redacted]	[redacted]
	Average	[redacted]	0.056	[redacted]	[redacted]

The majority of the QALY gain is from increased life years (84%), with the remainder due to increased quality of life.

AF-related mortality was reduced by 4% with dabigatran and warfarin treatments (9% down from 13%). This resulted in an average increase of life expectancy of 3 months.

The additional discounted cost of treatment was [redacted] of this was offset by a reduction in events such as ischemic stroke.

[iii] Note that this may not be the same as the total cost of the pharmaceutical treatment, as costs that are in the same in both treatment arms may have been excluded from the analysis.

6.1 Sensitivity Analyses

A key assumption in the analysis is which treatment patients will switch from. The base case assumes 75% of patients switch from warfarin and 25% from aspirin. The table below shows that if the proportion of patients switch from aspirin is varied from 10% to 50% the respective cost per QALYs are [redacted] QALYs gained per $1 million invested).

Cost effectiveness of dabigatran when the weight of the comparator is changed

Weight		Incr Cost	Incr Gain	Cost per QALY	QALY gained per $1 million invested
Aspirin	Warfarin				
10%	90%	[redacted]	0.02	[redacted]	[redacted]
25%	75%		0.06		
33%	67%		0.07		
50%	50%		0.11		

Further one-way sensitivity analysis was undertaken for a number of variables. The results are summarised in the table on the following pages.

Most of the variables only affect the cost effectiveness of dabigatran vs. aspirin, as dabigatran is assumed to have the same efficacy as warfarin. Consequently the impact of varying many of the variables has a relatively small impact on the overall result, despite having a larger impact on the comparison of aspirin and dabigatran.

Price of dabigatran
The price of dabigatran varied [redacted] per day; this is based on the uncertainty due to the capped rebate structure. The lower range was not tested because if additional patients take dabigatran instead of warfarin for indications outside AF There is no evidence those patients would receive any benefit. The estimated cost per QALY for the higher price is [redacted] QALYs gained per million).

Efficacy and Safety
The relative risks for each of the probabilities of events were varied over the reported 95% confidence limits in the trials. Varying ischemic stroke had the biggest effect; also it translated to the biggest change in absolute risk. Varying the annual absolute risk reduction from 0.9% to 2.2% for ischemic stroke resulted in a cost-per QALY range of [redacted] QALYs per million).

A distribution of cost per QALY results was calculated by applying distributions to the relative risks of the eight efficacy and safety outcomes. The resulting ranges were [redacted] QALYs gained per million) for the 2.5% and 97.5% limits.

Some of the ranges for the absolute risk reductions included positive and negative values. This is due to the reported results not being statistically significant at 95% confidence level.

Probability of death
A key assumption in the analysis was that reductions in events such as ischemic stroke resulted in a reduction in mortality. This was tested in the sensitivity analysis. If there is no correlation between events and overall survival (i.e. no difference in overall survival) then the estimated cost per QALY [redacted] QALYs per million). If the correlation is increased to 1:1 the result [redacted] QALYs per million).

Costs
The uncertainties of costs that had the biggest impact on the result were the cost of rest home care for stroke patients who do not recover (due to it relatively large cost) and the

cost of warfarin testing (because it effects 75% of patients). However the results did not vary dramatically due to changes in costs.

The costs were varied by 20%, as it is expected the value will fall within this range. The exception was for the cost of treating a minor bleed and a TIA. These costs were varied by 50% due to their greater uncertainty.

The additional time patients, who do not recover from a stroke, spent in rest homes was varied over from 1 year to 5 years. This resulted in a cost-per QALY range of [redacted] QALYs per million).

Utility

The model was the most sensitive to the base-line utility value, as this affects the disutility's for the events in the model and also the QALY loss from death. If it is assumed that there is no disutility from AF (i.e. a baseline utility value of 1), the cost per QALY decreases to [redacted] QALYs per million). If the lowest utility value identified for AF is used (utility of 0.81), the cost per QALY is [redacted] QALYs per million)

One-way sensitivity analysis

Variable	Base Case	Updated	Aspirin	Warfarin	Weighted Average	QALYs per $1m
Base Case			[redacted]	[redacted]	[redacted]	[redacted]
Daily Cost of dabigatran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischemic stroke; ARR of dabigatran/warfarin compared to aspirin	1.8%	2.2% 0.9%	[redacted]	[redacted]	[redacted]	[redacted]
Hemorrhagic stroke; ARR of dabigatran/warfarin compared to aspirin	-0.2%	0.0% -0.8%	[redacted]	[redacted]	[redacted]	[redacted]
Intracranial haemorrhage; ARR of dabigatran/warfarin compared to aspirin	-0.1%	0.0% -0.3%	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial Infarction; ARR of dabigatran/warfarin compared to aspirin	0.4%	0.7% 0.0%	[redacted]	[redacted]	[redacted]	[redacted]
Systemic embolism; ARR of dabigatran/warfarin compared to aspirin	0.1%	0.2% -0.2%	[redacted]	[redacted]	[redacted]	[redacted]
Transient Ischemic Attack; ARR of dabigatran/warfarin compared to aspirin	0.2%	0.5% -0.7%	[redacted]	[redacted]	[redacted]	[redacted]
Extracranial Haemorrhage; ARR of dabigatran/warfarin compared to aspirin	-1.1%	0.2% -3.7%	[redacted]	[redacted]	[redacted]	[redacted]
Minor Bleed; ARR of dabigatran/warfarin compared to aspirin	-6.5%	1.6% -25.1%	[redacted]	[redacted]	[redacted]	[redacted]
Death from MI; probability per MI	0.49	0.39 0.59	[redacted]	[redacted]	[redacted]	[redacted]

Variable	Base Case	Updated	Aspirin	Warfarin	Weighted Average	QALYs per $1m
Death from Ischemic stroke, Hemorrhagic Stroke and Intracranial Haemorrhage; probability per event	0.37	0.30	[redacted]	[redacted]	[redacted]	[redacted]
		0.44	[redacted]	[redacted]	[redacted]	[redacted]
Correlation between reduction in risk of events and death	0.8	0.0	[redacted]	[redacted]	[redacted]	[redacted]
		1.0	[redacted]	[redacted]	[redacted]	[redacted]
Cost of Ischemic Stroke; first year	$34,400	$27,520	[redacted]	[redacted]	[redacted]	[redacted]
		$41,280	[redacted]	[redacted]	[redacted]	[redacted]
Cost of Ischemic Stroke; Additional time in rest home (for patients not recovering)	3 years	1 year	[redacted]	[redacted]	[redacted]	[redacted]
		5 years	[redacted]	[redacted]	[redacted]	[redacted]
Cost of MI	$5,600	$4,480	[redacted]	[redacted]	[redacted]	[redacted]
		$6,720	[redacted]	[redacted]	[redacted]	[redacted]
Cost of Minor Bleed	$240	$120	[redacted]	[redacted]	[redacted]	[redacted]
		$360	[redacted]	[redacted]	[redacted]	[redacted]
Cost of Systemic Embolism	$5,300	$4,240	[redacted]	[redacted]	[redacted]	[redacted]
		$6,360	[redacted]	[redacted]	[redacted]	[redacted]
Cost of Transient Ischemic Stroke	$1,500	$750	[redacted]	[redacted]	[redacted]	[redacted]
		$2,500	[redacted]	[redacted]	[redacted]	[redacted]
Cost of warfarin testing	$255	$195	[redacted]	[redacted]	[redacted]	[redacted]
		$315	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation (baseline) utility	0.891	0.81	[redacted]	[redacted]	[redacted]	[redacted]
		1.00	[redacted]	[redacted]	[redacted]	[redacted]
Ischemic stroke first year utility	0.55	0.44	[redacted]	[redacted]	[redacted]	[redacted]
		0.65	[redacted]	[redacted]	[redacted]	[redacted]
Ischemic stroke, ongoing utility for those not recovered	0.63	0.51	[redacted]	[redacted]	[redacted]	[redacted]
		0.76	[redacted]	[redacted]	[redacted]	[redacted]
MI, utility for 1 month	0.28	0.22	[redacted]	[redacted]	[redacted]	[redacted]
		0.33	[redacted]	[redacted]	[redacted]	[redacted]
Average age of patients	78	70	[redacted]	[redacted]	[redacted]	[redacted]
		80	[redacted]	[redacted]	[redacted]	[redacted]
Discount Rate	3.5%	0.0%	[redacted]	[redacted]	[redacted]	[redacted]
		10.0%	[redacted]	[redacted]	[redacted]	[redacted]

Cost of dabigatran

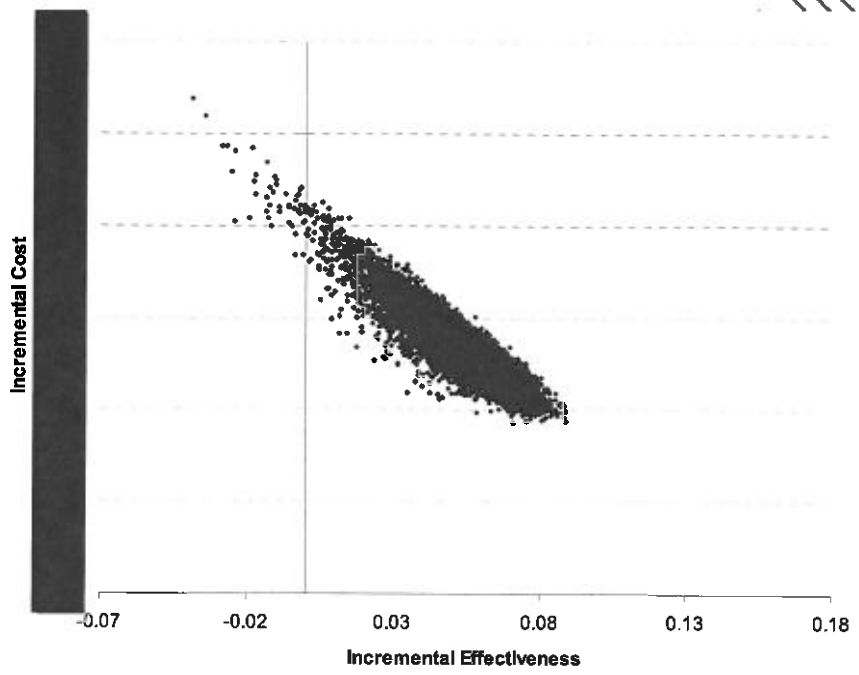
It is estimated that if the price of dabigatran [redacted] it will be cost saving to the health sector; in addition it would create health benefits, i.e. it would dominate current treatment.

For dabigatran to be cost saving compared to warfarin it is estimated the cost would have to fall below [redacted]. Compared with aspirin, at a cost of [redacted] dabigatran would be cost-saving.

Restricted Probabilistic Sensitivity analysis

A distribution of cost per QALY results was calculated by applying distributions[iv] to the relative risks of the eight efficacy and safety outcomes. The resulting ranges were [redacted] QALYs gained per million) for the 2.5% and 97.5% limits. The distribution of results is presented in the graph below.

Distribution of cost-effectiveness when applying distributions to the relative risk of out comes



If dabigatran is superior to warfarin

If the relative risks from the RE-LY trial are applied then the average cost per QALY is between dominant and [redacted] QALYs per $1 million invested). In this case there is a QALY gain when dabigatran is compared to warfarin. In addition, the cost effectiveness of dabigatran compared to aspirin is improved.

[iv] Normal distributions (not truncated) were used, these were based on the 95% confidence intervals reported.

7 Discussion

The plausible cost per QALY range is estimated to be [redacted] QALYs gained per $1 million invested). This is a three fold difference in results. This is due to multiple uncertainties, but most of it comes down to the comparative efficacy and safety of dabigatran to both warfarin and aspirin. The key modelled uncertainties can be summarised as:

- Efficacy of dabigatran: the base case analysis assumed that dabigatran was equally efficacious compared to warfarin (based on advice from the Cardiovascular Subcommittee and PTAC). Due to lack of evidence regarding the efficacy of dabigatran compared with aspirin, an indirect comparison of the evidence was necessary, which creates further uncertainty in the analysis.
- Reduction of overall mortality: the evidence suggests that warfarin and dabigatran reduce overall mortality in patients with AF compared with aspirin; however there is a lack of good evidence.
- Weight of comparators: it is assumed more patients would switch from warfarin than from aspirin, although the actual proportion of each patient group is uncertain.

Other uncertainties not included in the cost-utility analysis include the long term safety of dabigatran; potential cost of blood monitoring with dabigatran; and lack of an antidote for dabigatran.

Some consider that dabigatran may reduce hospitalisations compared to warfarin. However the reduction in hospitalisations reported in the RE-LY[6] trial was neither statistically or clinically significant.

Consideration of a lower dose was not made, only the 300mg daily dose was considered. It is unknown if a lower dose will be registered in New Zealand; and if a lower dose is registered it is unclear what it will be given the lower daily dose in the RE-LY trial was 220mg[6] but the FDA approved a dose of 150mg[7].

There are a number of uncertainties that have been included in the model; these have resulted in a relatively wide range of results. Without further evidence it is unlikely the uncertainty can significantly be reduced.

Appendix 1 Review of the supplier cost-utility analysis

A cost-utility analysis (CUA) was received from Boehringer Ingelheim NZ ltd; which PHARMAC staff have reviewed.

The economic evaluation estimated the cost-effectiveness of various proportions of dabigatran, warfarin, and aspirin for patients 60-89 years old with AF and moderate to high risk of ischemic stroke. A population based Markov model was built which follows 6 age groups in accordance with the findings from the NZ HealthStat GP database.

The following table summarises the main inputs and assumptions used in the supplier model:

Model Input / Assumption	Details	PHARMAC Comment
Type of analysis	[redacted]	The type of analysis undertaken was appropriate.
Target population	[redacted]	The analysis was based on the correct target population (i.e. the target population most likely to receive treatment). The analysis excluded [redacted]. The patients excluded are described at being 20% of the total population. Using [redacted] makes the analysis complex and is not considered to be necessary given CUAs are undertaken based on the 'average' patient.
Time horizon & cycle length	[redacted]	The time horizon was appropriate. Although, technically there shouldn't be a terminating age [redacted] The cycle length appears appropriate and justified in terms of the underlying disease and effect of the interventions.
Comparator	[redacted]	The weighted-average of the cost per QALY result (weighted by patient numbers prescribed the comparator treatment) was reported. The approach would have been more transparent if the cost per QALY results was reported separately as well. This would have improved the transparency of the model. The Prescriptions for Pharmacoeconomic Analysis (PFPA) states 'In cases where treatment regimens differ substantially throughout NZ, it is recommended that a range of

	[redacted]	comparators be used in the analysis. The results of the different analysis should be reported separately, as well as reporting a weighted-average (weighted by patient numbers prescribed comparator treatment) of the cost per QALY result"[15]. There was no justification as to the amount of patients switching from aspirin or warfarin. It is likely a greater proportion will switch from warfarin. Based on [redacted] and PTAC and Subcommittee advice. It was appropriate to exclude clopidogrel from the analysis as this treatment is currently not widely used for the treatment of AF in NZ.
Treatment regimen (including dose)	[redacted]	Although it seems reasonable the majority of patients would receive the higher dose of dabigatran, no rationale was given for the proportion of patients receiving the lower dose. Additionally, given the FDA subsequently has not approved the 110mg dose (but a lower dose)[7], it is now less certain that the 110mg dose will be approved in NZ. Dose adjustments are likely with the use of warfarin over time, however, this does not substantially impact the total cost of warfarin. The discontinuation rates seem reasonable.
Efficacy	[redacted]	PTAC and the Cardiovascular Subcommittee recommend that it should be assumed that dabigatran and warfarin have the same efficacy. An important consideration of the efficacy of warfarin is the INR control of the patient. In the RE-LY trial[6], there was a trend indicating that dabigatran had less comparative benefit in patients who had better INR

control when receiving warfarin[8,9,10]. There was no consideration of the INR control in the New Zealand setting and how this affects the relative efficacy of dabigatran compared to warfarin.

The Subcommittee also recommended that the efficacy of aspirin and dabigatran be based the BAFTA trial[11] that compares aspirin to warfarin.

It was not stated what the suppliers meta-analysis included, therefore the validity is uncertain.

The assumption that dabigatran reduces mortality is uncertain given the lack of good evidence. This is a key assumption as the majority of benefit is from the reduction in mortality.

PHARMAC's approach is to include reductions in mortality, using a similar method to the supplier, but scale down the effect by 20% because of the uncertainty.

The supplier based the case fatality rates on a study of NZ patients[16]. However, it is unclear how the rates were derived. PHARMAC's

	[redacted]	interpretation of the results are that case fatality rates are 37% and 49% for stroke and AMI respectively, adjusted for background mortality and based on patients aged 75 – 84.
Health states and model structure	[redacted]	Justification to the choice of health states within the model is provided and important health states do not appear to have been excluded from the model.
Sensitivity analysis	[redacted]	The supplier has not conducted sufficient sensitivity analysis to fully determine the effects of the assumptions have on the cost-effectiveness of dabigatran. The range and choice of variables used in the sensitivity analysis is inadequate and has not been justified. It is unclear what parameters in the model were varied when the report states 'no therapy'. Given it was assumed that the amount of patients not on treatment remained unchanged when dabigatran was funded it is expected this would not impact the result (especially by increasing and decreasing the result). It would have been clearer if the report further explained the sensitivity analysis.
Assumptions and inputs	[redacted]	As mentioned in the efficacy section above; the key assumption that dabigatran reduces mortality is uncertain. This is a key consideration in

	[redacted]	the updated model.
Quality of life	[redacted]	The base line utility value of AF patients was incorrectly reported in the write-up of the CUA. The application of the QoL scores is questionable, and was not adequately detailed in the report. After the patient had an event the QoL was applied for the rest of their life or until they had a different event. For a number of the events this is not appropriate as the impact on QoL is short-term. For example a transient ischemic event often last less than 24 hours, so if the disutility is applied for a lifetime the impact of the event is over-estimated. This resulted in the CUA overstating the benefit (gain in QALY) of dabigatran c PHARMAC's approach was to apply disutility values for set periods of time. In order to do this more health state were created to capture the different stage and outcomes from a stroke or intracranial haemorrhage. Given the baseline utility ($CADHS_2$ individual) affects all health states; at minimum this should have been included in the sensitivity analysis so it's effect on the result could be evaluated. PHARMACs approach to deriving the QoL scores was to map the health stated to the EQ-5D and use NZ specific utility values. This was done to increase consistency with other PHARAMC analyses.
Pharmaceutical cost	[redacted]	The pharmaceutical costs were calculated correctly. Generics for the comparators are already listed, so it is unlikely there would be any significant price reductions for these in the future.

		There are likely dose adjustments of warfarin over time, however, this does not substantially impact the total cost of warfarin.
Non-pharmaceutical cost	[redacted]	The cost of INR testing seems to be overestimated. The number of tests was based on a trial that is not likely to represent actual usage in New Zealand[29]. Based on NZ lab test data it is estimated patients will have 17 tests per year[24]. The estimated costs associated for the tests also seem high. PHARMAC's estimate of the annual cost for INR monitoring is $256. It is recommended in the PFPA that New Zealand cost data be used when estimating costs for a CUA. For the cost of stroke PHARMAC used estimates based on a study on the treatment of stroke in NZ. In addition there was a differentiation of the costs for those who recover and those who do not. The costs of a TIA are likely to be overstated as not all patients would be admitted to hospital.
Discount rate	[redacted]	The correct discount rate was used.

In the supplier analysis the cost per QALY result varied according to the substitution options (from 1-32) as given in the potential new practice. The cost per QALY result varies from [redacted]. The sensitivity analysis conducted by the supplier gives a range of cost per QALY result from [redacted] The sensitivity analysis conducted by the supplier is not sufficient to be confident of the relative cost-effectiveness of dabigatran.

PHARMAC staff altered the supplier model in order to be able to report the cost effectiveness of dabigatran compared to either aspirin or warfarin. The results are shown in the table below.

Pharmaceutical	Incremental Cost	Incremental QALY	Cost per QALY	Interpretation
Dabigatran vs. warfarin	[redacted]	- 0.017	[redacted]	Dabigatran [redacted] is less effective than warfarin
Dabigatran vs. aspirin	[redacted]	0.23	[redacted]	Dabigatran [redacted] is more effective than aspirin

The results show that when dabigatran was compared with warfarin, dabigatran was [redacted]

Therefore, the model shows that when an individual comparison is made of dabigatran vs. warfarin, dabigatran is not cost-effective. However, after further evaluation of the suppliers model, a number of modelling error's were identified that are likely to have caused this unexpected result. Once these errors were fixed the analysis showed that dabigatran was associated with a QALY gain compared to warfarin.

The results of the CUA show that when dabigatran is compared to aspirin, the cost per QALY result is approximately [redacted] However, PHARMAC staff note that it is unlikely that only warfarin intolerant patients would access dabigatran and that the result would be a lot higher if a significant portion of patients would use dabigatran instead of warfarin. In addition it is uncertain whether the efficacy of dabigatran compared to aspirin has been assessed correctly.

Given the errors in the TreeAge model, inconsistencies between the TreeAge model and CUA report, and uncertainty of key assumptions, PHARMAC staff consider that there is insufficient information to draw any firm conclusions about the cost-effectiveness of dabigatran compared to either warfarin or aspirin. Therefore, further assessment has been undertaken. This is detailed in the main body of this report.

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