BRISTOL-MYERS SQUIBB AUSTRALIA/ PFIZER AUSTRALIA

Submission to the Department of Health and Ageing

on

Review of Anticoagulation Therapies in Atrial Fibrillation

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1. BACKGROUND

On December 22nd 2011, the Commonwealth Department of Health and Ageing invited interested organisations and individuals to provide written submissions to inform a *Review of Anticoagulation Therapies in Atrial Fibrillation*. The basis of the review is to inform the Australian Government of potential options for improving the health outcomes of patients treated with anticoagulation therapies, including a re-evaluation of currently available treatments in Australia as well as examination of the future role of newer therapies for the treatment of atrial fibrillation.

The Terms of Reference (TOR) for the *Review of Anticoagulation Therapies in Atrial Fibrillation* are:

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

Bristol-Myers Squibb and Pfizer, together, are studying the potential of the oral anticoagulant apixaban (ELIQUIS®) in the prevention and treatment of a broad range of venous and arterial thrombotic conditions, including atrial fibrillation. [redacted]

Section 2 of this submission [TOR (a)] will not only examine the challenges associated with the current treatment options for Australian patients with atrial fibrillation (i.e. warfarin, aspirin), but will also provide a top-line comparison of the pharmacological and effectiveness profiles of the recently developed novel oral anticoagulants (NOACs; dabigatran, apixaban, rivaroxaban) – key future therapeutic options for Australian patients with atrial fibrillation. Section 3 of the submission [TOR (d)] will look specifically at the effectiveness profile of apixaban in the context of recent discussion/ debate specific to the effectiveness profile of dabigatran.

2. TERM OF REFERENCE (A): TO REPORT ON CURRENT AND FUTURE OPTIONS FOR IMPROVING THE HEALTH OUTCOMES OF PATIENTS WITH ATRIAL FIBRILLATION TREATED WITH ORAL ANTICOAGULANTS

2.1. Current Management Options in Australia

The incidence of atrial fibrillation (AF) appears to be increasing, even after adjustment for the ageing population (Miyasaka et al 2006). Twenty-five percent of people are projected to develop AF in their lifetime (Roger et al 2011). Patients with AF have a five-fold increased risk of stroke and it is estimated that 15% to 20% of all strokes are linked to AF (Lin et al 1996). Moreover, death and disability from stroke complicating AF are particularly high, and as such stroke related to AF is a substantial and growing public health burden (Granger and Armaganijan 2012).

Current international guidelines recommend that the selection of optimal antithrombotic prophylaxis should depend on a patient's ischaemic stroke risk and the balance between the benefits and risks of long-term warfarin relative to aspirin. Australian clinical practice guidelines reiterate the importance of balancing ischemic stroke risk with the risks of currently available therapies (Medi et al 2007, Singer et al 2008).

Although warfarin is around 2.5 times more effective than aspirin at reducing the risk of stroke, it is associated with a higher rate of major bleeding and requires regular dose modification through monitoring of a patient's blood levels (Hart et al 2007). As such, aspirin is commonly recommended in patients at a low-to-moderate risk of stroke, with warfarin reserved for patients at a moderate-to-high risk of stroke risk (Hankey et al 2001).

2.2. Challenges associated with Current Management Options in Australia

2.2.1. Warfarin

While warfarin results in a two-thirds reduction in stroke when used optimally (Hart et al 2007), it is i) significantly underused in the 'real-world' setting, and ii) when it is used, it is used sub-optimally. In addition, it is extremely difficult to stay within the target International normalised ratios (INR) and/ or is associated with very high rates of major bleeding (Granger and Armaganijan 2012).

Underuse/ suboptimal use:

Numerous published studies reviewing Australian utilisation patterns of anticoagulation therapy have reported that warfarin is underutilised in the Australian setting.

A study of antithrombotic use was conducted at the Royal Hobart Hospital between 2004-2006 (Jackson et al 2010). Patients were enrolled if they had a primary or secondary diagnosis of AF on admission to the cardiology or medical wards. Among the 135 patients in this study who had a stroke assessment (according to the criteria described by Hankey et al 2001), only 31% of patients at moderate-to-high risk of stroke were being treated with warfarin and 23% were not receiving any anticoagulant therapy for stroke prevention.

An analysis conducted by Deloitte Access Economics (September 2011) applied data from the above study (Jackson et al 2010) to estimate antithrombotic use across Australia, adjusted for people who remain undiagnosed with non-valvular AF. The results, presented in **Table 1** below, illustrate that less than one third of patients at a moderate-to-high stroke risk, including people who have undiagnosed AF, receive warfarin. In addition, around 40% of patients, including undiagnosed patients (around 20% of all AF patients) and approximately 25% of diagnosed patients, at a moderate-to-high stroke risk do not receive any anticoagulant treatment.

Table 1 – Antithrombotic use in Australia NVAF patients (adjusted for undiagnosed AF)

Stroke risk	Warfarin	Aspirin only	No treatment
	%	%	%
High	37.0 (32.2)	33.0 (28.7)	22.0 (39.1)
Moderate	36.0 (30.3)	33.0 (27.8)	26.0 (41.9)
Low	16.0 (12.7)	16.0 (12.7)	69.0 (74.7)

Notes: (a) Data derived from the pre-intervention cohort on admission, which best represents general practice (Jackson and Peterson, 2010). The unadjusted figures are derived directly from Jackson and Peterson (2010) and do not sum to 100%. The adjusted figures are re-scaled to sum to 100% and then adjusted for undiagnosed AF. The undiagnosed proportion of AF is assumed to be 20% for all risk groups (Medi et al, 2007).

Source: Deloitte Access Economics calculations using Jackson and Peterson (2010) and Medi et al (2007).

Reasons for underuse/ suboptimal use of warfarin and inability to consistently achieve a target INR relate to pharmacological properties of the drug, including unpredictable anticoagulant effects, genetic variability in metabolism, multiple food and drug interactions, a narrow therapeutic window, and the resulting need for inconvenient monitoring (Granger and Armaganijan 2012). In addition, age and ethnicity are seen as significant barriers to uptake and/or effective use of warfarin therapy

(Diug et al 2011, Shen et al 2005, Shen et al 2008, Absher et al 2002, El Rouby et al 2004, Dang et al 2005).

These data consistently indicate that the use of warfarin is under-utilised, and as this product is widely considered to be the mainstay of atrial fibrillation therapy, it is reasonable to state that this condition is under-treated in Australia.

Bleeding:

Another major concern and deterrent for warfarin use is the potential increased risk of bleeding complications (i.e. gastrointestinal bleeding and previous intracranial haemorrhage) and associated hospitalisations.

The average annual rate of fatal, major and major/minor bleeding during long term warfarin therapy have been reported to be 0.6, 3.0 and 9.6% respectively; these frequencies are approximately five times those expected without warfarin therapy (Levine et al 2001, Levine et al 1992, Landefeld & Beyth 1993). When treatment with patients using warfarin was measured against indicators developed by the Australian Council on Healthcare Standards for the year 2000, 5% of patients recorded an INR > 5, 1% had an abnormal bleed, 0.05% had a cerebral haemorrhage and 0.2% died (Runciman et al 2003).

In Australia, warfarin was the second most commonly reported medicine implicated in adverse drug reactions associated with hospital admissions in the year 2000 (Roughhead et al 2011). The Quality in Australian Health Care Study (1992) found that 10.7% of drug related adverse events during hospital admission were associated with anticoagulants, and 40% of these were highly preventable (Wilson et al 1995).

The BEACH-SAND report on AF/flutter in general practice patients (Block 127B, data collection period from 26/10/2010 to 29/11/2010) reported that the two major reasons for not taking warfarin were patient refusal (39%) and bleeding risk (17%). Not only is the bleeding risk associated with warfarin a deterrent to doctors and patients alike, it also comes with a significant cost impost for the Commonwealth. The Quality in Australian Health Care Study estimated the cost of adverse events from warfarin use to be over $100 million in direct hospital costs in 1992 (Rigby et al 1999).

In summary, warfarin has two major limitations – it is underutilised and is associated with a negative safety/ bleeding profile. While some of the gaps in warfarin prescribing in Australia may be overcome by better systems of care, the multi-layered complexity of factors that lead to current suboptimal use/ underuse in Australian clinical practice, deem it incorrect to think that warfarin will ever be a drug that can fulfil the enormous unmet medical need that currently exists.

2.2.2.Aspirin

For those patients whose risk of stroke is low or where warfarin is contraindicated, alternative therapies to treat AF include the use of aspirin. However, as noted in **Table 1**, the issues associated with warfarin have led to significant aspirin use in Australian patients with a medium to high risk of stroke and who are not contraindicated to warfarin. The fact that aspirin is only associated with a 30% risk reduction in stroke (Laupacis et al 1994) further emphasises the suboptimal outcomes that Australian patients with AF are currently experiencing.

New data has emerged to suggest that aspirin may not be as effective at preventing stroke in patients with AF as previously reported by Laupacis et al, and also that aspirin may not be any safer than warfarin (Sato et al 2006, Olesen et al 2011). The Japan Atrial Fibrillation Stroke Trial (Sato et al 2006) randomised AF patients to either aspirin (150-200 mg/day) or a control group without anti-platelet or anticoagulation therapy. The primary outcomes (3.1% per year) in the aspirin group were worse than in the control group (2.4% per year), and aspirin therapy caused a non-significant increased risk of major bleeding (1.6%) compared with control (0.4%). Based on the findings by Sato et al 2006, the European Society of Cardiology (ESC) guidelines were updated in 2010 to reflect these results and advised against using aspirin for stroke prevention in AF patients at low risk where possible (ESC 2010).

Further evidence post the Sato publication are also suggestive of an increased bleeding risk associated with aspirin, particularly in the gastrointestinal tract (Dorsch et al 2007, Palikhe et al 2008, Patel et al 2007).

Clearly, while Australian patients with AF do currently have treatment options available in warfarin and aspirin, there still exists significant clinical need in this patient group. The recent emergence of the NOACs (see below) provides an opportunity for the Australian Government to make an immediate and significant improvement in the health outcomes of Australian patients with AF.

2.3. Recent Emergence of Novel Oral Anticoagulants for the Treatment of AF

Several oral drugs directly inhibiting either coagulation factor II (thrombin) or factor Xa have recently been developed as alternatives to warfarin for stroke prevention in AF. Dabigatran was the first novel oral anticoagulation (NOAC) therapy to be registered in Australia for the treatment of AF.

A comparison of the pharmacological characteristics of warfarin and the NOACs specific to AF treatment is detailed in **Table 2** below. One key feature of the NOAC group is their shorter half-life. Warfarin's half-life is approximately 40 hours whereas the NOACs' half-lives range from 7-14 hours. The half-life for apixaban is approximately 12 hours.

Table 2 – Comparison of Pharmacological Characteristics of Warfarin and the NOACs

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Administration	Once a day	Twice a day	Once a day	Twice a day	Once a day
Target	Vitamin K–dependent factors	Factor II	Factor Xa	Factor Xa	Factor Xa
Time to peak effect	3–5 d	1 h	2.5–4 h	3 h	1–2 h
Dose	Variable	150 mg twice a day and 110 mg twice a day	20 mg every day (15 mg every day for renal impairment)	5 mg twice a day (2.5 mg twice a day for high risk)	30 mg every day and 60 mg every day (with adjustment for high exposure)
Half-life	40 h	12–14 h	7–11 h	12 h	9–11 h
Interactions	Multiple	Inhibitors of P-glycoprotein transporter*	Inhibitors of CYP 3A4 and P-glycoprotein transporter†	Inhibitors of CYP 3A4 and P-glycoprotein transporter†	Inhibitors of CYP 3A4 and prostaglandin transporter†
Renal clearance, %	0	80	35	25	40
Anticoagulation monitoring	Required	Not required	Not required	Not required	Not required
Antidote	Vitamin K	None	None	None	None

*Inhibitors of P-glycoprotein transporter include amiodarone (cautions with interaction) and verapamil.
†Inhibitors of CYP 3A4 and P-glycoprotein transporter include antifungals and protease inhibitors.

Source: Granger and Armaganijan (2012)

While the NOAC group of medicines are similar in that they each possess pharmacokinetic/ pharmacodynamic traits that present a marked improvement over warfarin, each displays unique pharmacokinetics that prevent a 'class effect' from being observed. For example, renal clearance is an important differentiating factor for apixaban over dabigatran. Apixaban's renal clearance is

approximately 25% in comparison to 80% for dabigatran. This high renal clearance rate for dabigatran has led to a recent TGA directive (Nov 2011) recommending renal monitoring for Australian patients with AF being treated with dabigatran.

Reviews show that literature is beginning to emerge comparing and contrasting the profiles of warfarin with the NOACs in the treatment of patients with AF. A recent review (Granger and Armaganijan 2012) looks at the warfarin/ NOAC dynamic from the perspective of pharmacokinetic and clinical effectiveness and concludes that:

- *The new oral anticoagulants are far more convenient than warfarin because they have predictable pharmacodynamic effects and, at doses tested in the large trials, have good efficacy and safety profiles without anticoagulation monitoring;*
- *All of the new agents have the advantage of rapid onset of action and relatively short half-life periods, making their use around the time of procedures more convenient than warfarin, without the need for bridging;*
- *All 3 new anticoagulants (dabigatran, rivaroxaban and apixaban) are at least as good as warfarin at preventing stroke, with dabigatran 150 mg twice daily and apixaban 5 mg twice daily more effective than warfarin in terms of preventing stroke (***Table 3***);*
- *Even more remarkable than the superior efficacy, the rate of hemorrhagic stroke was reduced by 40% to 70% and that of intracranial haemorrhage by ~ 50% with all 3 of the agents, suggesting a liability to warfarin in regard to intracranial haemorrhage;*
- *Both lower dose dabigatran and apixaban resulted in important reductions in major bleeding (***Table 3***);*
- *All 3 new anticoagulants result in an ~10% reduction in mortality, although this reached statistical significance only for apixaban; and*
- *The safety of the new drugs has been challenged because there is no reversal agent. Although this is true, surprisingly little is known about the effectiveness and time course of reversal of warfarin with vitamin K. The new agents have an important feature that leads to reversibility, that of a relatively short half-life. Despite the lack of a specific antidote, bleeding was both less common and less severe, at least with lower dose dabigatran and apixaban. All 3 agents substantially reduce the most serious type of bleeding, intracranial haemorrhage, and its consequences.*

Table 3 – Tabulation of Results from Pivotal NOAC AF Clinical Trials

	Novel Drug and Dose	Clinical Events		Hazard Ratio (95%CI)	P (Superiority)
		NOAC	Warfarin		
STROKE OR SYSTEMIC EMBOLISM, %/year					
RE-LY	Dabigatran 110 mg bd	1.53	1.69	0.91 (0.74-1.11)	0.34
	Dabigatran 150 mg bd	1.11	1.69	**0.66 (0.53-0.82)**	**<0.001**
ROCKET-AF	Rivaroxaban 20 mg d	2.12	2.42	0.88 (0.75-1.03)	0.12
ARISTOTLE	Apixaban 5 mg bd	1.27	1.60	**0.79 (0.66-0.95)**	**0.01**
HAEMORRHAGIC STROKE, %/year					
RE-LY	Dabigatran 110 mg bd	0.12	0.38	**0.31 (0.17-0.56)**	**<0.001**
	Dabigatran 150 mg bd	0.10	0.38	**0.26 (0.14-0.49)**	**<0.001**
ROCKET-AF	Rivaroxaban 20 mg d	0.26	0.44	0.59 (0.37-0.93)	0.02
ARISTOTLE	Apixaban 5 mg bd	0.24	0.47	**0.51 (0.35-0.75)**	**<0.001**
ISCHAEMIC OR UNCERTAIN STROKE, %/year					
RE-LY	Dabigatran 110 mg bd	1.34	1.20	1.11 (0.89-1.40)	0.35
	Dabigatran 150 mg bd	0.92	1.20	**0.76 (0.60-0.98)**	**0.03**
ROCKET-AF	Rivaroxaban 20 mg d	1.34	1.42	0.94 (0.75-1.17)	0.58
ARISTOTLE	Apixaban 5 mg bd	0.97	1.05	0.92 (0.74-1.13)	0.42
MAJOR BLEEDING, %/year					
RE-LY	Dabigatran 110 mg bd	2.71	3.36	**0.80 (0.69-0.93)**	0.003
	Dabigatran 150 mg bd	3.11	3.36	0.93 (0.81-1.07)	0.31
ROCKET-AF	Rivaroxaban 20 mg d	3.60	3.45	1.04 (0.90-1.20)	0.58
ARISTOTLE	Apixaban 5 mg bd	2.13	3.09	**0.69 (0.60-0.80)**	**<0.001**
DEATH, %/year					
RE-LY	Dabigatran 110 mg bd	03.75	4.13	0.91 (0.80-1.03)	0.13
	Dabigatran 150 mg bd	3.64	4.13	0.88 (0.77-1.00)	0.051
ROCKET-AF	Rivaroxaban 20 mg d	4.5	4.9	0.92 (0.82-1.03)	0.15
ARISTOTLE	Apixaban 5 mg bd	3.52	3.94	**0.89 (0.80-0.998)**	**0.047**

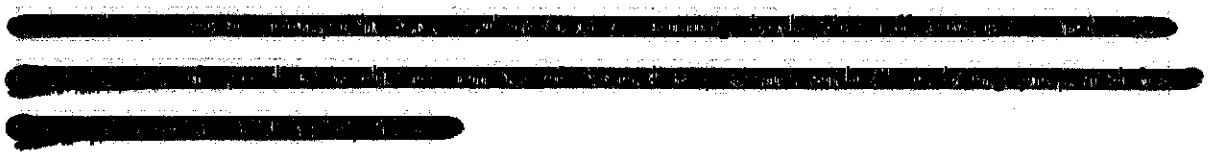
Source: Granger and Armaganijan 2012

Granger and Armaganijan (2012) end by stating that although warfarin has been a highly effective treatment to reduce stroke in AF, its limitations are significant and well known to both physicians and patients. The authors assert that NOACs have been shown to be convenient and to have important advantages in improving clinical outcomes, including fewer strokes, less intracranial haemorrhage, and lower mortality, and as such, the case for their use as a first-line treatment option for stroke prevention in AF is strong.

3. TERM OF REFERENCE (D): TO EXAMINE THE FUTURE ROLE OF NEWER ANTICOAGULANT THERAPIES FOR ATRIAL FIBRILLATION

While there is significant anticipation with respect to the addition of the NOACs to the AF treatment armamentarium, recent focus on aspects of the dabigatran RE-LY clinical trial data *(e.g. mean time in therapeutic range, incidence of MI, incidence of GI bleeding, requirement for renal monitoring)* have raised queries specific to the extent and/or cost-effectiveness of health outcome improvement that dabigatran will bring to Australian patients with AF.

The purpose of presenting apixaban AF clinical trial data in this section of the submission is twofold – firstly, to build upon the evidence that NOACs will play a key role in the future treatment of Australian patients with AF, and secondly, to illustrate that the abovementioned clinical queries are not relevant to apixaban.



3.1. Apixaban – MOA

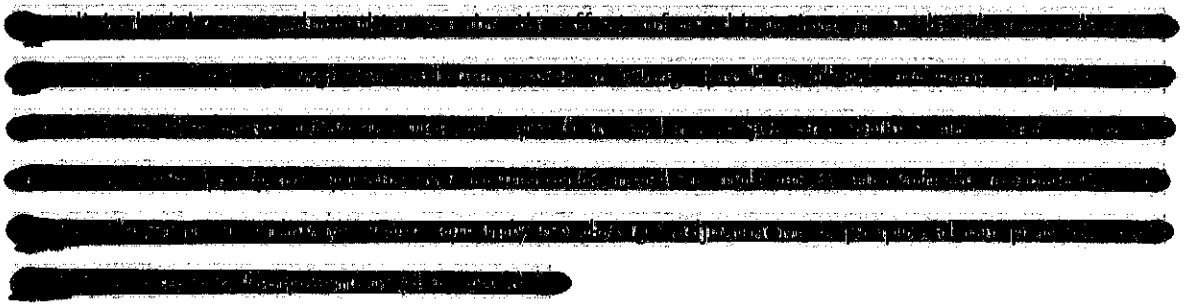
Apixaban is a reversible, direct and highly selective inhibitor of factor Xa. It does not require anti-thrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Factor Xa inhibitors act at factor Xa – the start of the common pathway of the coagulation cascade (i.e. above thrombin). By not inhibiting thrombin directly, these agents may allow some thrombin activity. In contrast, direct thrombin inhibitors (such as dabigatran) act less specifically, by binding the active site of thrombin itself. This may partially explain apixaban's favourable bleeding profile (Baur et al 2011).

Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. No routine coagulation monitoring is required and doses of apixaban up to 50mg have no effect on the QTc interval in humans (Eliquis approved Product Information 21 July 2011).

Apixaban's short half-life of 12 hours (**Table 2**) and rapid Cmax means that in the event a patient requires anticoagulation reversal, simply waiting 1-2 days will ensure plasma concentration and anticoagulation effect is rapidly reduced. This largely negates the need for an antidote. In contrast,

warfarin's long half life and narrow therapeutic index means an antidote is required (vitamin K) which itself takes several days to take effect.

Given a high proportion of the patient population taking anticoagulants for AF are likely to have some degree of renal impairment, the renal clearance is an important factor for prescribers to consider. Clinical data shows apixaban is only partially eliminated via renal excretion (25%).



3.2. Apixaban – AF Clinical Trial Data

This section provides a top line summary of two pivotal Phase III clinical trials comparing the effectiveness of apixaban with currently available therapies (warfarin & aspirin) in the prevention of stroke in patients with AF.

3.2.1 Apixaban versus Warfarin – ARISTOTLE:

ARISTOTLE (*Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation*) was a randomised, double-blind trial comparing apixaban (at a dose of 5 mg twice daily) with warfarin (target INR 2.0-3.0) in 18,201 patients with AF and at least one additional risk factor for stroke (Granger et al 2011). The trial employed a double-blind, double-dummy design in which patients were randomly assigned to treatment with apixaban or dose-adjusted warfarin. The primary objective was to determine whether apixaban (5 mg twice daily) was non-inferior to warfarin (2mg tablets and adjusted to achieve an INR of 2.0-3.0) in reducing the rate of stroke (ischaemic or haemorrhagic) or systemic embolism among patients with atrial fibrillation and at least one other risk factor for stroke. The primary safety outcome was major bleeding. Key secondary objectives were to determine whether apixaban was superior to warfarin with respect to the primary outcome and to the rates of major bleeding and death from any cause (**Table 4**).

Table 4 – Primary and Secondary Outcomes of the ARISTOTLE trial

Outcome	Definition
Primary Efficacy Outcome: Stroke or systemic embolism	Stroke was defined as a focal neurologic deficit, from a non-traumatic cause, lasting at least 24 hours and was categorised as ischaemic (with or without haemorrhagic transformation), haemorrhagic, or of uncertain type (in the case of patients who did not undergo brain imaging or in whom an autopsy was not performed).
Key secondary efficacy outcome: Death from any Cause	Death
Secondary efficacy outcome: Rate of myocardial infarction	Myocardial infarction
Primary safety outcome: Major bleeding	Defined according to the ISTH criteria as clinically overt bleeding accompanied by a decrease in the haemoglobin level of at least 2g per decilitre or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death.
Secondary safety outcome: Composite of major bleeding and clinically relevant non-major bleeding.	Clinically relevant non-major bleeding was defined as clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to hospital admission, physician-guided medical or surgical treatment, or a change in antithrombotic therapy.
Other safety outcomes: Any bleeding, other adverse events, liver-function abnormalities.	Any bleeding, other adverse events, liver-function abnormalities.

Source: Granger et al 2011

18,201 patients were recruited at 1034 clinical sites in 39 countries (including 322 patients from Australia). A total of 9,120 patients were assigned to the apixaban group and 9,081 to the warfarin group. The two groups were well balanced with respect to baseline characteristics (**Table 5**), with the median age being 70 years and the mean $CHADS_2$ score was 2.1.

Table 5 – Baseline characteristics of the ARISTOTLE trial

Baseline Characteristics	Apixaban n=9120	Warfarin n=9081
Age – yr	70	70
Median	63-76	63-76
Female sex – no (%)	3234 (35.5)	3182 (35.0)
Region – no (%)		
• North America	2249 (24.7)	2225 (24.5)
• Latin America	1743 (19.1)	1725 (19.0)
• Europe	3672 (40.3)	3671 (40.4)
• Asian Pacific	1456 (16.0)	1460 (16.1)
Systolic blood pressure – mm Hg		
Median	130	130
Weight – kg		
Median	82	82
Prior myocardial infarction – no (%)	1319 (14.5)	1266 (13.9)
Prior clinically relevant or spontaneous bleeding – no (%)	1525 (16.7)	1515 (16.7)
Type of atrial fibrillation – no (%)		
Paroxysmal	1374 (15.1)	1412 (15.5)
Persistent or permanent	7744 (84.9)	7668 (84.4)

Baseline Characteristics	Apixaban n=9120	Warfarin n=9081
Prior use of vitamin K antagonist for >30 consecutive days – no (%)	5208 (57.1)	5193 (57.2)
Qualifying risk factors		
Age ≥ 75 years – no (%)	2850 (31.2)	2828 (31.1)
Prior stroke, TIA or systemic embolism – no (%)	1748 (19.2)	1790 (19.7)
Heart failure of reduced left ventricular ejection fraction – no (%)	3235 (35.5)	3216 (35.4)
Diabetes – no (%)	2284 (25.0)	2263 (24.9)
Hypertension requiring treatment – no (%)	7962 (87.3)	7954 (87.6)
$CHADS_2$ score		
• Mean	2.1±1.1	2.1±1.1
• Distribution – no (%)		
• 1	3100 (34.0)	3083 (34.0)
• 2	3262 (35.8)	3254 (35.8)
• ≥3	2758 (30.2)	2744 (30.2)

Source: Granger et al 2011

The main primary and secondary efficacy outcome results from the ARISTOTLE trial are summarised in **Table 6** below.

Table 6 – Primary and Secondary Efficacy Outcomes from the ARISTOTLE trial

Outcome	Apixaban		Warfarin		Hazard Ratio (95% CI)	P Value
	Patients with event	Event rate (%/year)	Patients with event	Event rate (%/year)		
Efficacy Outcomes						
Primary outcome: Stroke or SEE	212	1.27	265	1.60	**0.79 (0.66-0.95)**	**0.01**
Stroke	199	1.19	250	1.51	**0.79 (0.65-0.95)**	**0.01**
Ischaemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74-1.13)	0.42
Haemorrhagic stroke	40	0.24	78	0.47	**0.51 (0.35-0.75)**	**<0.001**
Systemic embolism	15	0.09	17	0.10	0.87 (0.44-1.75)	0.70
Key secondary efficacy outcome: death from any cause	603	3.52	669	3.94	**0.89 (0.81-0.98)**	**0.047**
Other secondary outcomes						
Stroke, systemic embolism, or death from any cause	752	4.49	837	5.04	**0.89 (0.81-0.98)**	**0.02**
Myocardial infarction	90	0.53	102	0.61	0.88 (0.66-1.17)	0.37
Stroke, systemic embolism, myocardial infarction or death from any cause	810	4.85	906	5.49	**0.88 (0.80-0.97)**	**0.01**
Pulmonary embolism or deep-vein thrombosis	7	0.04	9	0.05	0.78 (0.29-2.10)	0.63
Bleeding outcomes and Net Clinical Outcomes						
Primary Safety Outcome: ISTH Major Bleeding	327	2.13	462	3.09	**0.69 (0.60-0.80)**	**<0.001**
Intracranial	52	0.33	122	0.80	**0.42 (0.30-0.58)**	**<0.001**
Other location	275	1.79	340	2.27	**0.79 (0.68-0.93)**	**0.004**
Gastrointestinal	105	0.76	119	0.86	0.89 (0.70-1.15)	0.37
Major or clinically relevant non-major bleeding	613	4.07	877	6.01	**0.68 (0.61-0.75)**	**<0.001**
GUSTO severe bleeding	80	0.52	172	1.13	**0.46 (0.35-0.60)**	**<0.001**
GUSTO moderate to severe bleeding	199	1.29	328	2.18	**0.60 (0.50-0.71)**	**<0.001**

Outcome	Apixaban		Warfarin		Hazard Ratio (95% CI)	P Value
	Patients with event	Event rate (%/year)	Patients with event	Event rate (%/year)		
TIMI major bleeding	148	0.96	256	1.69	**0.57 (0.46-0.70)**	**<0.001**
TIMI major or minor bleeding	239	1.55	370	2.46	**0.63 (0.54-0.75)**	**<0.001**
Any bleeding	2356	18.1	3060	25.8	**0.71 (0.68-0.75)**	**<0.001**
Net clinical outcomes						
Stroke, systemic embolism, or major bleeding	521	3.17	666	4.11	**0.77 (0.69-0.86)**	**<0.001**
Stroke, systemic embolism, major bleeding or death from any cause	1009	6.13	1168	7.20	**0.85 (0.78-0.92)**	**<0.001**

Source: Granger et al 2011

In brief, the primary outcome of stroke or systemic embolism occurred in 212 patients in the apixaban group (1.27% per year) as compared with 265 patients in the warfarin group (1.60% per year) (HR=0.79; 95% CI 0.66-0.95, p<0.001 for non-inferiority and p=0.01 for superiority). The rate of haemorrhagic stroke was 49% lower in the apixaban group than in the warfarin group and the rate of ischaemic or uncertain type of stroke was 8% lower in the apixaban group than in the warfarin group. Fatal or disabling stroke occurred in 84 patients in the apixaban group (0.5% per year) as compared with 117 patients in the warfarin group (0.71%) (HR=0.71, 95% CI 0.54 to 0.94). Ischaemic stroke occurred in 149 patients in the apixaban group and 155 patients in the warfarin group.

The rate of death from any cause was lower in the apixaban group than the warfarin group (3.52% per year vs 3.94% per year; HR=0.89, 95%CI: 0.80-0.99, p=0.047). The rate of myocardial infarction was also lower in the apixaban group than in the warfarin group but the difference was not significant (0.53% per year vs 0.61% per year; HR=0.88, 95%CI: 0.66-1.17, p=0.37)

Strikingly, major bleeding, as defined according to the ISTH criteria, occurred in 327 patients in the apixaban group (2.13% per year) as compared with 462 patients in the warfarin group (3.09% per year) (HR=0.69; 95% CI 0.60-0.80, p<0.001). There appeared to be an even greater reduction in the rate of serious bleeding as defined according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria for severe bleeding and according to the Thrombolysis in Myocardial Infarction (TIMI) criteria for major bleeding. The rate of intracranial haemorrhage (ICH) was 0.33% per year in the apixaban group and 0.80% per year in the warfarin group (HR=0.42, 95%CI 0.30-0.58, p<0.001) and the rate of any bleeding was 25.8% per year in the warfarin group and 18.1% per year in the apixaban group, an absolute reduction of 7.7 percentage points (p<0.001).

Adverse events occurred in almost equal proportions of patients in the apixaban and warfarin groups (81.5% of the patients in the apixaban group and 83.1% of patients in the warfarin group), as did serious adverse events (35.0% and 36.5% in the two groups, respectively). The rates of abnormalities on liver function testing and liver-related serious adverse events were similar in the two groups.

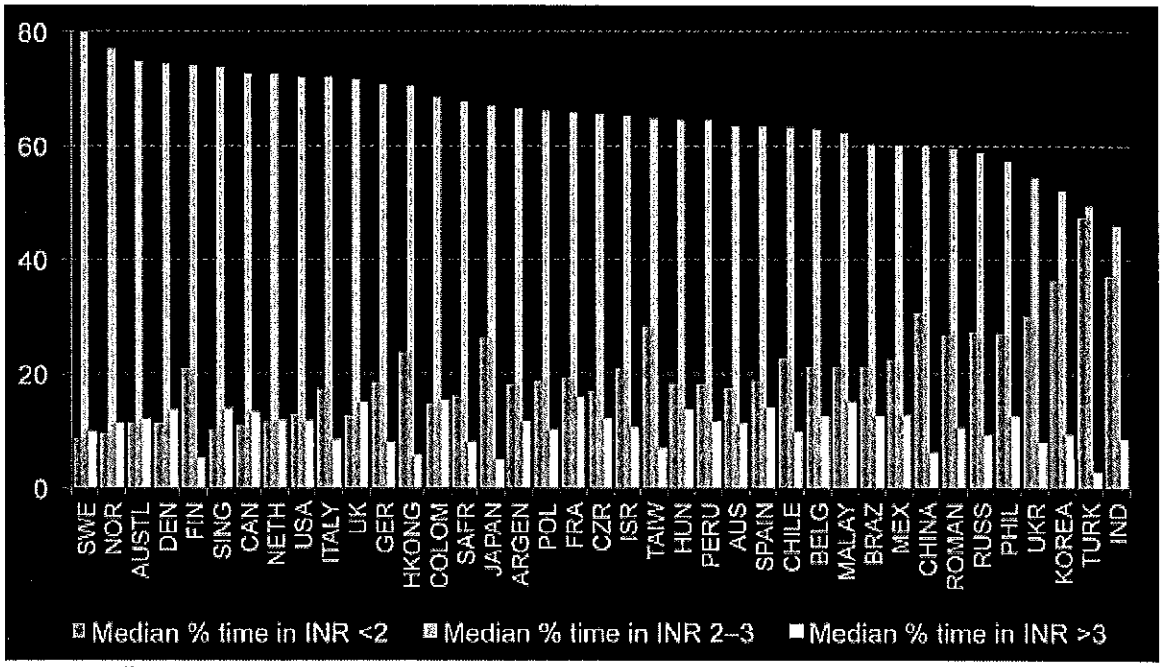
It can be seen from the ARISTOTLE trial results that apixaban is superior to warfarin in both the primary and secondary efficacy outcomes. In patients with atrial fibrillation and at least one additional risk factor for stroke, the use of apixaban as compared with warfarin significantly reduced the risk of stroke or systemic embolism by 21%, major bleeding by 31% and death by 11%. For every 1000 patients treated for 1.8 years, apixaban as compared with warfarin prevented a stroke in 6 patients, major bleeding in 15 patients and death in 8 patients. The predominant effect on stroke prevention was on haemorrhagic stroke, with prevention of haemorrhagic stroke in 4 patients per 1000 and prevention of an ischaemic or unknown type of stroke in 2 patients per 1000.

In summary, among patients with atrial fibrillation who are at risk for stroke, apixaban as compared with warfarin substantially reduced the risk of stroke, major bleeding and intracranial bleeding. The net clinical benefit of apixaban in these patients was therefore substantial.

Time Spent in Therapeutic Range - In the Dabigatran Public Summary Document (March 2011 PBAC Meeting p6), the PBAC noted that for *"patients in centres with a mean time in therapeutic range (cTTR) >72.6 with warfarin, the results demonstrated no statistically significant differences in the primary outcome of stroke/SEE. The PBAC noted that this subgroup included Australia, where the cTTR was measured in the RE-LY trial as 74%. However, the PBAC also noted that published studies and an unpublished survey suggested that the time spent in INR range varies between 50.4% and 68% in Australia."*

The overall efficacy and safety outcomes in ARISTOTLE have been discussed in the previous section using the ITT population, where patients in the warfarin group had an INR in the therapeutic range (2-3) for a median of 66.0% of the time and a mean of 62.2% of the time, after the exclusion of INR values during the first 7 days after randomisation and during study-drug interruptions. For Australian patients in the ARISTOTLE trial, the median of patients TTR (INR 2-3) in Australia was ~ 75%, similar to that seen in the RE-LY trial (**Figure 1**) (Wallentin L 2011).

Figure 1 – ARISTOTLE Median of Patients TTR in Different Countries



Source: Wallentin L 2011

An analysis (*The Efficacy and Safety of Apixaban Compared with Warfarin at Different Levels of INR Control for Stroke Prevention in Atrial Fibrillation*) has been conducted for the ARISTOLE Investigators by Lars Wallentin at the Uppsala Clinical Research Centre to determine whether the efficacy of apixaban compared with warfarin is different dependent upon the warfarin-treated patients' level of INR control (Wallentin L 2011).

The objective of the study was to determine the influence of centres' quality of INR control, as estimated in their warfarin-treated patients, on the effects of apixaban compared with warfarin on major outcome events (pre-specified outcomes including stroke or systemic embolism, mortality, composite of stroke, systemic embolism and myocardial infarction, major bleeding, a composite of major and clinically relevant non-major bleeding, haemorrhagic stroke and net clinical benefit which incorporates a composite of stroke, systemic embolism, myocardial infarction, death and major bleeding).

The methods outlined included calculating individual TTR for each warfarin-treated patient using the Rosendaal method. The first 7 days after randomisation and treatment interruptions were excluded and levels were determined until 2 days after the last day of warfarin (patients with less than two INR levels were excluded, n=210). The centre's TTR was calculated as the median of the individual

TTRs for its warfarin patients during the whole study. The centre's TTR was assigned as a proxy for centre's quality of INR control for all its patients. The interquartile cut-off limits for the centre's TTR were identified to keep the patient numbers within each quartile approximately balanced.

Outcomes were compared across the four groups defined by the quartiles of the centre's TTR as pre-specified. Hazard ratios and their 95% confidence intervals were determined. Tests for interactions between the centre's TTR and randomised treatment effects were evaluated by multivariable Cox regression analyses using the patients' assigned centre TTR value as a continuous variable. Interactions were adjusted for baseline variables potentially influencing both TTR and outcome: age, sex, body weight, $CHADS_2$ score, prior stroke, diabetes mellitus, hypertension, heart failure, baseline medications (aspirin, digoxin, amiodarone, lipid lowering drugs) and warfarin naïve/experienced status. Results are presented in **Table 7**.

Table 7 – Results of Outcomes in Relation to Centres' TTR

Centre TTR (%)	Apixaban		Warfarin		HR (95% CI)	Adjusted interaction
	Event?	Rate/100 person years	Event?	Rate/100 person years		
Stroke and Systemic Embolism (primary outcome) in Relation to Centre's TTR						
<58.0	70	1.75	88	2.28	0.77 (0.56, 1.06)	0.29
58.0-65.7	54	1.30	68	1.61	0.80 (0.56, 1.15)	
65.7-72.2	51	1.21	65	1.55	0.79 (0.54, 1.13)	
>72.2	36	0.83	44	1.02	0.81 (0.52, 1.26)	
Death in Relation to Centre's TTR						
<58.0	163	3.95	191	4.75	0.83 (0.68, 1.03)	0.39
58.0-65.7	158	3.71	177	4.10	0.91 (0.73, 1.12)	
65.7-72.2	147	3.44	174	4.07	0.84 (0.68, 1.05)	
>72.2	133	3.03	127	2.91	1.04 (0.82, 1.33)	
Composite Efficacy in Relation to Centre's TTR						
<58.0	212	5.31	254	6.57	**0.81 (0.67, 0.97)**	0.27
58.0-65.7	212	5.12	231	5.50	0.93 (0.77, 1.12)	
65.7-72.2	202	4.83	236	5.66	0.85 (0.71, 1.03)	
>72.2	180	4.18	185	4.33	0.96 (0.79, 1.18)	
Major bleeding in Relation to Centre's TTR						
<58.0	64	1.75	115	3.34	**0.53 (0.39, 0.72)**	0.10
58.0-65.7	61	1.60	102	2.68	**0.60 (0.43, 0.82)**	
65.7-72.2	103	2.68	109	2.89	0.93 (0.71, 1.21)	
>72.2	98	2.49	136	3.46	**0.72 (0.55, 0.93)**	
Major and clinically relevant bleeding in Relation to Centre's TTR						
<58.0	115	3.19	207	6.13	**0.53 (0.42, 0.66)**	0.005
58.0-65.7	125	3.32	195	5.24	**0.64 (0.51, 0.80)**	
65.7-72.2	179	4.75	220	5.99	**0.79 (0.65, 0.97)**	
>72.2	191	4.96	255	6.68	**0.74 (0.62, 0.90)**	
Haemorrhagic stroke in Relation to Centre's TTR						
<58.0	14	0.35	26	0.66	**0.52 (0.27, 1.00)**	0.5058
58.0-65.7	9	0.22	26	0.61	**0.35 (0.16, 0.75)**	
65.7-72.2	13	0.31	18	0.43	0.72 (0.35, 1.47)	
>72.2	4	0.09	8	0.18	0.50 (0.15, 1.66)	

[redacted]

It can be seen that the benefits of apixaban over warfarin in preventing stroke and reducing bleeding appear consistent regardless of centre's quality of INR control.

Although none of the results of the primary efficacy outcome reach statistical significance once categorised into the centre's TTR interquartile ranges, the point estimates all consistently favour apixaban compared with warfarin, regardless of comparison to warfarin and corresponding level of INR control. The non-statistical significance of these values are probably due to the smaller patient populations in each of these subgroups, as the ARISTOTLE clinical trial was not powered to detect a significant difference in these smaller subgroup analyses. With regard to bleeding outcomes, all point estimates favour apixaban compared with warfarin regardless of level of INR control.

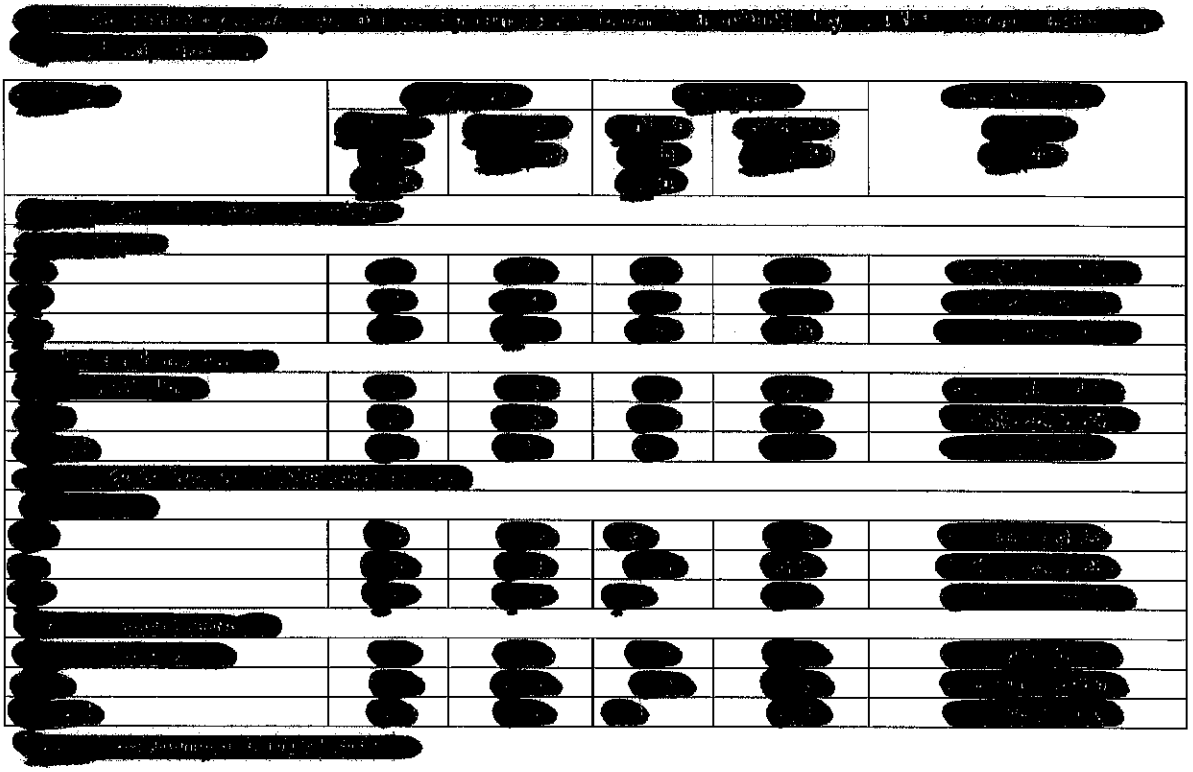
It is interesting to note the differing efficacy and safety profiles of apixaban and dabigatran across INR cTTR ranges (**Table 8**). The sponsor notes the different MoA and pharmacokinetic profile between the two medicines. The risk:benefit profile across INR cTTR ranges also appears to be different, noting the potential issues associated with comparisons across studies.

Table 8 – Tabulation of Results of Primary Efficacy and Safety Outcomes from ARISTOTLE and RE-LY (by INR control)

Outcome	Hazard ratio (95%CI) cf adjusted-dose warfarin					
	ARISTOTLE		RE-LY			
	ITT (reported in PSD)	cTTR>72.2% (Australian patients in ARISTOTLE had cTTR of ~75%)	ITT (reported in PSD)		cTTR>72.6% (Australian patients in RE-LY had cTTR of 74%)	
Dose	Apix	Apix	Dabi 110	Dabi 150	Dabi 110	Dabi 150
Stroke and SE	**0.79 (0.66,0.95)**	0.81 (0.52, 1.26)	0.90 (0.74, 1.10)	**0.65 (0.52, 0.81)**	0.92 (0.59, 1.45)	0.95 (0.61, 1.48)
Major bleeding	**0.69 (0.60,0.80)**	**0.72 (0.55, 0.93)**	**0.80 (0.70, 0.93)**	0.93 (0.81, 1.07)	0.90 (0.67, 1.21)	1.16 (0.88, 1.54)

Source: Granger et al 2011, Wallentin L 2011, Wallentin et al 2010.

[redacted]



Myocardial Infarction Event Rates – A trend towards an increase in myocardial infarction event rates in the dabigatran arms compared to the warfarin arm of the RE-LY trial has also triggered recent discussions specific to the safety profile of dabigatran. **Table 10** below illustrates that data from ARISTOTLE points towards a reduced rate of myocardial infarction associated with apixaban therapy compared to warfarin therapy.

Table 10 – Myocardial infarction event rates

Medicine	% per year*	Hazard ratio#	p value
Apixaban v warfarin	0.53% vs 0.61%	0.88 (0.66-1.17)	<0.37
Dabigatran 110 v warfarin	0.72% vs 0.53%	1.35 (0.98-1.87)#	<0.07
Dabigatran 150 v warfarin	0.74% vs 0.53%	1.38 (1.00-1.91)#	<0.051

Source: Granger et al 2011; Connolly et al 2009
* Format: NOAC vs comparator
#Dabigatran trials reported as Relative Risk

Gastrointestinal Bleeding - Bleeding rate is a critically important safety outcome measure for anti-coagulant therapy, including warfarin and also the newer agents used in this indication. A review of the bleeding data reveals another important point of difference between the apixaban ARISTOTLE and dabigatran RE-LY clinical trial results relating to the relative incidence of gastrointestinal bleeding (**Table 11**). It has been hypothesised that apixaban's reduced incidence of gastrointestinal

bleeding compared to dabigatran may be because of its more specific mode of action (factor Xa inhibitor versus direct thrombin inhibitor) coupled with a high bioavailability of approximately 50%. It should also be noted that in contrast to dabigatran, apixaban is not a pro-drug. Dabigatran is a pro-drug, encapsulated in tartric acid to facilitate absorption in the GI tract. Bioavailability of the active drug is ~6.5% (Dabigatran PI, 2012). This may also contribute to dabigatran's trend towards higher GI side effects.

Table 11 – Gastrointestinal bleeding event rates

Medicine	% per year*	Hazard ratio#	p value
Apixaban v warfarin	0.76% vs 0.86%	0.89 (0.66-1.17)	<0.37
Dabigatran110 v warfarin	1.12% vs 1.02%	1.10 (0.98-1.87)#	<0.43
Dabigatran 150 v warfarin	1.51% vs 1.02%	**1.50 (1.00-1.91)#**	**<0.001**

Source: Granger et al 2011; Connolly et al 2009
* Format: NOAC vs comparator
#Dabigatran trials reported as Relative Risk

In summary, the data from ARISTOTLE not only demonstrates that apixaban is superior to warfarin with respect to the key efficacy and safety outcomes, but that the question marks currently surrounding the dabigatran RE-LY results *(i.e. mean time in therapeutic range, incidence of MI, incidence of GI bleeding, requirement for renal monitoring)* are not applicable to apixaban.

3.2.2. Apixaban versus Aspirin – AVERROES:

AVERROES (*Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who have Failed or are Unsuitable for Vitamin K antagonist Treatment*) was a randomised, double-blind trial comparing apixaban (at a dose of 5 mg twice daily) with aspirin (81 to 324 mg per day) in 5,599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable (Connolly et al 2011). The primary outcome was the occurrence of stroke or systemic embolism.

The study was conducted at 522 centres in 36 countries (including Australia). Patients were randomly assigned to receive apixaban at a dose of 5 mg twice daily or aspirin at a dose of 81 to 324 mg per day. **Table 12** summarises the primary and secondary outcome definitions for the AVERROES trial.

Table 12 – Primary and Secondary Outcomes of the AVERROES trial

Outcome	Definition
Primary Efficacy Outcome: Stroke or systemic embolism	Stroke was a clinical diagnosis that was made on the basis of typical symptoms lasting at least 24 hours. Brain imaging, which was available in the vast majority of patients, was not required but was recommended for the general diagnosis of stroke; however, it was required to differentiate ischaemic from haemorrhagic events.
Secondary efficacy outcomes: Rate of myocardial infarction, death from vascular causes, death from any cause	Myocardial infarction, deaths from vascular causes, deaths from any cause.
Primary safety outcome: Major bleeding	Clinically overt bleeding accompanied by one or more of the following: a decrease in the haemoglobin level of 2g per decilitre or more over a 24-hour period, transfusion of 2 or more units of packed red cells, bleeding at a critical site (intracranial, intraspinal, pericardial, intrarticular, intramuscular with compartment syndrome, or retroperitoneal) or fatal bleeding.

Source: Connolly et al 2011

A total of 2,808 patients were assigned to the apixaban group and 2,791 patients to the aspirin group. The two groups were well balanced with respect to baseline characteristics (**Table 13**).

Table 13 – Baseline characteristics of the AVERROES trial

Baseline Characteristics	Apixaban n=2808	Aspirin n=2791
Age – yr	70±9	70±10
Male sex – no (%)	1660 (59)	1617 (58)
Systolic blood pressure – mm Hg	132±16	132±16
Heart rate – beats/min	74±14	74±14
Body-mass Index	28±5	28±5
Region – no (%)		
• North America	408 (15)	396 (14)
• Latin America	589 (21)	596 (21)
• Western Europe	625 (22)	633 (23)
• Eastern Europe	639 (23)	611 (22)
• Asia and South Africa	547 (19)	555 (20)
Baseline electrocardiographic findings – no (%)		
• Atrial fibrillation	1923 (68)	1894 (68)
• Atrial flutter	19 (1)	20 (1)
• Sinus rhythm	707 (25)	730 (26)
• Paced or other rhythm	147 (5)	139 (5)
• Left ventricular hypertrophy	490 (17)	498 (18)
Risk factors for stroke – no (%)		
• Prior stroke or TIA	390 (14)	374 (13)
• Hypertension, receiving treatment	2408 (86)	2429 (87)
• Heart failure	1118 (40)	1053 (38)
○ NYHA class 1 or 2	932 (33)	878 (31)
○ NYHA class 3 or 4	186 (7)	175 (6)
• Left ventricular ejection fraction ≤35%	144 (5)	144 (5)
• Peripheral artery disease	66 (2)	87 (3)
• Diabetes, receiving treatment	537 (19)	559 (20)
• Mitral stenosis	64 (2)	50 (2)
Type of atrial fibrillation – no (%)		
Paroxysmal	760 (27)	752 (27)
Persistent	587 (21)	590 (21)
Permanent	1460 (52)	1448 (52)
$CHADS_2$ score		
• Mean score	2.0±1.1	2.1±1.1
	1004 (36)	1022 (37)

Baseline Characteristics	Apixaban n=2808	Aspirin n=2791
• 0 or 1 • 2 • ≥ 3	1045 (37) 758 (27)	954 (34) 812 (29)
Use of vitamin K antagonist within 30 days of screening – no (%)	401 (14)	426 (15)
Use of aspirin within 30 days of screening – no (%)	2137 (76)	2081 (75)
Study dose or aspirin or aspirin placebo – no (%) • 81 mg • 162 mg • 243 mg • 324 mg • Data not available	 1816 (65) 718 (26) 73 (3) 193 (7) 7 (<1)	 1786 (64) 750 (27) 60 (2) 184 (7) 11 (<1)
Study dose of apixaban or apixaban-placebo 2.5 mg twice daily – no (%)	179 (6)	182 (7)

Source: Connolly et al 2011

The main primary and secondary efficacy outcome results from the AVERROES trial are presented in **Table 14** below. In brief, there were 51 primary outcome events (a rate of 1.6% per year) among patients assigned to apixaban and 113 (3.7% per year) among patients assigned to aspirin (HR=0.45, 95%CI 0.32-0.62, p<0.001). The corresponding rates of ischaemic stroke were 1.1% per year and 3.0% per year (HR=0.37, 95% CI 0.25-0.55, p<0.001). There were six cases of haemorrhagic stroke (intra-cerebral haemmorhage) among patients receiving apixaban and nine among those receiving aspirin. The rate of death was 3.5% per year in the apixaban group and 4.4% per year in the aspirin group (HR=0.79, 95%CI 0.62-1.02). The rate of hospitalisation for cardiovascular causes was lower in the apixaban group than in the aspirin group (12.6% per year vs 15.9% per year (HR=0.79, 95%CI 0.69-0.91, p<0.001). In an analysis that included all events up to the final study visit, there were 56 primary outcome events (a rate of 1.6% per year) in the apixaban group and 126 (3.6% per year) in the aspirin group (HR=0.44, 95%CI 0.32-0.60, p<0.001).

Table 14 – Outcomes of the AVERROES trial

Outcome	Apixaban		Aspirin		Hazard Ratio (95% CI)	P Value
	Patients with event	Event rate (%/year)	Patients with event	Event rate (%/year)		
Stroke or systemic embolism	51	1.6	113	3.7	**0.45 (0.32-0.62)**	**<0.001**
Stroke, systemic embolism or death	143	4.6	223	7.2	**0.64 (0.51-0.78)**	**<0.001**
Stroke, systemic embolism, myocardial infarction or death from any vascular cause	132	4.2	197	6.4	**0.66 (0.53-0.83)**	**<0.001**
Stroke, systemic embolism, myocardial infarction, death from vascular cause, or major bleeding event.	163	5.3	220	7.2	**0.74 (0.60-0.90)**	**0.003**
Stroke	49	1.6	105	3.4	**0.46 (0.33-0.65)**	**<0.001**
• Ischaemic	35	1.1	93	3.0	**0.37 (0.25-0.55)**	**<0.001**
• Haemorrhagic	6	0.2	9	0.3	0.67 (0.24-1.88)	0.45
• Unspecified	9	0.3	4	0.1	2.24 (0.69-7.27)	0.18

Outcome	Apixaban		Aspirin		Hazard Ratio (95% CI)	P Value
	Patients with event	Event rate (%/year)	Patients with event	Event rate (%/year)		
• Disabling or fatal	31	1.0	72	2.3	**0.43 (0.28-0.65)**	**<0.001**
Systemic embolism	2	0.1	13	0.4	**0.15 (0.03-0.68)**	**0.01**
Myocardial infarction	24	0.8	28	0.9	0.86 (0.50-1.48)	0.59
Death						
• From any cause	111	3.5	140	4.4	0.79 (0.62-1.07)	0.07
• From any vascular cause	84	2.7	96	3.1	0.87 (0.65-1.17)	0.37
Bleeding event						
• Major	44	1.4	39	1.2	1.13 (0.74-1.75)	0.57
o Intracranial	11	0.4	13	0.4	0.85 (0.38-1.90)	0.69
▪ Subdural	4	0.1	2	0.1	-	-
▪ Other	1	<0.1	2	0.1	-	-
o Extracranial/unclassified	33	1.1	27	0.9	1.23 (0.74-2.05)	0.42
▪ Gastrointestinal	12	0.4	14	0.4	0.86 (0.40-1.86)	0.71
▪ Non-gastrointestinal	20	0.6	13	0.4	1.55 (0.77-3.12)	0.22
o Fatal	4	0.1	6	0.2	0.67 (0.19-2.37)	0.53
• Clinically relevant non-major	96	3.1	84	2.7	1.15 (0.86-1.54)	0.35
• Minor	188	6.3	153	5.0	1.24 (1.00-1.53)	0.05

Source: Connolly et al 2011

In summary, among patients with atrial fibrillation who are at high risk for stroke and for whom vitamin K antagonist therapy is unsuitable, apixaban as compared with aspirin substantially reduced the risk of stroke, with no significant increase in the risk of major bleeding or intracranial bleeding. The net clinical benefit of apixaban in these patients was therefore substantial.

4. CONCLUSION

Although warfarin is regarded as the mainstay of AF therapy in Australia, significant issues specific to safety, convenience and use translate to a disease area where a major improvement in Australian patient health outcomes is desperately needed.

The data presented in this submission clearly demonstrates that apixaban 5 mg twice daily is more effective than warfarin in terms of preventing stroke, major bleeding and death in patients with AF. Significantly, the issues of design, applicability and transferability associated with the dabigatran RE-LY clinical trial are not of concern for the apixaban ARISTOTLE and AVERROES clinical trials. Bristol-Myers Squibb and Pfizer believe that the clinical profile of apixaban will lead to this medicine playing a key role in the future standard of care for the prevention of stroke in Australian patients with AF.

As such, Bristol-Myers Squibb and Pfizer appreciate the opportunity to submit apixaban clinical trial data to the *Review of Anticoagulation Therapies in Atrial Fibrillation* and looks forward to the findings of the review as well as discussions with the Commonwealth through the upcoming PBAC evaluation process.

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