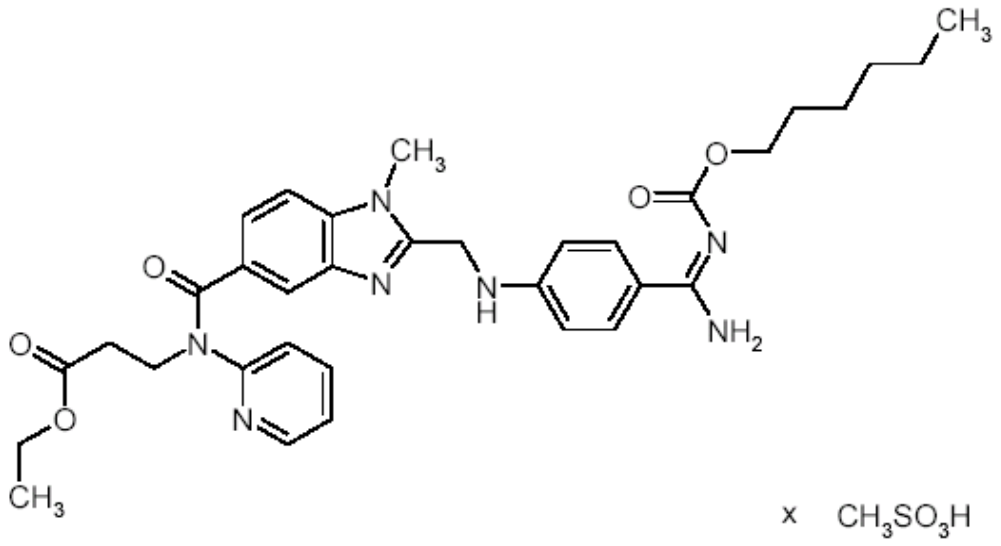
APPENDIX A: DABIGATRAN PRODUCT INFORMATION

PRADAXA®
(dabigatran etexilate)

NAME OF THE MEDICINE

Dabigatran etexilate mesilate is Ethyl N-{[2-({[4-((E)-amino{[hexyloxy)carbonyl]imino}methyl) phenyl]amino}methyl)-1-methyl-1H-benzimidazol-5-yl]carbonyl}-N-pyridin-2-yl-β-alaninate methanesulfonate.



Molecular Formula: $C_{35}H_{45}N_7O_8S$

Molecular Weight: 627.75 (free base)

723.86 (mesilate salt)

CAS Registry Number: 211915-06-9 (free base)

593282-20-3 (mesilate)

DESCRIPTION

Dabigatran etexilate mesilate is a yellow-white to yellow crystalline powder; the crystals have a rod-like habit. It contains two weak basic centers with pKa-values of 4.0 ± 0.1 (benzimidazol moiety) and 6.7 ± 0.1 (carbamic acid hexyl ester moiety). Its solubility in water is strongly pH dependent with rather high solubility in acidic media (>50 mg/mL in 0.1 N HCl) and very poor solubility in neutral and basic media (0.003 mg/mL at pH 7.4). The solubility in water is 1.8 mg/mL (0.18%). In its neutral form it is very lipophilic (log P = 3.8, determined in different mixtures of aqueous solution and n-octanol).

75 mg hard capsules. Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 2 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R75.

110 mg hard capsules. Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 1 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R110.

150 mg hard capsules. Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 0 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R150.

Excipients

Capsule fill: Tartaric acid, acacia, hypromellose, dimeticone 350, talc, hydroxypropylcellulose

HPMC capsule shell: Carrageenan, potassium chloride, titanium dioxide, sunset yellow FCF CI15985, indigo carmine CI73015, hypromellose, water - purified

Printing ink: Shellac, tert-butyl alcohol, isopropyl alcohol, methylated spirit - industrial, iron oxide black CI77499, water - purifed, propylene glycol.

PHARMACOLOGY

Dabigatran etexilate 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 competitive (K_i = 4.5 nM) and reversible direct thrombin inhibitor and is the main metabolite of dabigatran etexilate 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 etexilate after oral administration in various animal models of venous thrombosis.

There is a close correlation between plasma dabigatran concentration and degree of anticoagulant effect. Prothrombin time (PT, expressed as International Normalised Ratio (INR)) is too insensitive to reliably detect anticoagulant activity of dabigatran and is therefore not recommended as a suitable tool for monitoring anticoagulant activity. Ecarin Clotting Time (ECT) and Thrombin Time (TT) are sensitive assays that increase in direct proportion to dabigatran plasma concentration without any deviation from linearity at high plasma concentrations. However, ECT is not readily available in clinical practice. Activated Partial Thromboplastin Time (aPTT) increases in a non-linear manner to dabigatran concentration and is less proportional at higher

dabigatran concentrations (see Precautions, Effect on laboratory tests). ECT, TT and aPTT are not standardised or validated with dabigatran for commercial use. In cases of emergency, TT and aPTT are the most accessible qualitative methods for determining the presence or absence of the anticoagulant effect of dabigatran.

Interpretation of coagulation assay results should consider time of dabigatran etexilate administration relative to time of blood sampling (see Pharmacokinetics, Absorption).

In patients undergoing elective hip replacement surgery, greater test variability with aPTT and ECT was observed. The mechanisms for this variability immediately after surgery are unclear and aPTT and ECT levels measured in the first 2-3 days following surgery should be interpreted with caution.

PHARMACOKINETICS

Absorption

After oral administration of dabigatran etexilate in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterised by a rapid increase in plasma concentrations with C_{max} attained within 0.5 and 2.0 hours post administration. C_{max} and the area under the plasma concentration-time curve were dose proportional. After C_{max}, plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 12–14 hours in elderly healthy volunteers and 14–17 hours in patients undergoing major orthopaedic surgery. The half-life was independent of dose. However, half-life is prolonged if renal function is impaired as shown below, in Table 1.

Table 1: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function

Glomerular filtration rate (CrCL) [mL/min]	gMean (gCV%; range) half-life [h]
>80	13.4 (25.7%; 11.0–21.6)
>50–≤80	15.3 (42.7%; 11.7–34.1)
>30–≤50	18.4 (18.5%; 13.3–23.0)
≤30	27.2 (15.3%; 21.6–35.0)

gMean – Geometric mean
gCV% - Geometric coefficient of variation

Upon administration of the dabigatran etexilate HPMC capsules together with a high fat, high caloric breakfast, the average total exposure (AUC) of dabigatran increased by 27% and the maximum exposure on average by 8.5%. The time to peak plasma concentrations was delayed by 2 hours. The relative increase of bioavailability was considered of no clinical relevance.

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate was approximately 6.5%.

The oral bioavailability was increased by about 1.8-fold (+75%) compared to the reference capsule formulation when the pellets are taken without the HPMC capsule

shell. Hence, the integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate. Therefore, patients should be advised not to open the capsules and take the pellets alone (e.g. sprinkled over food or into beverages) (see Dosage and Administration).

A study evaluating post-operative absorption of dabigatran etexilate, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration, or at 7 to 9 hours following surgery. It is noted however that contributing factors such as anaesthesia, gastrointestinal paresis, and surgical effects will mean that a proportion of patients will experience absorption delay independent of the oral drug formulation. Although this study did not predict whether impaired absorption persists with subsequent doses, it was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after drug administration.

Distribution

Low (34-35%) concentration independent binding of dabigatran to human plasma proteins was observed. The volume of distribution of dabigatran of 60–70 L exceeded the volume of total body water indicating moderate tissue distribution of dabigatran.

Metabolism and elimination

Metabolism and excretion of dabigatran were studied following a single intravenous dose of radiolabelled dabigatran in healthy male subjects. After an intravenous dose, the dabigatran-derived radioactivity was eliminated primarily in the urine (85%). Faecal excretion accounted for 6% of the administered dose. Recovery of the total radioactivity ranged from 88–94% of the administered dose by 168 hours post dose. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 mL/min corresponding to the glomerular filtration rate.

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. Dabigatran is subject to conjugation forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounts for less than 10% of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods.

Special populations

Renal impairment

An open, parallel-group single-centre study compared dabigatran pharmacokinetics in healthy subjects and patients with mild to moderate renal impairment receiving a single dose of dabigatran etexilate 150 mg. Based on pharmacokinetic modeling, estimated exposure to dabigatran increases with the severity of renal function impairment (Table 2).

Table 2: Estimated Pharmacokinetic Parameters of Dabigatran by Renal Function

Renal Function	CrCL (mL/min)	Increase in AUC	Increase in Cmax	$t_{1/2}$ (h)
Normal	80	1x	1x	13
Mild	50	1.5x	1.1x	15
Moderate	30	3.2x	1.7x	18

Similar findings were observed in the RE-LY study. The median CrCL in RE-LY was 68.4 mL/min. Almost half (45.8%) of the RE-LY patients had a CrCL between 50-80 mL/min. When compared with patients without renal impairment (CrCL ≥80 mL/min), patients with moderate renal impairment (CrCL between 30-50 mL/min) had pre- and post-dose dabigatran plasma concentrations 2.29-fold and 1.81-fold higher on average, respectively.

In a small number of volunteers with severe renal insufficiency (CrCL 10–30 mL/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency (see Dosage and Administration and Contraindications).

Elderly patients

The $AUC_{T,ss}$ and $C_{max,ss}$ in male and female elderly subjects (>65 years) were approximately 1.9 fold and 1.6 fold higher for elderly females compared to young females and 2.2 and 2.0 fold higher for elderly males than in male subjects of 18-40 years of age.

The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance. The effect by age on exposure to dabigatran was confirmed in the RE-LY study: Compared with subjects aged <65 years, dabigatran trough concentrations were 28% higher in subjects aged between 65 and 75 years and 68% higher in subjects aged ≥75 years. (see Precautions, Use in the elderly and Dosage and Administration).

Hepatic insufficiency

No change in dabigatran exposure was seen in 12 subjects in a phase 1 study with moderate hepatic insufficiency (Child-Pugh B) compared to 12 controls.

- *Prevention of venous thromboembolic events (VTE) in adult patients who have undergone major orthopaedic surgery:* Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes ≥2 X Upper Limit Normal (ULN) were excluded in clinical trials.

- *Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:* Patients with active liver disease including but not limited to the persistent elevation of liver enzymes ≥2 X ULN or hepatitis A, B or C were excluded in clinical trials.

Body weight

The dabigatran trough concentrations were about 20% lower in subjects with a body weight >100 kg compared with subjects of 50–100 kg. The dabigatran trough concentrations were about 20% higher in subjects with a body weight <50 kg compared with subjects of 50-100 kg. Comparing the extremes, <50 kg versus >100 kg, the median dabigatran trough concentrations differed by 53%. The majority (80.8%) of the subjects were in the ≥50 kg and <100 kg category with no clear difference detected.

Gender

Drug exposure in the primary VTE prevention studies was about 1.4- to 1.5-fold (+40% to 50%) higher in female patients. In atrial fibrillation, female patients had on average 1.3-fold (+30%) higher trough and post-dose concentrations. This finding had no clinical relevance.

Ethnic origin

The pharmacokinetics of dabigatran was investigated in Caucasian and Japanese volunteers after single and multiple doses. Ethnic origin does not affect the pharmacokinetics of dabigatran in a clinically relevant manner. Limited pharmacokinetic data in black patients are available which suggest no relevant differences.

CLINICAL TRIALS

Prevention of venous thromboembolic events (VTE) in adult patients who have undergone major orthopaedic surgery

In 2 large randomised, parallel group, double-blind, dose–confirmatory trials, patients undergoing elective major orthopaedic surgery (one for knee replacement surgery and one for hip replacement surgery) received dabigatran etexilate 75 mg or 110 mg within 1–4 hours of surgery followed by 150 or 220 mg once daily thereafter,

haemostasis having been secured, or enoxaparin 40 mg on the day prior to surgery and once daily thereafter.

Both trials were performed in centres of countries located on 3 continents (Africa, Australia and Europe).

In the RE-MODEL trial (knee replacement) treatment was for 6–10 days and in the RE-NOVATE trial (hip replacement) for 28–35 days. Totals of 2076 patients (knee) and 3494 (hip) were treated respectively.

Enrolled patients were scheduled to have total knee or hip replacement surgery; 18 years of age or older and weighing at least 40 kg. Patients were excluded if there was a history of bleeding diathesis; coagulation disorders; major surgery or trauma (e.g. hip fracture) within the last 3 months; recent unstable cardiovascular disease or history of myocardial infarction within the last 3 months; greater than 3 attempts or traumatic placement for spinal or epidural anaesthesia; history of haemorrhagic stroke or intracranial pathology such as bleeding, neoplasm, AV malformation or aneurysm; history of VTE or pre-existing condition requiring anticoagulant therapy; clinically relevant bleeding within the last 6 months; gastric or duodenal ulcer within the last 6 months; liver disease which was expected to have a potential impact on survival; elevated AST or ALT >2 X ULN; severe renal insufficiency (CrCl <30 mL/min); elevated creatinine which contraindicated venography; treatment within 7 days with anticoagulants – clopidogrel, ticlopidine, abciximab, aspirin >160 mg/day or NSAID with $t_{1/2}$ >12 hours or requiring these medicines during the study treatment period; intermittent pneumatic compression and electric stimulation of lower limb; pregnant or nursing women and pre-menopausal women without acceptable birth control; allergy to radio-opaque contrast media or iodine; thrombocytopenia or platelet count <100,000 cells/µL; allergy to heparins or dabigatran and dabigatran etexilate; active malignant disease or currently receiving cytostatic treatment; participated in a clinical trial in the last 30 days; leg amputee; alcohol or drug abuse and contraindications to enoxaparin.

For the knee study (RE-MODEL), the median age was 68 years for all treatment groups. The majority of patients were female in all treatment groups (64.2–68.9%). The mean BMI was also similar in all 3 treatment groups with 29.9 (dabigatran etexilate 220 mg), 30.1 (dabigatran etexilate 150 mg), and 29.8 kg/m^2 (enoxaparin), respectively.

For the hip study (RE-NOVATE), the median age was 65 years for all treatment groups. The majority of patients were female in all treatment groups (55.5–57.4%) and almost all patients were of white ethnic origin. The median BMI was 27.3 kg/m^2 in both dabigatran etexilate groups and 27.1 kg/m^2 in the enoxaparin group.

The most widely used type of anaesthesia was spinal anaesthesia. The second most frequent type of anaesthesia was general anaesthesia.

Both the knee (RE-MODEL) and the hip (RE-NOVATE) studies were non-inferiority studies. For determination of the minimal important difference against enoxaparin, the placebo-controlled studies with enoxaparin 40 mg QD were pooled and the incidences of deep vein thrombosis (DVT), total VTE and all-cause mortality for enoxaparin against placebo for each indication analysed. For the knee study (RE-

MODEL), one third of the lower boundary of the 95% CI, i.e. 9.2%, was chosen to represent a rather strict and conservative estimate of the non-inferiority margin. For the hip study (RE-NOVATE), one third of the lower boundary of the 95% CI, 7.7% was chosen as the non-inferiority margin.

The results of the knee study (RE-MODEL) with respect to the primary end-point, total venous thromboembolism (VTE) including asymptomatic VTE plus all-cause mortality showed that the antithrombotic effect of both doses of dabigatran etexilate were statistically non-inferior to that of enoxaparin.

Similarly, total VTE including asymptomatic VTE and all-cause mortality constituted the primary end-point for the hip study (RE-NOVATE). Again dabigatran etexilate at both once daily doses was statistically non-inferior to enoxaparin 40 mg daily.

Data for the major VTE and VTE-related mortality end-point and adjudicated major bleeding endpoints are shown in Table 3 below. VTE was defined as the composite incidence of deep vein thrombosis and pulmonary embolism.

A third trial involving patients undergoing total knee replacement surgery received dabigatran etexilate 75 mg or 110 mg within 6–12 hours of surgery followed by 150 mg and 220 mg once daily thereafter for 12–15 days (RE-MOBILIZE). The comparator dosage of enoxaparin was 30 mg twice daily according to the US label. In the RE-MOBILIZE trial, non-inferiority was not established. There were no statistical differences in bleeding between the comparators.

A fourth trial involving patients undergoing hip replacement surgery received dabigatran etexilate 110 mg on the day of surgery followed by 220 mg once daily thereafter, or enoxaparin 40 mg on the day prior to surgery and daily thereafter (RE-NOVATE II). The duration of treatment was 28-35 days. In the RE-NOVATE II trial, dabigatran etexilate was statistically non-inferior to enoxaparin 40 mg daily for total VTE events and all-cause mortality.

In addition, a randomised, parallel group, double-blind, placebo-controlled phase II study, in Japanese patients where dabigatran etexilate 110 mg, 150 mg and 220 mg was administered once daily beginning the next day after elective total knee replacement surgery, was evaluated. The Japanese study showed an inverse relationship between dabigatran etexilate dose and the incidence of the primary endpoint (total VTE and all-cause mortality). The highest dabigatran etexilate dose resulted in the lowest incidence of total VTE and all-cause mortality.

In RE-MODEL and RE-NOVATE and RE-NOVATE II the randomisation to the respective study medication was done pre-surgery, and in the RE-MOBILIZE and Japanese placebo-controlled trial the randomisation to the respective study medication was done post-surgery. This is of note especially in the safety evaluation of these trials. In Table 3, three of the trials have been grouped in to pre- and post surgery randomised trials.

Table 3: Analysis of major VTE and VTE-related mortality during the treatment period in the orthopaedic surgery studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
Pre-operative randomisation studies			
RE-NOVATE (hip)			
N	909	888	917
Incidences (%)	28 (3.1)	38 (4.3)	36 (3.9)
Risk differences vs. enoxaparin (%)	- 0.8	0.4	
95% CI	- 2.5, 0.8	- 1.5, 2.2	
Risk ratio over enoxaparin	0.78	1.09	
95% CI	0.48, 1.27	0.70, 1.70	
RE-NOVATE II (hip)			
N	805		794
Incidences (%)	18 (2.2)		33 (4.2)
Risk differences vs. enoxaparin (%)	- 1.92		
95% CI	- 3.64, - 0.2		
Risk ratio over enoxaparin	0.49		
95% CI	0.28, 0.86		
RE-MODEL (knee)			
N	506	527	511
Incidences (%)	13 (2.6)	20 (3.8)	18 (3.5)
Risk differences vs. enoxaparin (%)	- 1.0	0.3	
95% CI	- 3.1, 1.2	-2.0, 2.6	
Risk ratio over enoxaparin	0.73	1.08	
95% CI	0.36, 1.47	0.58, 2.01	
Post-operative randomisation studies			
Japanese knee study			
			Placebo
N	102	113	104
Incidences (%)	0	2 (1.8)	6 (5.8)
Risk differences vs. placebo (%)	−5.8	−4.0	
95% CI	(−10.3, −1.3)	(−9.1, 1.1)	

Table 4 presents the combined incidences of major VTE and VTE related mortality for RE-MODEL and RE-NOVATE trials. The most frequent component of the composite endpoint was proximal DVT in all three treatment groups. Non-fatal pulmonary embolism (PE) during the treatment period in the two trials were observed in 1 patient in the dabigatran etexilate 150 mg group, 3 patients receiving enoxaparin and 5 patients receiving dabigatran etexilate 220 mg. VTE related mortality was observed for 1 patient in each of the dabigatran etexilate 220 mg and enoxaparin groups and for 4 patients in the dabigatran etexilate 150 mg group.

Table 4: Summary of primary endpoint components (N [%]) in the RE-NOVATE and RE-MODEL trials

Study	Worst event	Dabigatran 220 mg N (%)	Dabigatran 150 mg N (%)	Enoxaparin 40 mg N (%)
RE-MODEL and RE-NOVATE Knee/Hip Pivotal	FAS-major*	1415 (100.0)	1415 (100.0)	1428 (100.0)
	VTE-death	1 (0.1)	4 (0.3)	1 (0.1)
	PE	5 (0.4)	1 (0.1)	3 (0.2)
	Proximal DVT	35 (2.5)	53 (3.7)	50 (3.5)
	Major VTE/VTE mortality	41 (2.9)	58 (4.1)	54 (3.8)

* Full analysis set – major

Table 5: Major bleeding events by treatment in the individual RE-MODEL and the RE-NOVATE studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
Treated patients N	1146	1163	1154
Number of MBE N(%)	23 (2.0)	15 (1.3)	18 (1.6)
RE-NOVATE II (hip)			
Treated patients N	1010		1003
Number of MBE N(%)	14 (1.4)		9 (0.9)
RE-MODEL (knee)			
Treated patients N	679	703	694
Number of MBE N(%)	10 (1.5)	9 (1.3)	9 (1.3)

Major bleeding events (MBE) followed the International Society on Thrombosis and Haemostasis (ISTH) criteria and the EMEA guideline (including surgical wound site bleedings)

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

The clinical evidence for the efficacy of dabigatran etexilate is derived from the RE-LY study (Randomised Evaluation of Long–term anticoagulant therapy) a multi-centre, multinational, randomised parallel group study of two blinded doses of dabigatran (110 mg twice daily and 150 mg twice daily) compared to open-label warfarin in patients with non-valvular atrial fibrillation (AF) at moderate to high risk of stroke or systemic embolism. This trial used the Prospective Randomised Open label trial with Blinded Evaluation of outcomes (PROBE) design. The primary objective in this study was to determine if dabigatran was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke and systemic embolic events (SEE).

In the RE-LY study, a total of 18,113 patients were randomised, with a mean age of 71.5 years and a mean $CHADS_2$ score of 2.1. The population had approximately equal proportions of patients with $CHADS_2$ score 1, 2 and ≥3. The patient population was 64% male, 70% Caucasian and 16% Asian. RE-LY had a median treatment of 20 months with dabigatran etexilate given as fixed dose without coagulation

monitoring. In addition to documented non-valvular AF e.g. persistent, paroxysmal or permanent AF, patients had one of the following additional risk factors for stroke:

- Previous stroke, transient ischaemic attack or systemic embolism
- Left ventricular ejection fraction ≤40%
- Symptomatic heart failure, ≥NYHA Class 2
- Age ≥75 years
- Age ≥65 years associated with one of the following: diabetes mellitus, coronary artery disease (CAD), or hypertension.

Patients were excluded if they had prosthetic heart valves requiring anticoagulation or with haemodynamically relevant valve disease that was expected to require surgical intervention during the course of the study; severe disabling stroke within the previous 6 months or any stroke within the previous 14 days; conditions associated with an increased risk of bleeding – major surgery in the previous month, planned surgery or intervention in the next 3 months, history of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding unless the causative factor has been permanently eliminated or repaired (e.g. by surgery); gastrointestinal haemorrhage within the past year unless the cause has been permanently eliminated (e.g. surgery); symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days; haemorrhagic disorder or bleeding diathesis; need for anticoagulant treatment for disorders other than atrial fibrillation; fibrinolytic agents within 48 hours of study entry; uncontrolled hypertension (SBP >180 mmHg and/or DBP >100 mmHg); recent malignancy or radiation therapy (≤6 months) and not expected to survive 3 years; contraindication to warfarin treatment; reversible causes of atrial fibrillation (e.g. cardiac surgery, pulmonary embolism, untreated hyperthyroidism); plan to perform a pulmonary vein ablation or surgery for cure of the AF; severe renal impairment (estimated creatinine clearance ≤30 mL/min); active infective endocarditis; active liver disease, including but not limited to persistent ALT, AST, alkaline phosphatase ≥2 X ULN, known active hepatitis C, active hepatitis B, active hepatitis A; women who were pregnant, lactating or of childbearing potential who refused to use a medically acceptable form of contraception throughout the study; anaemia (haemoglobin <100 g/L) or thrombocytopenia (platelet count <100 X 10^9/L); patients who had developed transaminase elevations upon exposure to ximelagatran; patients who had received an investigational drug in the past 30 days or were participating in another drug study; patients considered unreliable by the investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration.

The concomitant diseases of patients in this trial included hypertension 79%, diabetes 23% and CAD 28%. 50% of the patient population was vitamin K antagonist (VKA) naïve defined as less than 2 months total life time exposure. 32% of the population had never been exposed to a VKA. For those patients randomised to warfarin, the time in therapeutic range (INR 2 to 3) for the trial was a median of 67%. Concomitant medications included aspirin (25% of subjects used at least 50% of the time in study), clopidogrel (3.6%), ASA+clopidogrel (2%), NSAIDs (6.3%), beta-blockers (63.4%), diuretics (53.9%), statins (46.4%), ACE-inhibitors (44.6%), angiotensin receptor blockers (26.1%), oral hypoglycaemics (17.5%), insulin (5.2%), digoxin (29.4%), amiodarone (11.3%), diltiazem (8.9%), verapamil (5.4%) and proton pump inhibitors (17.8%).

For the primary endpoint, stroke and systemic embolism, no subgroups (i.e. age, weight, gender, renal function, ethnicity, etc.) were identified with a different risk ratio compared to warfarin.

Based on the intent to treat population analysis, this study demonstrated that dabigatran etexilate, at a dose of 150 mg twice daily, is superior to warfarin in the prevention of stroke and systemic embolism in patients with atrial fibrillation. The lower dose of 110 mg twice daily is non-inferior to warfarin (see Table 6).

Dabigatran etexilate 150 mg twice daily reduces other clinically relevant endpoints: ischaemic stroke, haemorrhagic stroke, intracranial haemorrhage and total bleeding compared to warfarin, with similar rates of major bleeding (see Tables 7 and 17). Dabigatran etexilate 110 mg twice daily reduces the risk of intracranial haemorrhage, major bleeding and total bleeding (see Table 17). The yearly event rate for vascular death for dabigatran etexilate 150 mg twice daily was 2.28%, 110 mg twice daily was 2.43% and warfarin was 2.69%.

There was an increased frequency in myocardial infarction events in subjects treated with dabigatran etexilate compared to warfarin treated subjects, which was not statistically significant (yearly event rate: 150 mg twice daily 0.81%, 110 mg twice daily 0.83%, warfarin 0.64%). Patients had similar baseline characteristics across the treatment groups, with respect to cardiovascular risk factors: hypertension, diabetes, prior coronary artery disease, prior MI, prior stroke, and active smoking. The baseline use of anti-platelet and antithrombotic therapies was similar across the three treatment groups. The reason for this finding is unknown.

Gastrointestinal (GI) haemorrhage occurred at a higher frequency with dabigatran etexilate compared to warfarin. The underlying mechanism of the increased rate of GI bleeding has not been established.

Figure 1: Kaplan-Meier curve estimate of time to first stroke or systemic embolism in RE-LY

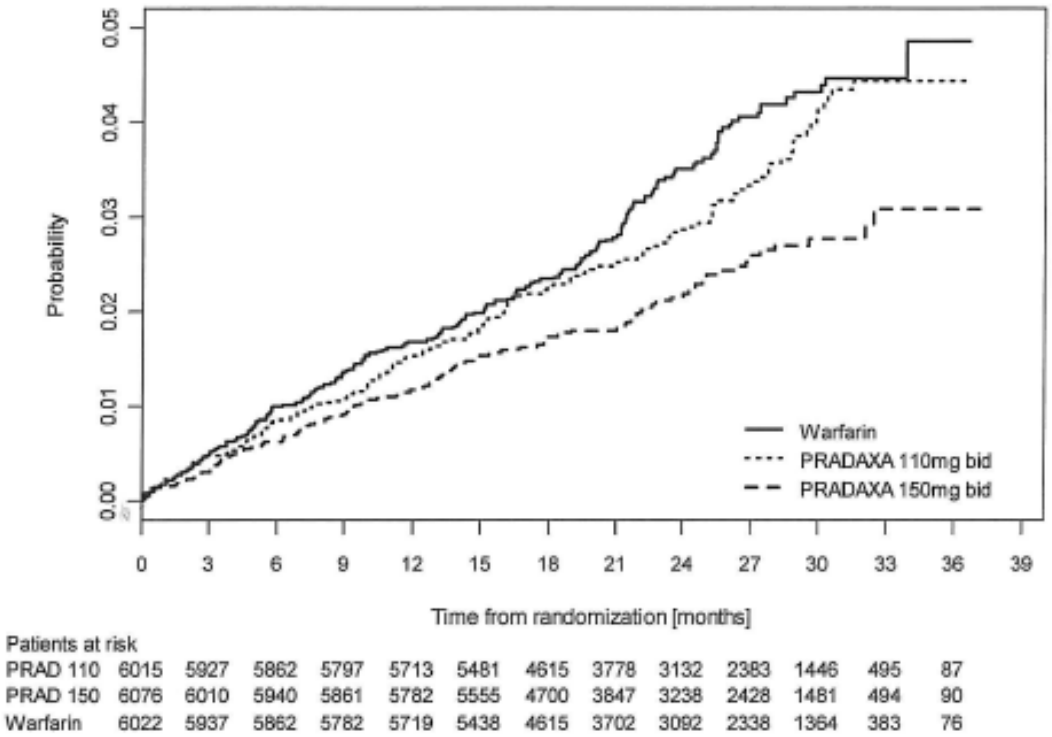


Table 6: Analysis of first occurrence of stroke or systemic embolism (primary endpoint) during the study period in RE-LY

	Dabigatran etexilate 150 mg twice daily	Dabigatran etexilate 110 mg twice daily	Warfarin
Subjects randomised	6076	6015	6022
Subject-years	12033	11899	11794
Stroke and/or SEE			
Yearly event rate (%)	134 (1.11)	183 (1.54)	202 (1.71)
Hazard ratio over warfarin (95% CI)	0.65 (0.52, 0.81)	0.90 (0.74, 1.10)	
p-value superiority	0.0001	0.2943	
p-value noninferiority	<0.0001	<0.0001	

% refers to yearly event rate (calculated as number of subjects with events divided by subject-years and multiplied by 100)

Table 7: Analysis of first occurrence of stroke, systemic embolism, ischaemic or haemorrhagic strokes during the study period in RE-LY

	Dabigatran etexilate 150 mg twice daily	Dabigatran etexilate 110 mg twice daily	Warfarin
Subjects randomised	6076	6015	6022
Subject-years	12033	11899	11794
Stroke			
Yearly event rate (%)	122 (1.01)	171 (1.44)	186 (1.58)
Hazard ratio vs. warfarin (95% CI)	0.64 (0.51, 0.81)	0.91 (0.74, 1.12)	
SEE			
Yearly event rate (%)	13 (0.11)	15 (0.13)	21 (0.18)
Hazard ratio vs. warfarin (95% CI)	0.61 (0.30, 1.21)	0.71 (0.37, 1.38)	
Ischaemic stroke			
Yearly event rate (%)	103 (0.86)	152 (1.28)	134 (1.14)
Hazard ratio vs. warfarin (95% CI)	0.75 (0.58, 0.97)	1.13 (0.89, 1.42)	
Haemorrhagic stroke			
Yearly event rate (%)	12 (0.10)	14 (0.12)	45 (0.38)
Hazard ratio vs. warfarin (95% CI)	0.26 (0.14, 0.49)	0.31 (0.17, 0.56)	

% refers to yearly event rate (calculated as number of subjects with events divided by subject-years and multiplied by 100)

Table 8: Analysis of pulmonary embolism and myocardial infarction during the study period in RE-LY

	Dabigatran etexilate 150 mg twice daily	Dabigatran etexilate 110 mg twice daily	Warfarin
Subjects randomised	6076	6015	6022
Subject-years	12033	11899	11794
Pulmonary embolism			
Yearly event rate (%)	18 (0.15)	14 (0.12)	12 (0.10)
Hazard ratio vs. warfarin (95% CI)	1.41 (0.71, 3.06)	1.16 (0.54, 2.51)	
Myocardial infarction			
Yearly event rate (%)	97 (0.81)	98 (0.82)	75 (0.64)
Hazard ratio vs. warfarin (95% CI)	1.27 (0.94, 1.71)	1.29 (0.96, 1.75)	

% refers to yearly event rate (calculated as number of subjects with events divided by subject-years and multiplied by 100)

Table 9: Major bleeding events by age group during the study period in RE-LY

Age (years)	# of subjects	Dabigatran etexilate 110 mg twice daily Yearly event rate (%/ year)	Dabigatran etexilate 150 mg twice daily Yearly event rate (%/ year)	Warfarin Yearly event rate (%/ year)
<65	2981	0.81	0.88	2.43
>65 - <75	7894	2.29	2.60	3.24
≥ 75	7238	4.44	5.12	4.39

% refers to yearly event rate (calculated as number of subjects with events divided by subject-years and multiplied by 100)

INDICATIONS

Prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement). (see Dosage and Administration section for details of treatment duration).

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.

CONTRAINDICATIONS

- Known hypersensitivity to dabigatran or dabigatran etexilate or to one of the excipients of the product.
- Severe renal impairment (CrCl <30 mL/min).
- Haemorrhagic manifestations, patients with a bleeding diathesis, or patients with spontaneous or pharmacological impairment of haemostasis.
- Organ lesions at risk of clinically significant bleeding, including haemorrhagic stroke within the last 6 months, active peptic ulcer disease with recent bleeding.
- Indwelling spinal or epidural catheter and during the first two hours after removal (see Precautions).
- Hepatic impairment or liver disease expected to have any impact on survival.
- History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding.
- Gastrointestinal haemorrhage within the past year unless the cause has been permanently eliminated, e.g. by surgery.
- Conditions associated with increased risk of bleeding (see Precautions, Haemorrhagic risk, Table 10 Diseases / procedures with special haemorrhagic risks).
- Concomitant treatment with systemic ketoconazole (see Precautions).

- Simultaneous initiation of treatment with dabigatran etexilate and oral verapamil.

- Treatment initiation with oral verapamil in patients following major orthopaedic surgery who are already treated with dabigatran etexilate.

PRECAUTIONS

Haemorrhagic risk

Dabigatran etexilate increases the risk of bleeding and can cause significant and sometimes fatal bleeding. As with all anticoagulants, dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding. Bleeding can occur at any site during therapy with dabigatran. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.

The INR test is unreliable in patients on PRADAXA and false positive INR elevations have been reported. Therefore INR tests should not be performed. Tests of anticoagulant activity such as thrombin time (TT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) are available to detect excessive dabigatran activity. Dabigatran related anticoagulation can be assessed by ECT or TT. If ECT or TT is not available, the aPTT test provides an approximation of PRADAXA's anticoagulant activity.

In atrial fibrillation patients in RE-LY an aPTT of greater than 2.0–3.0 fold of normal range was associated with an increased risk of bleeding.

Pharmacokinetic studies demonstrated an increase in drug exposure in patients with reduced renal function including age-related decline of renal function. Dabigatran etexilate is contraindicated in cases of severe renal impairment (CrCL <30 mL/min).

Patients who develop acute renal failure should discontinue dabigatran etexilate.

Factors, such as decreased renal function (30–50 mL/min CrCL), age ≥75 years or strong P-glycoprotein (P-gp) inhibitor comedication are associated with increased dabigatran plasma levels. The presence of one or more of these factors may increase the risk of bleeding (see Dosage and Administration).

The concomitant use of PRADAXA with the following treatments has not been studied and may increase the risk of bleeding: unfractionated heparins (except at doses necessary to maintain patency of central venous or arterial catheter) and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, rivaroxaban, prasugrel, ticagrelor, vitamin K antagonists, and the P-gp inhibitors itraconazole, tacrolimus, cyclosporin, ritonavir, tipranavir, nelfinavir and saquinavir (see Interactions with other medicines, Anticoagulants and platelet aggregation agents).

The concomitant use of dronedarone increases exposure of dabigatran and is not recommended.

Bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (SSRI).

Close clinical surveillance (looking for signs of bleeding or anaemia) is recommended throughout the treatment period, especially if risk factors (as summarised in Table 10) are combined.

Table 10: Factors known to increase the haemorrhagic risk as identified in clinical studies

Factors increasing dabigatran plasma levels	• Moderate renal impairment (30-50 mL/min CrCL) • Selected P-glycoprotein-inhibitor comedication
Pharmacodynamic interactions	• Acetylsalicylic acid (ASA) • Non Steroidal Antiinflammatory Drugs (NSAID) • Clopidogrel
Diseases / procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Active ulcerative gastrointestinal disease • Recent gastro-intestinal bleeding • Recent biopsy or major trauma • Recent intracranial haemorrhage • Brain, spinal or ophthalmic surgery • Bacterial endocarditis
Others	• Age ≥ 75 years

NSAIDs (half-lives <12 hours) given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. For the 220 mg dose of dabigatran etexilate, the bleeding incidence associated with NSAIDs is 1.5% compared to 1.4% for all patients. Concomitant use of NSAIDs with half-lives greater than 12 hours should be undertaken with caution.

The increase in yearly event rates of major bleeds by concomitant medications in the RE-LY study are shown in Table 11.

Table 11: Analysis of increase in major bleeding events by concomitant medications in RE-LY

Concomitant Medication	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
	Fold Increase in Yearly Event Rates of Major Bleeding		
Acetylsalicylic Acid (ASA)	1.91	1.95	1.93
Clopidogrel	2.06	1.92	2.02
COX-2 Inhibitors	1.63	1.60	1.81
Non Steriodal Antiinflammatory Drugs (NSAIDs)	1.53	1.36	1.49
Proton Pump Inhibitors	2.57	3.45	2.72
Verapamil	1.10	1.33	1.06
H2 blockers	2.59	2.30	2.35

Patients taking dabigatran etexilate with PPIs or H2-blockers may be at increased risk of gastrointestinal bleeding due to the associated gastrointestinal conditions for which these drugs are prescribed.

Gastrointestinal bleeds

Gastrointestinal (GI) haemorrhage occurred at a higher frequency with dabigatran etexilate compared to warfarin (see Adverse Effects, Table 18). The underlying mechanism of the increased rate of GI bleeding has not been established. Patients with an increased risk of bleeding (e.g. recent gastrointestinal bleeding), should be closely monitored clinically (looking for signs of bleeding or anaemia). In such patients, a dose of 220 mg, given as 110 mg twice daily may be considered. A coagulation test, such as aPTT (see Precautions, Effect on laboratory tests), may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure.

Achlorhydria

See Interactions with other medicines, Co-medication with gastric pH-elevating agents, Pantoprazole for effect of elevated gastric pH on dabigatran bioavailability.

Myocardial Infarction

There was an increased frequency in myocardial infarction events in subjects treated with dabigatran etexilate compared to warfarin treated subjects, which was not statistically significant (see Clinical Trials and Adverse Effects).

Interaction with P-glycoprotein inducers

The concomitant use of dabigatran etexilate with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St John's Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should generally be avoided (see Precautions, Interactions with other medicines).

Interaction with P-glycoprotein inhibitors

Coadministration of dabigatran etexilate with strong P-gp inhibitors (amiodarone, clarithromycin, nelfinavir, ritonavir, saquinavir, and verapamil) should be used with caution and close clinical surveillance (looking for signs of active bleeding or anaemia) is required, due to a potential risk of higher plasma levels of dabigatran and consequent potentially exaggerated pharmacodynamic effect of dabigatran etexilate (notably bleeding risk) (see Precautions, Interactions with other medicines). The concomitant use of dabigatran etexilate with cyclosporin, tacrolimus or itraconazole is not recommended.

Hepatic Impairment

Patients with liver disease expected to have any impact on survival or with elevated liver enzymes >2 Upper Limit Normal (ULN) were excluded in clinical trials. Therefore the use of dabigatran etexilate is contraindicated in this population. A liver function test is recommended prior to initiating treatment.

Renal Impairment

Pharmacokinetic studies demonstrated up to a 3 fold increase in drug exposure in patients with reduced renal function including age-related decline of renal function (see Pharmacokinetics). In patients with moderate renal impairment in RE-LY, the observed major bleeding rate was comparable between dabigatran 110 mg and 150 mg (dabigatran 110 mg 5.65%/year versus dabigatran 150 mg 5.27%/year versus warfarin 5.68%/year). Based on theoretical considerations of drug exposure a reduced dose may be considered in these patients (see Dosage and Administration). The presence of one or more factors known to increase haemorrhagic risk (see Table 10) may increase the risk of bleeding. Caution should be exercised. Close clinical surveillance is recommended.

Dabigatran etexilate is contraindicated in cases of severe renal impairment (CrCL < 30 mL/min).

Patients who develop acute renal failure should discontinue dabigatran etexilate.

Surgery and Interventions

Patients on dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore surgical interventions may require the temporary discontinuation of dabigatran etexilate.

<u>Preoperative Phase</u>

Due to an increased risk of bleeding dabigatran etexilate may be stopped temporarily in advance of invasive or surgical procedures. If possible, dabigatran etexilate should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete haemostasis may be required, consider stopping dabigatran etexilate 2-4 days before surgery. Clearance of dabigatran in patients with renal insufficiency may take

longer. This should be considered in advance of any procedures (see Table 12 below).

Table 12: Discontinuation rules before invasive or surgical procedures

Renal function (CrCL in mL/min)	Estimated half-life (hours)	Stop dabigatran before elective surgery	
		High risk of bleeding or major surgery	Standard risk
≥80	~13*	2 days before	24 hours before
≥50-<80	~15*	2-3 days before	1-2 days before
≥30-<50	~18*	4 days before	2-3 days before (>48 hours)

*for more details see Pharmacokinetics, Absorption, Table 1

Dabigatran etexilate is contraindicated in patients with severe renal dysfunction (CrCL <30 mL/min) but should this occur then dabigatran etexilate should be stopped at least 5 days before major surgery.

If an acute intervention is required, dabigatran etexilate should be temporarily discontinued. A surgery/ intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed there may be an increase in the risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention (for cardioversion see Dosage and Administration, Special patient populations).

Spinal Anaesthesia/Epidural Anaesthesia/Lumbar Puncture

Procedures such as spinal anaesthesia may require complete haemostatic function. In patients treated with dabigatran etexilate and who undergo spinal or epidural anaesthesia, or in whom lumbar puncture is performed in follow-up to surgery, the formation of spinal or epidural haematomas that may result in long-term or permanent paralysis cannot be excluded.

The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged postoperative use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms.

Post Procedural Period

Resume treatment after complete haemostasis is achieved.

Hip fracture surgery

There is no data on the use of dabigatran etexilate in patients undergoing hip fracture surgery. Therefore treatment is not recommended.

Effects on fertility

Rat fertility was unaffected by treatment with dabigatran etexilate at oral doses of up to 200 mg/kg/day (approximately 4-5 times clinical exposure, based on AUC). There

was a significant decrease in the number of implantations at 70 and 200 mg/kg/day (3 and 4 times clinical exposure, respectively based on AUC), which was associated with an increase in pre-implantation loss. The effect on human fertility is unknown.

Use in pregnancy (Category C)

Anticoagulants and thrombolytic agents can produce placental haemorrhage and subsequent prematurity and foetal loss. There are no adequate and well-controlled studies in pregnant women. It is not known whether dabigatran etexilate can cause foetal harm when administered to pregnant women. Dabigatran etexilate should not be used during pregnancy.

Studies in rats have shown that small amounts of dabigatran and/or its metabolites cross the placenta.

Embryofoetal development studies with oral dabigatran etexilate showed delayed ossification and general disturbances in foetal development of rats at 15 and 70 mg/kg/day (1 to 4 fold anticipated human exposure based on AUC). The delayed ossification, however, was transient, since offspring of rats treated with 15, 30 and 70 mg/kg/day during gestation and lactation showed normal body weights, normal body weight development, normal survival after birth and normal physical postnatal development. Morphogenic effects such as cleft thoracal vertebral body (rats) and dilated cerebral ventricles (rabbits) were seen at a maternotoxic dose of 200 mg/kg/day (relative exposure of 8 and 13, respectively). Maternal toxicity in rats at >70 mg/kg/day was associated with an increased rate of resorptions, and a significant decrease in viable foetuses was seen at 200 mg/kg/day. In rats allowed to deliver, mortality due to excessive vaginal bleeding was seen at 70 mg/kg/day and in one dam at 15 mg/kg/day. An increase in post-implantation loss was seen at 70 mg/kg/day in these animals.

Use in lactation

Dabigatran and/or its metabolites were present in the milk of lactating rats given oral doses of dabigatran etexilate. The ratio of the dabigatran concentration in rat milk to that in the plasma of the mothers was 0.4. No clinical data are available. As a precaution, use of dabigatran etexilate is not recommended in women who are breast-feeding.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Paediatric use

There is no experience in children. Dabigatran etexilate has not been investigated in patients <18 years of age. Treatment of children with dabigatran etexilate is not recommended.

Use in the elderly

The clinical studies have been conducted in a patient population with a mean age >65 years. Patients should be treated with the dose of dabigatran etexilate as recommended in the Dosage and Administration section. Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function (see Precautions, Renal Impairment). The risk of stroke is higher in the elderly, however the risk of bleeding increases with increasing age (see Table 9). Careful clinical observation is advised and a dosage adjustment may be necessary in elderly patients (≥75 years) due in part to age-related impairment of renal function (see Table 10). These patients should be treated with caution (see Dosage and Administration), particularly if they are also taking a drug which is a P-glycoprotein inhibitor (see Precautions, Interaction with P-glycoprotein inhibitors).

Trauma

Patients who are at increased risk of trauma accidents or surgery may have a higher risk of traumatic bleeding.

Body Weight

Limited data in patients <50 kg are available (see Pharmacokinetics, Special populations, Body weight).

Carcinogenicity

Carcinogenicity studies were performed with dabigatran etexilate in mice and rats for up to 2 years. An increased incidence of granulosa cell tumours without increased incidence of preneoplastic precursor lesions was seen in the ovaries of rats treated at 100 and 200 mg/kg/day (3 and 8 times clinical exposure, respectively based on AUC). 10 adverse event reports referring to ovarian masses or adnexal masses were observed during the RE-LY trial. The mechanism for the ovarian effects in animals is unclear and the long term effects for humans are unknown, although dabigatran etexilate is not expected to pose a carcinogenic risk to humans. No tumours were seen in rats at 30 mg/kg/day (similar to clinical exposure at the maximum recommended dose) or in studies in mice.

Genotoxicity

Dabigatran etexilate and its active moiety, dabigatran, were not mutagenic in a bacterial reverse mutation assay (Ames test) and did not induce mutations or chromosome damage in mouse lymphoma cells. Dabigatran etexilate was negative at doses of up to 2000 mg/kg in rats in the mammalian erythrocyte micronucleus test.

Excipients

The product contains the excipient sunset yellow FCF CI15985, which may cause allergic reactions.

Interactions with other medicines

Interaction studies have only been performed in adults.

Anticoagulants and platelet aggregation agents

The following treatments are not recommended concomitantly with dabigatran etexilate: unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, dextran, sulfinpyrazone and vitamin K antagonists. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter (see Dosage and Administration and Precautions, Haemorrhagic risk).

Enoxaparin: The switch from enoxaparin to dabigatran has been clinically tested in a phase I study. After 3 days treatment of once daily 40 mg enoxaparin s.c., dabigatran exposure was slightly lower 24 hours following the last dose of enoxaparin than after administration of dabigatran etexilate (single dose of 220 mg) alone. A higher anti-FXa/FIIa activity was observed after dabigatran administration with enoxaparin pre-treatment compared to that after treatment with dabigatran alone, which was considered to be due to the carry-over effect of enoxaparin treatment. The other dabigatran-related anti-coagulation tests, i.e., aPTT, ECT and TT, were mainly not affected after a 24 hour washout of enoxaparin.

Interactions linked to dabigatran etexilate and dabigatran metabolic profile

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and had no *in vitro* effects on human cytochrome P450 enzymes. This has been confirmed by *in vivo* studies with healthy volunteers, who did not show any interaction between this treatment and the following drugs: atorvastatin (CYP3A4) and diclofenac (CYP2C9). Therefore, related medicinal product interactions are not expected with dabigatran.

Atorvastatin: When dabigatran etexilate was coadministered with atorvastatin, exposure of atorvastatin, atorvastatin metabolites and of dabigatran were unchanged indicating a lack of interaction.

Diclofenac: When dabigatran etexilate was coadministered with diclofenac, the plasma exposure of both medicinal products remained unchanged indicating a lack of a pharmacokinetic interaction between dabigatran etexilate and diclofenac. However, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives >12 hours, close observation for signs of bleeding is recommended (see Precautions, Haemorrhagic risk).

P-glycoprotein inhibitors/inducers

The pro-drug dabigatran etexilate but not dabigatran is a substrate of the efflux transporter P-gp. Therefore, co-administration of dabigatran etexilate and a P-gp inhibitor or inducer may alter the plasma dabigatran concentration. Co-medications with P-gp transporter inhibitors and inducers have been investigated.

Co-medication with P-glycoprotein inhibitors

Amiodarone: When dabigatran etexilate was coadministered with a single dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and C_{max} were increased by about 1.6-fold and 1.5-fold (+60% and 50%), respectively. The mechanism of the interaction has not been completely clarified. In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone.

Verapamil: When dabigatran etexilate was coadministered with oral verapamil, the C_{max} and AUC of dabigatran were increased depending on timing of administration and formulation of verapamil.

The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to dabigatran etexilate intake (increase of C_{max} by about 2.8-fold (+180%) and AUC by about 2.5-fold (+150%)). The effect was progressively decreased with administration of an extended release formulation (increase of C_{max} by about 1.9-fold (+90%) and AUC by about 1.7-fold (+70%)) or administration of multiple doses of verapamil (increase of C_{max} by about 1.6-fold (+60%) and AUC by about 1.5-fold (+50%)). This can be explained by the induction of P-gp in the gut by chronic verapamil treatment.

There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_{max} by about 10% and AUC by about 20%). This is explained by completed dabigatran absorption after 2 hours.

No data are available for the parenteral application of verapamil; based on the mechanism of the interaction, no meaningful interaction is expected.

In the RE-LY study, patients treated concomitantly with verapamil had on average a 16% higher trough dabigatran plasma concentration and a 20% higher 2 hours post-dose dabigatran plasma concentration only, compared to patients who were not on concomitant verapamil. Accordingly, the annualised bleeding rates in patients who had used verapamil at least once together with warfarin, dabigatran etexilate 110 mg twice daily or 150 mg twice daily were 3.33%, 3.09% and 3.92%, respectively.

Clarithromycin: When clarithromycin 500 mg bid was administered together with dabigatran etexilate no clinically relevant PK-interaction was observed (increase of C_{max} by about 19% and AUC by about 15%).

Ketoconazole: Systemic ketoconazole increased total dabigatran $AUC_{0-\infty}$ and C_{max} values by about 2.4-fold (+138% and 135%), respectively, after a single dose of 400 mg, and about 2.5-fold (+153% and 149%), respectively, after multiple dosing of 400 mg ketoconazole once daily. The time to peak, terminal half-life and mean residence

time were not affected by ketoconazole. Concomitant administration of systemic ketoconazole is contraindicated.

Quinidine: Quinidine was given as 200 mg dose every 2nd hour up to a dose of 1000 mg. Dabigatran etexilate was given twice daily over 3 consecutive days, on the 3rd day with or without quinidine. Dabigatran $AUC_{\tau,ss}$ and C_{max},ss were increased on average by about 1.5-fold (+53% and 56%), respectively with concomitant quinidine.

Co-medication with P-glycoprotein inducers

Rifampicin: Pre-dosing of the probe inducer rifampicin at a dose of 600 mg once daily for 7 days decreased total dabigatran peak and total exposure by 65.5% and 67%, respectively. The inducing effect was diminished resulting in dabigatran exposure close to the reference by day 7 after cessation of rifampicin treatment. No further increase in bioavailability was observed after another 7 days.

The concomitant use of PRADAXA with P-gp inducers reduces exposure to dabigatran and should generally be avoided.

Co-medication with P-glycoprotein substrates

Digoxin: When dabigatran etexilate was coadministered with digoxin, no changes to digoxin plasma levels and no clinically relevant changes to dabigatran exposure have been observed.

Co-medication with platelet inhibitors

Acetylsalicylic acid (ASA, aspirin): The effect of concomitant administration of dabigatran etexilate and ASA on the risk of bleeds was studied in patients with atrial fibrillation in a phase II study in which randomised ASA coadministration was applied. Based on logistic regression analysis, co-administration of ASA and 150 mg dabigatran etexilate twice daily may increase the risk for any bleeding from 12% to 18% and 24% with 81 mg and 325 mg ASA, respectively.

From the data gathered in the phase III study RE-LY it was observed that ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110 mg or 150 mg twice daily may increase the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was, however, also observed for warfarin (see Precautions, Haemorrhagic risk, Table 11).

NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. There is limited evidence regarding the use of regular NSAID medication with half-lives of less than 12 hours during treatment with dabigatran etexilate and this has not suggested additional bleeding risk.

NSAIDs increased the risk of bleeding in RE-LY in all treatment groups.

Clopidogrel: In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times (CBT) compared to clopidogrel monotherapy. In addition, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ and the coagulation

measures for dabigatran effect, aPTT, ECT or TT (anti FIIa), or the inhibition of platelet aggregation (IPA) as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective monotreatments. With a loading dose of 300 or 600 mg clopidogrel, dabigatran $AUC_{t,ss}$ and $C_{max,ss}$ were increased by about 1.3- to 1.4-fold (+30% to 40%) (see ASA section above).

Antiplatelets or other anticoagulants: The concomitant use of dabigatran etexilate and antiplatelets or other anticoagulants may increase the risk of bleeding. See ASA and Clopidogrel sections above.

Co-medication with selective serotonin re-uptake inhibitors

SSRIs increased the risk of bleeding in RE-LY in all treatment groups.

Co-medication with gastric pH-elevating agents

Pantoprazole: When dabigatran etexilate was coadministered with pantoprazole, a decrease in dabigatran area under the plasma concentration – time curve of approximately 30% was observed. Pantoprazole and other proton-pump inhibitors (PPIs) were co-administered with dabigatran etexilate in clinical trials and no effects on bleeding or efficacy were observed.

Ranitidine: Ranitidine administration together with dabigatran etexilate had no meaningful effect on the extent of absorption of dabigatran.

The changes in dabigatran exposure determined by population pharmacokinetic analysis caused by PPIs and antacids were not considered clinically relevant because the magnitude of the effect was minor (fractional decrease in bioavailability not significant for antacids and 14.6% for PPIs).

In the phase III study RE-LY PPI co-medication did not result in lower trough levels and on average only slightly reduced post-dose concentrations (-11%). Accordingly, PPI comedication seemed to not be associated with a higher incidence of stroke or systemic embolism, especially in comparison with warfarin, and hence, the reduced bioavailability by pantoprazole co-administration seemed to be of no clinical relevance. An increased risk of bleeding with PPIs and H2 antagonists was observed for both the dabigatran and warfarin treatment groups (see Precautions, Haemorrhagic risk, Table 11). Patients taking PPIs or H2-blockers may be at increased risk of gastrointestinal bleeding due to the associated gastrointestinal conditions for which these drugs are prescribed.

Effect on laboratory tests

The aPTT test may be useful in determining an excess of anticoagulant activity. Dabigatran concentration exceeding 450 – 500 ng/mL would result in an aPTT of greater than 2.5 times control. An aPTT greater than 2.5 times control is suggestive of excess anticoagulation (see Pharmacology).

ADVERSE EFFECTS

The safety of dabigatran etexilate has been evaluated overall in 22,687 patients.

In the primary VTE prevention trials after major orthopaedic surgery a total of 10,596 patients were treated in 5 controlled studies with at least one dose of study medication. Of these 5,674 were treated with 150 or 220 mg once daily of dabigatran etexilate, while 522 received doses less than 150 mg once daily and 1,168 received doses in excess of 220 mg once daily.

In the RE-LY trial investigating the prevention of stroke and systemic embolism in patients with atrial fibrillation a total of 12,091 patients were enrolled. Of these 6,076 were treated with 150 mg twice daily of dabigatran etexilate, while 6,015 received doses of 110 mg twice daily.

In total, about 9% of patients treated for elective hip or knee surgery (short-term treatment for up to 42 days) and 22% of patients with atrial fibrillation treated for the prevention of stroke and systemic embolism (long-term treatment for up to 3 years) experienced adverse reactions.

Bleeding

Bleeding is the most relevant side effect of dabigatran etexilate. Depending on the indication treated, bleeding of any type or severity occurred in approximately 14% of patients treated short-term for elective hip or knee replacement surgery and in 16.5% yearly of AF patients treated long-term for the prevention of stroke and systemic embolism.

Although rare in frequency in clinical trials, major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

Prevention of venous thromboembolic events (VTE) in adult patients who have undergone major orthopaedic surgery

A total of 10,596 patients were treated in 5 controlled VTE prevention trials with at least one dose of study medication. Of these 5,674 were treated with 150 or 220 mg daily of dabigatran etexilate, while 522 received doses less than 150 mg daily and 1,168 received doses in excess of 220 mg daily.

The adverse reactions that can with reasonable certainty be attributed to dabigatran, and occurred with a similar frequency with enoxaparin, are those of bleeding or signs of bleeding e.g. anaemia and wound discharge. The definition of major bleeding events (MBE) followed the International Society on Thrombosis and Haemostasis (ISTH) criteria and the EMEA guideline. According to the MedDRA coding system, bleeding events are distributed over several System Organ Classes (SOC); therefore, a summary description of major and any bleeding is given in Table 13 below.

Table 13 shows the number (%) of patients experiencing major and total bleeding event rates during the treatment period in the VTE prevention randomised clinical trials, according to dose.

Table 13: Bleeding broken down to randomisation procedure, severity and dosage of dabigatran etexilate and enoxaparin

Pre-operative randomisation trials			
	150 mg N (%)	220 mg N (%)	Enoxaparin 40 mg N (%)
Pooled data BISTRO II, RE-MODEL, RE-NOVATE trials (1160.19, 1160.25, and 1160.48)			
Treated	1866 (100.0)	1825 (100.0)	2240 (100.0)
Major Bleeding	24 (1.3)	33 (1.8)	35 (1.6)
Any bleeding	258 (13.8)	251 (13.8)	290 (12.9)
Pooled data from hip and knee studies, RE-MODEL and RE-NOVATE trials (1160.25, 1160.48)			
Treated	1866 (100.0)	1825 (100.0)	1848 (100.0)
Major Bleeding	24 (1.3)	33 (1.8)	27 (1.5)
Any bleeding	258 (13.8)	251 (13.8)	247 (13.4)
Post-operative randomised trials			
RE-MOBILIZE trial (1160.24)			
Treated	871 (100.0)	857 (100.0)	868 (100.0)
Major Bleeding	5 (0.6)	5 (0.6)	12 (1.4)
Any bleeding	72 (8.3)	74 (8.6)	84 (9.7)
Japanese knee study (1160.50)			
	150 mg N (%)	220 mg N (%)	Placebo N (%)
Treated	126 (100.0)	129 (100.0)	124 (100.0)
Major Bleeding	0 (0.0)	3 (2.3)	1 (0.8)
Any bleeding	13 (10.3)	14 (10.9)	10 (8.1)
Pooled data RE-MOBILIZE and Japanese knee study (1160.24, and 1160.50)			
	150 mg N (%)	220 mg N (%)	Enoxaparin 60 mg* N (%)
Treated	997 (100.0)	986 (100.0)	868 (100.0)
Major Bleeding	5 (0.5)	8 (0.8)	12 (1.4)
Any bleeding	85 (8.5)	88 (8.9)	84 (9.7)

*Bleeding data for Enoxaparin 60 mg is from RE-MOBILIZE study (1160.24)

Overall bleeding rates were similar between treatment groups and not significantly different.

Adverse reactions classified by System Organ Class (SOC) and preferred terms reported from any treatment group of all controlled VTE prevention studies are shown in the tables below.

Table 14: Adverse Reactions ≥1:100

SOC / Preferred Term.	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Numbers of patients	2737 (100)	2682 (100)	3181 (100)
Blood and lymphatic system			
Anaemia	110 (4.0)	117 (4.4)	141 (4.5)
Vascular disorders			
Haematoma	38 (1.4)	37 (1.4)	55 (1.8)
Wound haemorrhage	35 (1.3)	28 (1.0)	31 (1.0)
Investigations			
Haemoglobin decreased	45 (1.6)	35 (1.3)	74 (2.4)
Injury, poisoning and procedural complications			
Wound secretion	130 (4.7)	130 (4.8)	93 (3.0)
Post-procedural haematoma	66 (2.4)	45 (1.7)	78 (2.5)
Post-procedural haemorrhage	28 (1.5)	43 (2.4)	32 (1.7)
Anaemia post-operative	37 (1.4)	54 (2.0)	56 (1.8)
Traumatic haematoma	37 (1.4)	41 (1.5)	51 (1.6)
Post-procedural discharge	31 (1.1)	34 (1.3)	31 (1.0)
Renal and urinary			
Haematuria	34 (1.2)	31 (1.2)	25 (0.8)

Table 15: Adverse Reactions >1:1000 <1:100

SOC / Preferred Term.	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Numbers of patients	2737 (100)	2682 (100)	3108 (100)
Vascular disorders			
Haemorrhage	5 (0.2)	18 (0.7)	21 (0.7)
Musculoskeletal and cumulative tissue disorders			
Haemarthrosis	9 (0.3)	7 (0.3)	17 (0.5)
Blood and lymphatic system			
Thrombocytopenia	5 (0.2)	2 (0.1)	5 (0.2)
Respiratory and thoracic system			
Epistaxis	19 (0.7)	15 (0.6)	13 (0.4)
Gastro-intestinal disorders			
Gastro-intestinal haemorrhage	1 (0.0)	1 (0.0)	3 (0.1)
Haemorrhoidal haemorrhage	4 (0.1)	8 (0.3)	2 (0.1)
Rectal haemorrhage	12 (0.4)	15 (0.6)	5 (0.2)
Skin and sub-cutaneous tissue disorders			
Ecchymosis	16 (0.6)	16 (0.6)	21 (0.7)
General disorders and administration site conditions			
Bloody discharge	2 (0.1)	6 (0.2)	6 (0.2)
Catheter site haemorrhage	2 (0.1)	1 (0.0)	6 (0.2)
Investigations			
Occult blood positive	6 (0.2)	3 (0.1)	1 (0.0)
Blood urine present	4 (0.1)	2 (0.1)	0 (0.0)
Haematocrit decrease	0 (0.0)	6 (0.2)	4 (0.1)
Injury, poisoning and procedural complications			
Incision site haemorrhage	12 (0.4)	8 (0.3)	10 (0.3)
Surgical and medical procedures			
Post-procedural drainage	11 (0.4)	13 (0.5)	16 (0.5)
Wound drainage	1 (0.0)	4 (0.1)	2 (0.1)
Hepatobiliary disorders / Investigations *			
Alaninine aminotransferase increased	18 (0.7)	7 (0.3)	28 (0.9)
Aspartate aminotransferase increased	9 (0.3)	5 (0.2)	15 (0.5)
Hepatic enzyme increased	4 (0.1)	5 (0.2)	11 (0.4)
Hepatic function abnormal / Liver function test abnormal*	6 (0.2)	10 (0.4)	7 (0.2)
Transaminases increased	0 (0.0)	2 (0.1)	1 (0.1)

* SOC pooled because of equivalence of some preferred terms

Table 16: Beyond the reported ALT findings the following laboratory chemistry data had been measured in phase III controlled VTE prevention studies.

	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Numbers of patients	2737 (100)	2682 (100)	3108 (100)
Alaninine aminotransferase increased 3 x ULN	68 (2.5)	58 (2.2)	95 (3.5)

The pattern of adverse events for RE-NOVATE II (1160.64) was similar to RE-NOVATE (1160.48).

For RE-NOVATE II (1160.64), the incidence of MBEs was 1.4% for patients in the dabigatran etexilate 220 mg group and 0.9% for patients in the enoxaparin 40 mg group (p=0.4022). For any bleeding event the incidence was 9.7% for patients in the dabigatran group compared with 8.3% for patients in the enoxaparin group (p=0.2626). In both treatment groups most elevated LFTs occurred in the immediate post-operative period, during the first 10 days of treatment with trial medication, and most were transient. The estimated cumulative incidence of an ALT value >3 x ULN from surgery up to Day 10 was 3.1% for dabigatran patients and to the end of the trial it was 3.6%. Corresponding figures for enoxaparin showed a slightly higher cumulative incidence: 5.0% to Day 10 and 5.4% to the end of the trial. ALT elevations >10 x ULN were higher for dabigatran patients (0.4%) than enoxaparin patients (0.1%). Three patients (all dabigatran group) had alanine transaminase (ALT) elevations above 3 x the upper limit of the normal range (ULN) in combination with elevated bilirubin values above 2 x ULN. In two of these three patients alternative explanations (viral hepatitis) were reported.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

Two doses (110 mg and 150 mg twice daily) of dabigatran etexilate were compared to warfarin in the RE-LY study (Randomised Evaluation of Long - term anticoagulant therapy), the Phase III trial in the prevention of thromboembolic stroke and systemic embolism for safety in more than 18,000 atrial fibrillation patients with a median duration of 20 months.

<u>Drug Discontinuation</u>

Over the course of the trial, the total number of patients with adverse events leading to treatment discontinuation was 19% for dabigatran etexilate 110 mg, 20.5% for dabigatran etexilate 150 mg and 15.6% for warfarin. The most frequent adverse events leading to discontinuation were gastrointestinal events.

Bleeding Definitions

In the RE-LY study, bleeding was classified as major using the following guidelines.

Major bleeding fulfilled one or more of the following criteria:

- Bleeding associated with a reduction in haemoglobin of at least 20 grams per liter or leading to a transfusion of at least 2 units of blood or packed cells;
- Symptomatic bleeding in a critical area or organ: intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding.

Major bleeds were classified as life-threatening if they fulfilled one or more of the following criteria:

- Fatal bleed; symptomatic intracranial bleed; reduction in haemoglobin of at least 50 grams per litre; transfusion of at least 4 units of blood or packed cells; a bleed associated with hypotension requiring the use of intravenous inotropic agents; a bleed that necessitated surgical intervention.

Bleeding

Table 17 shows the number of patients experiencing major and total bleeding event rates during the treatment period in the RE-LY study, with the yearly bleeding rate in (%). Both dabigatran etexilate doses were associated with a lower yearly event rate for life-threatening bleeds, intracranial haemorrhage and any bleeds as compared with warfarin treatment. Subjects randomised to dabigatran etexilate 110 mg twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.80 [p=0.0026]).

In Table 17, the category of major bleeds includes both life-threatening and non-life threatening bleeds. Within life-threatening, intracranial bleeds are a subcategory of life-threatening bleeds. Intracranial bleeds include intracerebral (haemorrhagic stroke), subarachnoid and subdural bleeds. For this reason, these events may be counted in multiple categories.

Table 17: Frequency and yearly event rate (%) of major and other bleeding events in RE-LY.

	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Number of subjects	6015	6076	6022
Subject-years	11899	12033	11794
Major bleeds*	342 (2.87)	399 (3.32)	421 (3.57)
Hazard ratio vs. warfarin (95% CI)	0.80 (0.70, 0.93)	0.93 (0.81, 1.07)	
p-value	0.0026	0.3146	
Life threatening MBEs	147 (1.24)	179 (1.49)	218 (1.85)
Hazard ratio vs. warfarin (95% CI)	0.67 (0.54, 0.82)	0.80 (0.66, 0.98)	
p-value	0.0001	0.0305	
ICH+	27 (0.23)	38 (0.32)	90 (0.76)
Hazard ratio vs. warfarin (95% CI)	0.30 (0.19, 0.45)	0.41 (0.28, 0.60)	
p-value	<0.0001	<0.0001	
Any bleeds#	1754 (14.74)	1993 (16.56)	2166 (18.37)
Hazard ratio vs. warfarin (95% CI)	0.78 (0.73, 0.83)	0.91 (0.85, 0.96)	
p-value	<0.0001	0.0016	

*Adjudicated Bleeds
+ICH consists of adjudicated haemorrhagic stroke and subdural and/or subarachnoid haemorrhage.
Investigator-reported bleeding events

Table 18: Frequency and yearly event rate (%) of major, life-threatening and any gastrointestinal bleeding in RE-LY.

	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Number of subjects	6015	6076	6022
Major GI bleeds	134 (1.14)	186 (1.57)	125 (1.07)
Hazard ratio vs. warfarin (95% CI)	1.07 (0.84, 1.36)	1.47 (1.17, 1.85)	
GI life-threatening bleeds	67 (0.57)	94 (0.79)	57 (0.49)
Hazard ratio vs. warfarin (95% CI)	1.17 (0.82, 1.67)	1.62 (1.17, 2.26)	
Any GI bleeds	600 (5.41)	681 (6.13)	452 (4.02)
Hazard ratio vs. warfarin (95% CI)	1.35 (1.19, 1.53)	1.52 (1.35, 1.72)	

The risk of major bleeding with dabigatran etexilate 110 mg and 150 mg was consistent across all major subgroups of baseline characteristics with the exception of age. There was a higher risk of bleeding with dabigatran etexilate 150 mg in patients ≥75 years of age (hazard ratio vs. warfarin (95% CI) 1.18 (0.98, 1.43)).

GI/dyspepsia

Dabigatran etexilate subjects had the highest incidence of GI AEs (34.6%, 34.5%, and 24.0% for dabigatran etexilate 110 mg, dabigatran etexilate 150 mg, and warfarin, respectively). Additional GI events that were reported more frequently with dabigatran etexilate treatment included upper abdominal pain, gastritis, abdominal discomfort, gastroesophageal reflux disease, dysphagia, and flatulence (Table 19). There was no consistent dose-response relationship with respect to GI AEs.

Table 19: Number (%) of subjects with dyspepsia and gastritis-like symptoms (safety set) in RE-LY.

Preferred term/investigator term	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Number of subjects	5983	6059	5998
Total with dyspepsia/gastritis	983 (16.4)	940 (15.5)	470 (7.8)
Dyspepsia*	761 (12.7)	738 (12.2)	354 (5.9)
Gastritis-like symptoms#**	297 (5.0)	257 (4.2)	142 (2.4)

Percentages were calculated using total number of subjects per treatment as the denominator.
*Dyspepsia includes dyspepsia, abdominal pain upper, abdominal pain, abdominal discomfort, epigastric discomfort
**Gastritis-like symptoms includes gastritis, GERD, oesophagitis, gastritis erosive, gastric haemorrhage, gastritis haemorrhagic, haemorrhagic erosive gastritis
Represents a composite of sponsor-identified AEs (preferred terms) that were similar and likely reporting the same subject.

Liver Function Tests

In the RE-LY study, potential abnormalities of liver function tests (LFT) occurred with a comparable or lower incidence in dabigatran etexilate vs. warfarin treated patients (Table 20).

Table 20: Summary of abnormal liver function tests, Number (%) of subjects (safety set) in RE-LY.

	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Total treated	5983	6059	5998
ALT or AST > 3xULN	118 (2.0)	106 (1.7)	125 (2.1)
ALT or AST > 5xULN	36 (0.6)	45 (0.7)	50 (0.8)
ALT or AST > 3xULN + Bilirubin >2xULN	11 (0.2)	14 (0.2)	21 (0.4)

Subjects were counted in each category if the respective abnormal LFT event occurred between first dose of study medication and study termination visit.

Myocardial Infarction

There was an increased frequency in myocardial infarction events in subjects treated with dabigatran etexilate compared to warfarin treated subjects which was not statistically significant (yearly event rate: 150 mg twice daily 0.81%, 110 mg twice daily 0.83%, warfarin 0.64%) (see Clinical Trials).

Overview of adverse events from RE-LY

The incidence of AEs was similar between subjects treated with dabigatran etexilate 110 mg twice daily and dabigatran etexilate 150 mg twice daily (78.6% and 78.3%, respectively) versus 75.9% of subjects treated with warfarin. The incidence of SAEs was similar across treatment groups. However, dabigatran etexilate subjects had a lower incidence of fatal AEs, life-threatening AEs, and events that required hospitalisation as compared to warfarin subjects.

Adverse events classified by SOC and preferred terms reported ≥2% from any treatment group of the RE-LY study are shown in Table 21 below. Diarrhoea, dyspepsia, and nausea were the most frequently reported GI AEs, all of which were reported at a higher frequency with dabigatran etexilate 110 mg and dabigatran etexilate 150 mg treatment, particularly for dyspepsia (6.2%, 5.7%, and 1.4% for dabigatran etexilate 110 mg, dabigatran etexilate 150 mg, and warfarin, respectively).

Table 21: AEs reported in at least 2.0% of subjects in dabigatran etexilate arms (safety set).

System organ class/ Preferred term	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Number of subjects	5983 (100.0)	6059 (100.0)	5998 (100.0)
Infections and infestations			
Nasopharyngitis	315 (5.3)	309 (5.1)	327 (5.5)
Urinary tract infection	242 (4.0)	252 (4.2)	316 (5.3)
Upper respiratory tract infection	266 (4.4)	262 (4.3)	297 (5.0)
Bronchitis	262 (4.4)	277 (4.6)	285 (4.8)
Pneumonia	226 (3.8)	219 (3.6)	236 (3.9)
Influenza	138 (2.3)	144 (2.4)	132 (2.2)
Sinusitis	80 (1.3)	98 (1.6)	120 (2.0)
Blood and lymphatic system disorders			
Anaemia	181 (3.0)	207 (3.4)	165 (2.8)
Metabolism and nutrition disorders			
Gout	125 (2.1)	116 (1.9)	162 (2.7)
Nervous system disorders			
Dizziness	457 (7.6)	458 (7.6)	554 (9.2)
Headache	253 (4.2)	236 (3.9)	242 (4.0)
Syncope	155 (2.6)	150 (2.5)	155 (2.6)
Cardiac disorders			
Atrial fibrillation	303 (5.1)	313 (5.2)	327 (5.5)
Cardiac failure congestive	196 (3.3)	187 (3.1)	210 (3.5)
Cardiac failure	169 (2.8)	171 (2.8)	201 (3.4)
Palpitations	141 (2.4)	138 (2.3)	162 (2.7)
Angina pectoris	124 (2.1)	113 (1.9)	125 (2.1)
Vascular disorders			
Hypertension	253 (4.2)	234 (3.9)	266 (4.4)
Hypotension	120 (2.0)	127 (2.1)	130 (2.2)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	498 (8.3)	526 (8.7)	551 (9.2)

System organ class/ Preferred term	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Cough	320 (5.3)	310 (5.1)	346 (5.8)
Epistaxis	109 (1.8)	127 (2.1)	178 (3.0)
Dyspnoea exertional	110 (1.8)	120 (2.0)	116 (1.9)
Gastrointestinal disorders			
Dyspepsia	368 (6.2)	345 (5.7)	83 (1.4)
Diarrhoea	355 (5.9)	367 (6.1)	328 (5.5)
Nausea	245 (4.1)	259 (4.3)	208 (3.5)
Constipation	188 (3.1)	177 (2.9)	167 (2.8)
Abdominal pain upper	177 (3.0)	170 (2.8)	80 (1.3)
Gastritis	147 (2.5)	127 (2.1)	87 (1.5)
Abdominal pain	130 (2.2)	137 (2.3)	141 (2.4)
Vomiting	132 (2.2)	124 (2.0)	117 (2.0)
Abdominal discomfort	119 (2.0)	112 (1.8)	64 (1.1)
Gastrooesophageal reflux disease	117 (2.0)	99 (1.6)	46 (0.8)
Skin and subcutaneous tissue disorders			
Rash	114 (1.9)	142 (2.3)	159 (2.7)
Musculoskeletal and connective tissue disorders			
Arthralgia	248 (4.1)	313 (5.2)	329 (5.5)
Back pain	295 (4.9)	289 (4.8)	331 (5.5)
Pain in extremity	227 (3.8)	228 (3.8)	212 (3.5)
Osteoarthritis	129 (2.2)	140 (2.3)	142 (2.4)
Musculoskeletal pain	120 (2.0)	121 (2.0)	116 (1.9)
General disorders and administration site conditions			
Oedema peripheral	446 (7.5)	442 (7.3)	453 (7.6)
Fatigue	370 (6.2)	367 (6.1)	353 (5.9)
Chest pain	287 (4.8)	355 (5.9)	342 (5.7)
Asthenia	165 (2.8)	157 (2.6)	161 (2.7)
Chest discomfort	129 (2.2)	110 (1.8)	88 (1.5)
Injury, poisoning and procedural complications			
Fall	183 (3.1)	178 (2.9)	234 (3.9)
Contusion	149 (2.5)	152 (2.5)	197 (3.3)

Percentages were calculated using total number of subjects per treatment as the denominator.

Adverse reactions (<2%) observed with exposure to dabigatran 110 mg twice daily and 150 mg twice daily during the RELY trial are listed below by system organ class and frequency according to the following categories:

Common ≥1% and <10%, Uncommon ≥0.1% and <1%, Rare ≥0.01% and <0.1%

Blood and lymphatic system disorders

Uncommon: thrombocytopenia

Immune system disorders

Uncommon: drug hypersensitivity (including drug hypersensitivity, pruritus, rash, urticaria, bronchospasm)

Nervous system disorders
Uncommon: intracranial haemorrhage

Vascular disorders
Uncommon: haematoma, haemorrhage

Respiratory, thoracic and mediastinal disorders
Uncommon: haemoptysis

Gastrointestinal disorders
Uncommon: dysphagia, gastrointestinal ulcer, gastrooesophagitis

Hepatobiliary disorders
Uncommon: hepatic function abnormal

Skin and subcutaneous tissue disorders
Uncommon: skin haemorrhage

Musculoskeletal and connective tissue disorders
Rare: haemarthrosis

Renal and urinary disorders
Common: urogenital haemorrhage
Uncommon: haematuria

General disorders and administration site conditions
Rare: catheter site haemorrhage, injection site haemorrhage

Injury, poisoning and procedural complications
Rare: traumatic haematoma, incision site haemorrhage

DOSAGE AND ADMINISTRATION

PRADAXA should be swallowed whole with a full glass of water, with or without food.

The capsule should not be chewed, broken, or opened as this may increase the risk of bleeding (see Pharmacokinetics, Absorption).

Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement)

The recommended dose of PRADAXA is 220 mg once daily taken as 2 capsules of 110 mg. Patients with moderate renal impairment (30–50 mL CrCL/min) have an increased risk for bleeding. For those patients the recommended dose of PRADAXA is 150 mg once daily, taken as 2 capsules of 75 mg.

Treatment of PRADAXA should be initiated orally within 1–4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for the required duration. If haemostasis is not secured, initiation of

treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

VTE prevention following knee replacement surgery: Treatment for a total of 10 days.

VTE prevention following hip replacement surgery: Treatment for a total of 28–35 days.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

The recommended daily dose of PRADAXA is 300 mg taken orally as a 150 mg capsule twice daily.

In patients with moderate renal impairment (30–50 mL CrCL/min) a reduced dose of 220 mg given as a 110 mg capsule twice daily may be considered.

Patients aged 75 years and above should be treated with a daily dose of 220 mg taken orally as a 110 mg capsule twice daily.

For patients with a potentially higher risk of major bleeding (see Precautions, Haemorrhagic risk, Table 10) a reduced dose of 220 mg given as 110 mg twice daily may be considered.

Treatment should be continued life-long.

Special patient populations

Hepatic impairment

Patients with liver disease expected to have any impact on survival or with elevated liver enzymes >2 ULN were excluded in clinical trials. Therefore the use of PRADAXA is not recommended in this population.

Renal impairment

Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCL <30 mL/min). Treatment in patients with severe renal impairment (CrCL <30 mL/min) with PRADAXA is not recommended (see Contraindications). There are no data to support use in this population.

While on treatment renal function should be assessed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications).

In patients with moderate renal impairment (CrCL 30-50 mL/min) the renal function should be assessed at least once a year.

- *Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement):* After i.v.

application 85% of dabigatran in plasma is cleared through the kidneys. Patients with moderate renal impairment (30–50 mL/min creatinine clearance) appear to be at higher risk of bleeding. Dosing should be reduced to 150 mg PRADAXA taken once daily as 2 capsules of 75 mg in patients with moderate renal impairment.

- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:* In patients with moderate renal impairment (30–50 mL/min creatinine clearance) a reduced dose of 220 mg given as a 110 mg capsule twice daily may be considered.

Elderly

Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function. As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCL <30 mL/min). The renal function should also be assessed at least once a year in patients treated with PRADAXA or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications).

See also Dosage and Administration, Renal impairment section above.

- *Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement):* No dose adjustment necessary, patients should be treated with 220 mg PRADAXA taken once daily as 2 capsules of 110 mg.

- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:* Patients aged 75 years and above should be treated with a daily dose of 220 mg taken orally as a 110 mg capsule twice daily.

Weight

No dose adjustment is necessary.

Post-surgical patients with an increased risk for bleeding

Patients at risk for bleeding or patients at risk of overexposure, notably patients with moderate renal impairment (creatinine clearance 30–50 mL/min), should be treated with caution (see Precautions and Pharmacology).

Children and adolescents

There is no experience in children and adolescents. PRADAXA is not recommended for use in patients below 18 years due to lack of data on safety and efficacy.

Concomitant use of Pradaxa with strong P-glycoprotein inhibitors e.g. amiodarone, quinidine or oral verapamil

Simultaneous initiation of treatment with PRADAXA and oral verapamil should be avoided (see Contraindications).

- *Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement):* Dosing should be reduced to PRADAXA 150 mg taken once daily as 2 capsules of 75 mg in patients who receive concomitant PRADAXA and amiodarone or quinidine (see Precautions, Interaction with other medicines).

  Dosing should be reduced to PRADAXA 150 mg taken once daily as 2 capsules of 75 mg and maintained on that dose when patients are commenced on PRADAXA whilst receiving existing oral verapamil treatment (see Contraindications, Precautions, Interaction with other medicines).

  Treatment initiation with oral verapamil should be avoided in patients following major orthopaedic surgery who are already treated with PRADAXA.

- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:* P-gp inhibitors verapamil, amiodarone and quinidine do not require dose adjustments (see Precautions, Interactions with other medicines). Patients should be treated with a daily dose of 300 mg taken orally as a 150 mg capsule twice daily.

  The effect of individual P-gp inhibitors vary and results should not be extrapolated to other P-gp inhibitors.

  When verapamil needs to be initiated on stable dabigatran etexilate therapy or dabigatran etexilate and verapamil need to be initiated concurrently, dabigatran etexilate should be given at least 2 hours before verapamil for the first three days.

Switching from Pradaxa treatment to parenteral anticoagulant

- *Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement):* Wait 24 hours after the last dose before switching from PRADAXA to a parenteral anticoagulant.

- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:* Wait 12 hours after the last dose before switching from PRADAXA to a parenteral anticoagulant.

Switching from parenteral anticoagulants treatment to Pradaxa

PRADAXA should be given 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous unfractionated heparins).

Switching from Vitamin K antagonists to Pradaxa

The vitamin K antagonist should be stopped. PRADAXA can be given as soon as the INR is <2.0.

Switching from Pradaxa to Warfarin

When converting from PRADAXA to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:

- For CrCL >50 mL/min, start warfarin 3 days before discontinuing PRADAXA.
- For CrCL 31-50 mL/min, start warfarin 2 days before discontinuing PRADAXA.
- For CrCL 15-30 mL/min, start warfarin 1 day before discontinuing PRADAXA.
- For CrCL <15 mL/min, no recommendations can be made.

Because PRADAXA can contribute to an elevated INR, the INR will better reflect warfarin's effect after PRADAXA has been stopped for at least 2 days.

Cardioversion

Patients can stay on PRADAXA while being cardioverted.

Missed dose

- *Prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery:* The patient should continue with their remaining daily doses of PRADAXA at the same time the next day. Do not take a double dose to make up for missed individual doses.

- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:* A missed PRADAXA dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted. Do not take a double dose to make up for missed individual doses.

OVERDOSAGE

For information on the management of overdose contact the Poisons Information Centre on 13 11 26 (Australia).

Overdose following administration of dabigatran etexilate may lead to haemorrhagic complications due to its pharmacodynamic properties. A specific antidote antagonising the pharmacodynamic effect of dabigatran etexilate is not available.

Doses of dabigatran etexilate beyond those recommended expose the patient to increased risk of bleeding. Excessive anticoagulation may require discontinuation of dabigatran etexilate. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. Appropriate standard treatment, e.g. surgical haemostasis as indicated and blood volume replacement should be undertaken. In addition, consideration may be given to the use of fresh whole blood or fresh frozen plasma.

As protein binding is low dabigatran is dialysable, however there is limited clinical experience in using dialysis in this setting.

Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX or X may be considered. There is some experimental evidence to support the role of activated prothrombin complex concentrate and factor VIIa in reversing the anticoagulant effect of dabigatran but their usefulness in clinical settings has not yet been systematically demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used. All symptomatic treatment has to be given according to the physician's judgement.

PRESENTATION AND STORAGE CONDITIONS

Capsules 75 mg:	Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 2 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R75. Blister packs: 10, 30, 60 capsules. Bottle: 60 capsules.
Capsules 110mg:	Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 1 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R110. Blister packs: 10, 30, 60 capsules. Bottle: 60 capsules.
Capsules 150 mg:	Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 0 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R150. Blister packs: 10, 60 capsules. Bottle: 60 capsules.
Capsules (blister packs):	Store below 30°C. Protect from moisture.
Capsules (bottle):	Store below 30°C. Protect from moisture. Once opened, the bottle must be used within 4 months. Keep the bottle tightly closed.

Not all pack sizes and presentations are being distributed in Australia.

NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited
ABN 52 000 452 308
78 Waterloo Road
North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF APPROVAL

TGA approval date: 25 August 2011

Date of most recent amendment: 9 November 2011

APPENDIX B: DABIGATRAN PUBLIC SUMMARY DOCUMENT

PUBLIC SUMMARY DOCUMENT
Product: Dabigatran etexilate, capsules, 110 mg and 150 mg (as mesilate), Pradaxa®
Sponsor: Boehringer Ingelheim Pty Ltd
Date of PBAC Consideration: March 2011

1. Purpose of Application

The submission sought an extension to the current Authority Required listing to include the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (NVAF) who are at moderate to high risk of developing stroke or systemic embolism, who meet certain criteria. The submission requested an Authority Required (STREAMLINED) listing for this indication.

2. Background

The PBAC had not previously considered dabigatran for this indication.

Dabigatran etexilate capsules, 75 mg and 110 mg have been PBS listed since 1 April 2010 for the prevention of venous thromboembolism in a patient undergoing total hip or total knee replacement.

3. Registration Status

Dabigatran etexilate was TGA registered on 24 November 2008 for the prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement).

As at 29 April 2011, dabigatran etexilate TGA registered indications were extended to include for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)
Prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation who are at a moderate-to-high risk of developing stroke or systemic embolism as evidenced by one or more of the following risk factors:
Age ≥ 75 years;
Hypertension;
Diabetes mellitus;
Heart failure or left ventricular dysfunction (ejection fraction < 40%) or a history of coronary artery disease;
Previous stroke or transient ischaemic attack or systemic embolism.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Atrial fibrillation (AF) is a cardiac arrhythmia characterised by uncoordinated atrial activation with consequent deterioration of mechanical function. The disturbed atrial and ventricular activation causes the stoppage of blood flow which may lead to thrombus clot formation, increasing the risk of stroke and other thromboembolic events.

AF is the most common form of arrhythmia and affects approximately 2% of the general population. The prevalence of AF rises with age, increasing to around 15% in those aged 80 years and above.

Non-valvular atrial fibrillation (NVAF) is a significant risk factor for thromboembolic events, particularly ischaemic stroke (IS).

The submission proposed that the place in therapy of dabigatran is as an alternative to adjusted-dose warfarin and aspirin as a first line treatment for the prevention of stroke or systemic embolism in moderate-to-high risk patients with NVAF.

6. Comparator

The submission nominated adjusted-dose warfarin and aspirin as the main comparators, which the PBAC considered to be appropriate.

7. Clinical Trials

The submission presented one randomised trial comparing dabigatran 150 mg twice daily (bd) and 110 mg bd with adjusted-dose warfarin in patients with NVAF (the RE-LY trial). The submission also presented six randomised controlled trials comparing adjusted-dose warfarin and aspirin to inform an indirect comparison between dabigatran and aspirin, using adjusted-dose warfarin as the common reference.

The trials published at the time of submission are presented in the table below**:**

Trial ID/First author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Dabigatran 110 mg & 150 mg vs adjusted-dose warfarin		
RE-LY BI 1160.26		
Connolly S et al	Dabigatran versus warfarin in patients with atrial fibrillation.	New England Journal of Medicine 2009;361(12):1139-1151
Connolly S et al	Newly Identified Events in the RE-LY Trial	New England Journal of Medicine 2010;363(19):1875-1876
Wallentin L et al	Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial	Lancet 2010; 307;7945:975-983
Indirect comparison: adjusted-dose warfarin as common reference		
Adjusted-dose warfarin vs aspirin		
AFASAK I Petersen P et al	Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study.	Lancet 1989; 1:175-179.
Petersen P et al	Prevention of stroke in atrial fibrillation. (to the editor)	New England Journal of Medicine 1990; 323:482.

AFASAK II Gulløv AL et al	Fixed mini-dose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation Study.	Archives of Internal Medicine 1998. 158: 1513-1521.
Gulløv AL et al	Bleeding during warfarin and aspirin therapy in patients with atrial fibrillation.	Archives of Internal Medicine 1999. 159: 1322-1328.
BAFTA Mant J et al	Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study; BAFTA): a randomised controlled trial.	Lancet 2007. 370: 493-503.
Chinese ATAFS Hu D et al	The randomized study of efficiency and safety of antithrombotic therapy in nonvalvular atrial fibrillation: warfarin compared with aspirin.	Zhonghua Xin Xue Guan Bing Za Zhi 2006. 34: 295-298.
SPAF II	Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study.	Lancet 1991. 343: 687-691.
WASPO Rash A et al	A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO).	Age and Ageing 2007. 36: 151-156.

8. Results of Trials

The results for the primary outcome of RE-LY, stroke/SEE are summarised below.

Non-inferiority of both dabigatran doses (110 mg bd and 150 mg bd) compared to adjusted-dose warfarin was demonstrated in the RE-LY trial for the primary efficacy outcome, based on non-inferiority thresholds of 1.46 and 1.38: The hazard ratio (HR) for dabigatran 110 mg bd = 0.90 (95% CI 0.74, 1.10) and for dabigatran 150 mg bd = 0.65 (95% CI 0.52, 0.81). Dabigatran 150 mg bd was also demonstrated to be superior to adjusted-dose warfarin for the primary endpoint of stroke/SEE, with a hazard ratio of 0.65 (95% CI 0.52, 0.81).

The mean time in therapeutic range (TTR) for patients enrolled from different countries in the RE-LY trial, for warfarin at different levels of international normalised ratio (INR) control (2-3) (Wallentin 2010) indicated that patients enrolled in Australian sites had a mean time in therapeutic range for warfarin of 74% based on a small number of patients.

The PBAC noted that published studies and an unpublished survey suggested that the time spent in target INR range varies between 50.4% and 68% in Australia.

The results for patients enrolled in centres with rates of centres mean time in therapeutic range (cTTR) >72.6%, compared with those reported in the ITT population are summarised in the following table:

Outcome	**Hazard ratio (95% CI) cf with adjusted-dose warfarin**			
	ITT (reported in submission/ used in model)		**cTTR >72.6% (Australian patients in RE-LY had cTTR of 74%)**	
	Dabigatran110	**Dabigatran 150**	**Dabigatran**	**Dabigatran**

			110	150
Stroke and systemic embolism [a]	0.90 (0.74, 1.10)	0.65 (0.52, 0.81)	0.92 (0.59, 1.45)	0.95 (0.61, 1.48)
Non-haemorrhagic stroke and systemic embolism	NR	NR	1.13 (0.69, 1.87)	1.21 (0.74, 1.98)
Intracranial bleeding [b]	0.30 (0.19, 0.45)	0.41 (0.28, 0.60)	0.27 (0.11, 0.66)	0.39 (0.18, 0.84)
Major bleeding	0.80 (0.70, 0.93)	0.93 (0.81, 1.07)	0.90 (0.67, 1.21)	1.16 (0.88, 1.54)
Major gastrointestinal bleeding	NR	NR	1.46 (0.89, 2.41)	2.00 (1.25, 3.21)
Total bleeding [b]	0.78 (0.73, 0.83)	0.91 (0.85, 0.96)	0.84 (0.74, 0.95)	1.00 (0.89, 1.12)
Stroke, SEE, PE, MI, death and major bleeding	0.92 (0.84, 1.01)	0.90 (0.82, 0.99)	1.07 (0.87, 1.30)	1.11 (0.91, 1.35)
Stroke, SEE, PE, MI and CV death	NR	NR	1.27 (0.97, 1.67)	1.19 (0.90, 1.57)
Non-haemorrhagic stroke, SEE, PE, MI and CV death	NR	NR	1.29 (1.01, 1.64)	1.17 (0.91, 1.50)
Total death	0.90 (0.79, 1.03)	0.88 (0.77, 1.00)	1.18 (0.89, 1.57)	1.08 (0.81, 1.44)

SEE=systemic embolism; PE=pulmonary embolism; MI=myocardial infarction; CV=cardiovascular, NR=not reported

[a] primary outcome

[b] adjudicated events reported for ITT

In the ITT population, superiority was demonstrated for dabigatran 150 mg strength in reduction of stroke/systemic embolism (composite primary outcome), ischaemic stroke, haemorrhagic stroke, intracranial bleeding and death, although the latter was not quite statistically significant (HR 0.88, 95% CI 0.77, 1.00). For patients in centres with a mean time in therapeutic range (cTTR) >72.6% with adjusted-dose warfarin, the results demonstrated no statistically significant differences in the primary outcome of stroke/SEE in a post-hoc analysis.

The results for stroke/SEE reported in the aspirin trials and an indirect comparison with dabigatran showed that when all aspirin trials are considered, no statistically significant difference between adjusted-dose warfarin and aspirin was observed. However, excluding AFASAK II, a trial that was prematurely terminated, the results indicated that adjusted-dose warfarin is statistically significantly better than aspirin in preventing stroke/SEE.

Dabigatran and adjusted-dose warfarin are both associated with an increased risk of bleeding. Dabigatran is also associated with gastric adverse events.

9. Clinical Claim

The submission described dabigatran as superior in terms of comparative effectiveness and superior in terms of comparative safety over adjusted-dose warfarin. The PBAC accepted this claim, *see Recommendation and Reasons*.

The submission described dabigatran as superior in terms of comparative effectiveness and superior in terms of comparative safety over aspirin. The PBAC agreed that the indirect comparison demonstrated that dabigatran is more effective than aspirin but is likely to cause more bleeding.

10. Economic Analysis

The submission presented a modelled economic evaluation.

The base case assumed that dabigatran 150 mg and 110 mg are used 50:50 and that the comparators (adjusted-dose warfarin and aspirin) are also used 50:50.

The results of the economic evaluation, using total RE-LY data, produced a base case incremental cost/extra QALY over lifetime of less than $15,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated by the submission to be greater than 200,000 in Year 5.

The financial cost/year to the PBS was estimated by the submission to be greater than $100 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended the listing of dabigatran 150 mg and an extension to the listing of dabigatran 110 mg for the prevention of stroke or systemic embolism in moderate-to-high risk patients with non-valvular atrial fibrillation on the basis of acceptable cost effectiveness. Based on the high incidence of atrial fibrillation and the financial estimates in the submission over the first four years of listing, the Committee noted that the opportunity cost to the Commonwealth of listing dabigatran would be significant.

The requested restriction was considered to be consistent with the subjects enrolled in the main clinical trial (the RE-LY trial) and therefore appropriate. Although Medicare Australia would not be able to enforce compliance with the risk factors under the requested 'streamlined' authority, it would need to increase its workforce substantially to deal with the number of telephone requests, if listed as 'Authority Required'.

The PBAC noted that a number of patients who are reluctant to take warfarin because of the stringent monitoring requirements and interactions with other drugs and foods, but who should be taking oral anticoagulation, would now be treated with dabigatran and this would likely lead to additional benefits and costs not measured in the trial. The listing of dabigatran may also result in patients at low risk currently managed on aspirin or no treatment being unnecessarily transferred to dabigatran at a much higher cost.

The PBAC considered the comparators in the submission, adjusted-dose warfarin and aspirin, to be appropriate.

The PBAC noted that the RE-LY trial had been designed to test the non-inferiority of dabigatran 150 mg twice daily and 110 mg twice daily compared with adjusted-dose warfarin. However, the results of the trial suggested that although dabigatran 110 mg bd was non-inferior to adjusted-dose warfarin, dabigatran 150 mg bd was both non-inferior and superior to adjusted-dose warfarin. In the ITT population, superiority was demonstrated for the 150 mg strength in reduction of stroke/systemic embolism (composite primary outcome), ischemic stroke, haemorrhagic stroke, intracranial bleeding and death, although the latter was

not quite statistically significant (HR 0.88, 95% CI 0.77, 1.00). 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 sub-group included Australia, where the cTTR was measured in the RE-LY trial as 74% (refer to "Results of Trials"). However, the PBAC also noted that published studies and an unpublished survey suggested that the time spent in target INR range varies between 50.4% and 68% in Australia.

The PBAC also accepted that dabigatran is of similar overall safety to adjusted-dose warfarin, i.e. superior in terms of life-threatening and minor bleeds and inferior in terms of gastrointestinal adverse events. The PBAC noted reduced intracranial bleeding with dabigatran, an important benefit for patients.

However, although dabigatran 150 mg twice daily was superior to adjusted-dose warfarin in the RE-LY ITT population, this superiority may or may not be reflected in the Australian population, depending on the compliance of the patients prescribed daily warfarin and how compliant they might be with dabigatran twice daily. Further, the effectiveness of dabigatran in patients who are not fully compliant is unknown, but given its pharmacology is highly likely to be less than demonstrated in the RE-LY trial.

However, overall, the PBAC relied on the ITT results for both arms of the trial when forming its clinical conclusion that dabigatran is superior to warfarin and based its recommendation to list dabigatran on that analytical approach. Although the results for dabigatran 110 mg bd did not demonstrate superiority over adjusted-dose warfarin in the ITT population, the PBAC considered that this dose would be reserved for patients with renal insufficiency, in whom the lower dose would be highly likely to result in similar benefits over warfarin to dabigatran 150 mg bd in patients without renal impairment. The PBAC also agreed that the indirect comparison demonstrated that dabigatran is more effective than aspirin but is likely to cause more bleeding.

The results of the modelled economic evaluation were considered robust and remained within an acceptable range under sensitivity analysis, unless the duration of the model was reduced to 5 or 10 years, which the PBAC acknowledged was unreasonable. The Committee agreed that a duration of 20 years was reasonable for which the base case increased slightly per QALY. Issues were identified with non-significant point estimates being used in the model, but the PBAC noted that removal of these actually reduced the ICERs. Issues were also noted about the disutilities applied in the model, but the model was not found to be sensitive to these.

The PBAC considered the predicted utilisation of dabigatran in the submission may be underestimated, particularly if lower risk patients are prescribed the drug. The financial implications were predicted to be greater than $100 million in Year 5, although there would be some savings to the MBS with a reduction in INR testing.

The PBAC recommended that dabigatran etexilate is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements as a shared care model.

Recommendation:

DABIGATRAN ETEXILATE, capsule, 150 mg (as mesilate)

Restriction: Authority Required (STREAMLINED)
Prevention of stroke or systemic embolism in a patient with non-valvular atrial fibrillation who are at moderate-to-high risk of developing stroke or systemic embolism as evidenced by one or more of the following risk factors:
i) Age 75 years or older;
ii) Hypertension;
iii) Diabetes mellitus;
iv) Heart failure or left ventricular dysfunction (ejection fraction less than 40%) or history of coronary artery disease;
v) Previous stroke or transient ischaemic attack or systemic embolism.

NOTE
No applications for increased maximum quantities will be authorised.
Shared Care Model
For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.

Max qty: 60
Repeats: 5

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Boehringer Ingelheim welcomes the recommendation of the PBAC and looks forward to the availability of dabigatran on the PBS for Australians with non-valvular atrial fibrillation at moderate-to-high risk of developing stroke or systemic embolism.

APPENDIX C: CONSUMER MARKET RESEARCH REPORT

Boehringer Ingelheim – Project Pulse

Final Report February 2012

A study to understand the experiences and attitudes of patients suffering from A.F. and designed to assess:

- Current perceptions, experiences and issues with treatment options and in particular Warfarin
- Unmet needs for alternative treatment options
- Patient awareness and response to Pradaxa product description

Prepared for
Boehringer Ingelheim

Prepared by UltraFeedback




Background & Research Objectives

- **Boehringer Ingelheim is planning to launch Pradaxa, a novel anticoagulant treatment for atrial fibrillation into Australia.**
- **In response to a decision by the government to delay PBS reimbursement of Pradaxa, research was conducted to:**
  - ***Determine the nature and extent of issues and unmet needs in current treatment experience***
  - ***Evaluate the potential interest in a new product option***
  - ***Measure patient views of the PBS decision***

Methodology – Patient Research

Qualitative

Sydney

11 Depth Interviews

face to face x 3, telephone x 8

Quantitative

National online survey

N= 200 A.F. sufferers

<u>200 A.F. Patients</u>

-ages 55 - 80+

- 61 current warfarin users

- 60% male/40% female

Online Research Design

- Sample
- Questionnaire Outline

On-line survey sample
N=200 patients with atrial fibrillation

	Initial	Final
Atrial Fibrillation Sufferers	433	200
Concession Card Holders	373	174
Non Concession Card Holders	60	26
Warfarin Users	61	61
Non Warfarin Users	372	139

Qualification criteria:

- **Diagnosed with atrial fibrillation (irregular heart beat or flutter)**
- **Never used an anticoagulant medication called Pradaxa**

Additional quota requirements:

- **A minimum of 60 respondents (30% of the sample) must be users of Warfarin,**
- **A minimum of 30 respondents (15% of the sample) must be non concession card holders**

The survey was launched on 23 January and is currently still open.

- 433 patients with Atrial Fibrillation have responded.

- 200 respondents meet qualification criteria.

Questionnaire – Key Themes

Profile

- Demographics
- Health Card carrier
- History of A/F condition, stroke

Current treatment

- Spontaneous and prompted awareness of treatment options, current/past use of treatment options
- Perceptions of Warfarin
- Impact of Warfarin Requirements
- Satisfaction with current treatment

Ideal/new treatment

- Attributes of ideal treatment and current treatment
- Likely take up of new product
- Likelihood to travel for script

PBS delay response

- Polling question on Government deferral of new treatment

Key Outcomes – Quantitative Topline

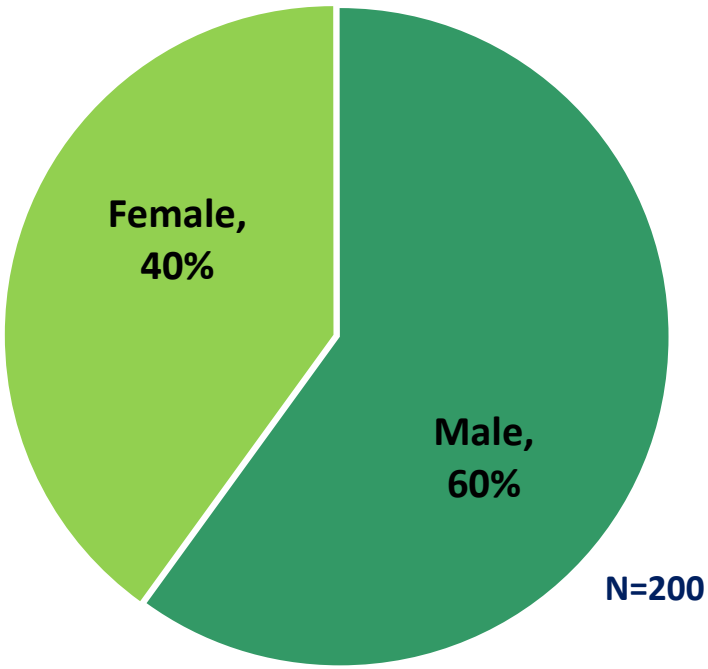
- Treatment Needs
- Response to PBS delay

Key Topline Findings

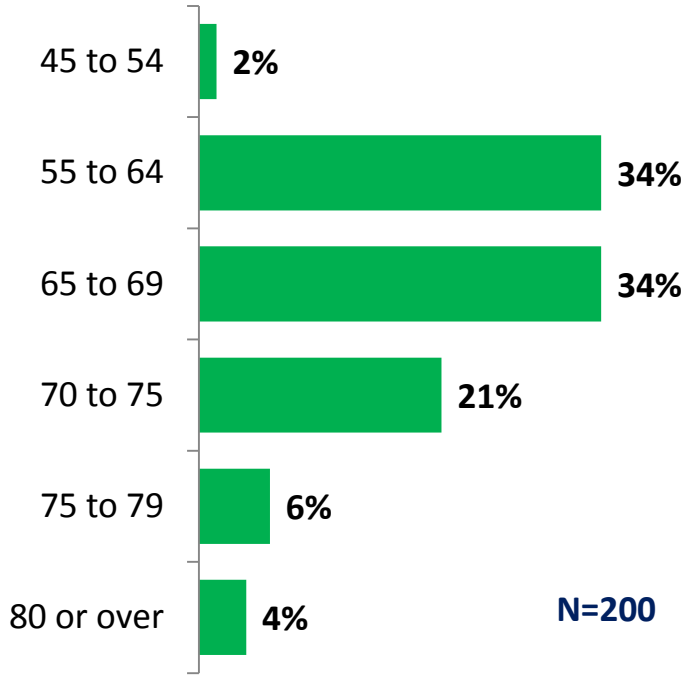
- The quantitative research indicates that there are a variety of experiences with A.F. Some patients are very concerned about the symptoms while others appear to live with the diagnosis without it having a major impact on their lives.
- Patients on Warfarin appear well educated as to the reasons for the treatment (to thin blood, to prevent it clotting and causing stroke).
- Warfarin users perceive a gap in the treatment and ideally would like a safe but more convenient treatment form.
- Based on a product concept description appeal for a new superior treatment is high.
- Patients overall did indicate concern about the delays in the PBS scheduling of the New Product.

Demographics: age profile 55 to 80+

Gender (Are you…)
(% of respondents with Atrial Fibrillation)



Age (In which age group do you belong?
% of respondents with Atrial Fibrillation)



Median age is 67 years

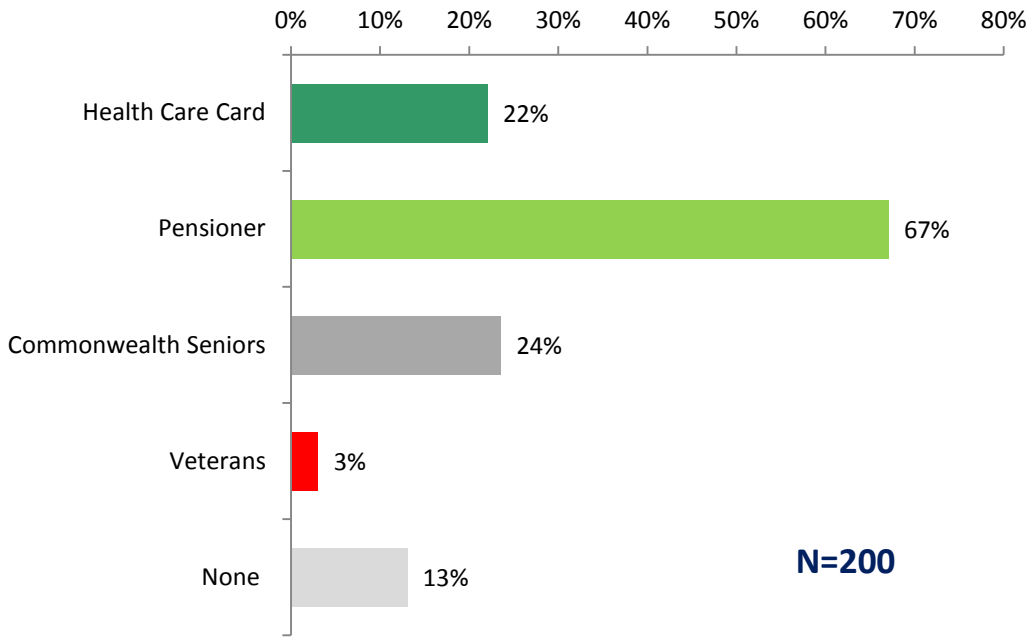
Demographics :
Majority have health cards

Region (a representative sample from Australia, regional and metro)

Health Cards

Which of the following concession cards issued by the Australian Government do you hold?

(% of respondents with Atrial Fibrillation)



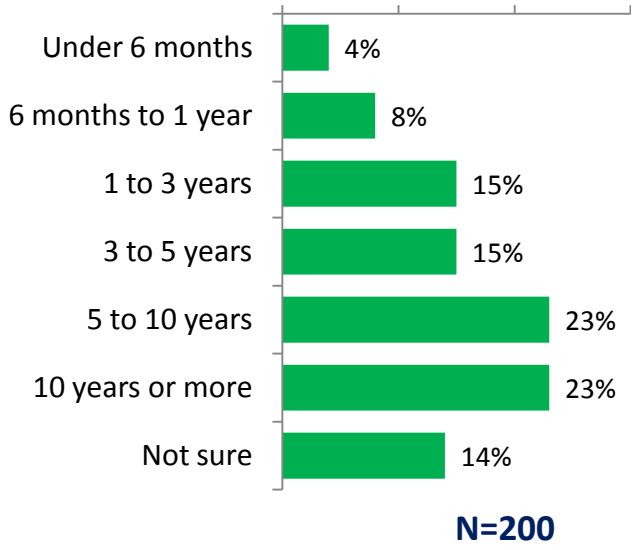
N=200

26 qualified respondents do not hold a health card

About Your Atrial Fibrillation

How Long have you had AF?

(% of filtered base)



N=200

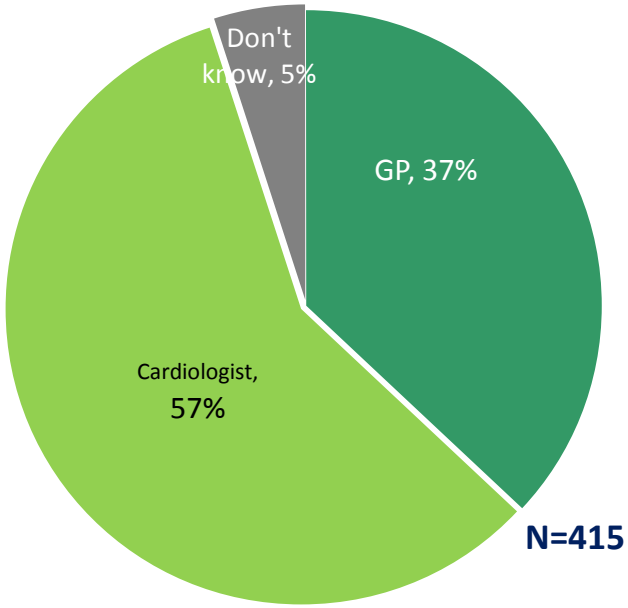
What is your greatest concern about having AF?

- *Heart attack*
- *Stroke*
- *Blocked artery*
- *That my heart will stop*
- *Wakes me in the middle of the night making me feel unwell and on several occasions putting me in hospital until it can be stabilised*
- *Where is it going, does it lead to something worse?*

Atrial Fibrillation Profile Continued

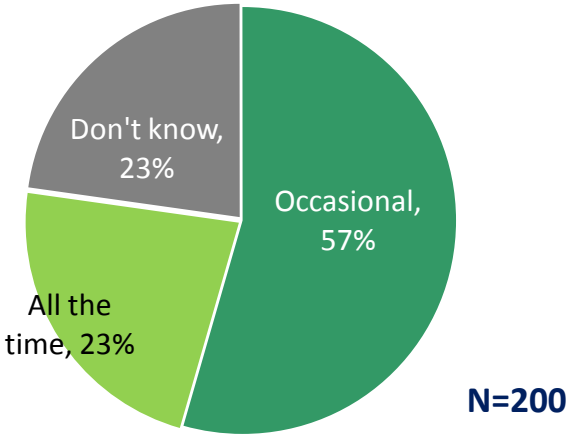
Who initially diagnosed you with Atrial Fibrillation ?

(% of respondents with Atrial Fibrillation)



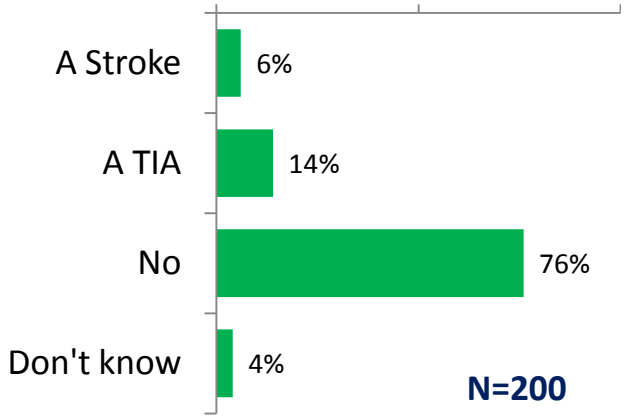
Is your AF occasional or all the time?

(% of filtered base)



Have you ever had a stroke or a TIA?

(% of filtered base)



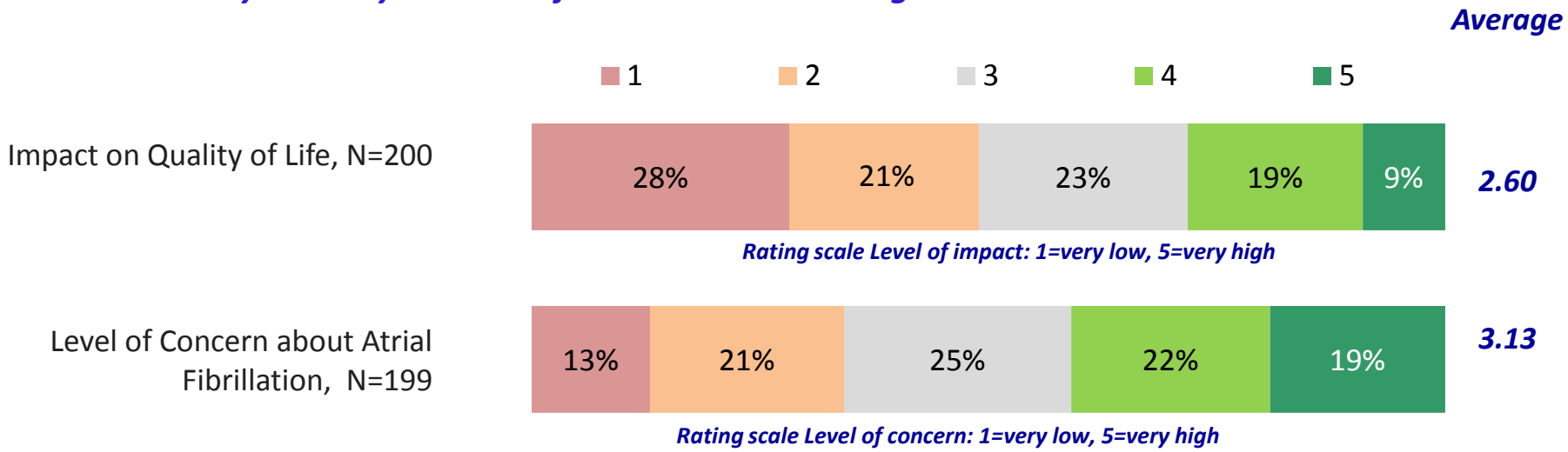
Atrial Fibrillation – Impact

Impact varies from low to medium

Level of concern varies – moderate overall

Please rate the impact Atrial Fibrillation (Irregular heartbeat/flutter) has on your quality of life

How would you rate your level of concern about having this condition?

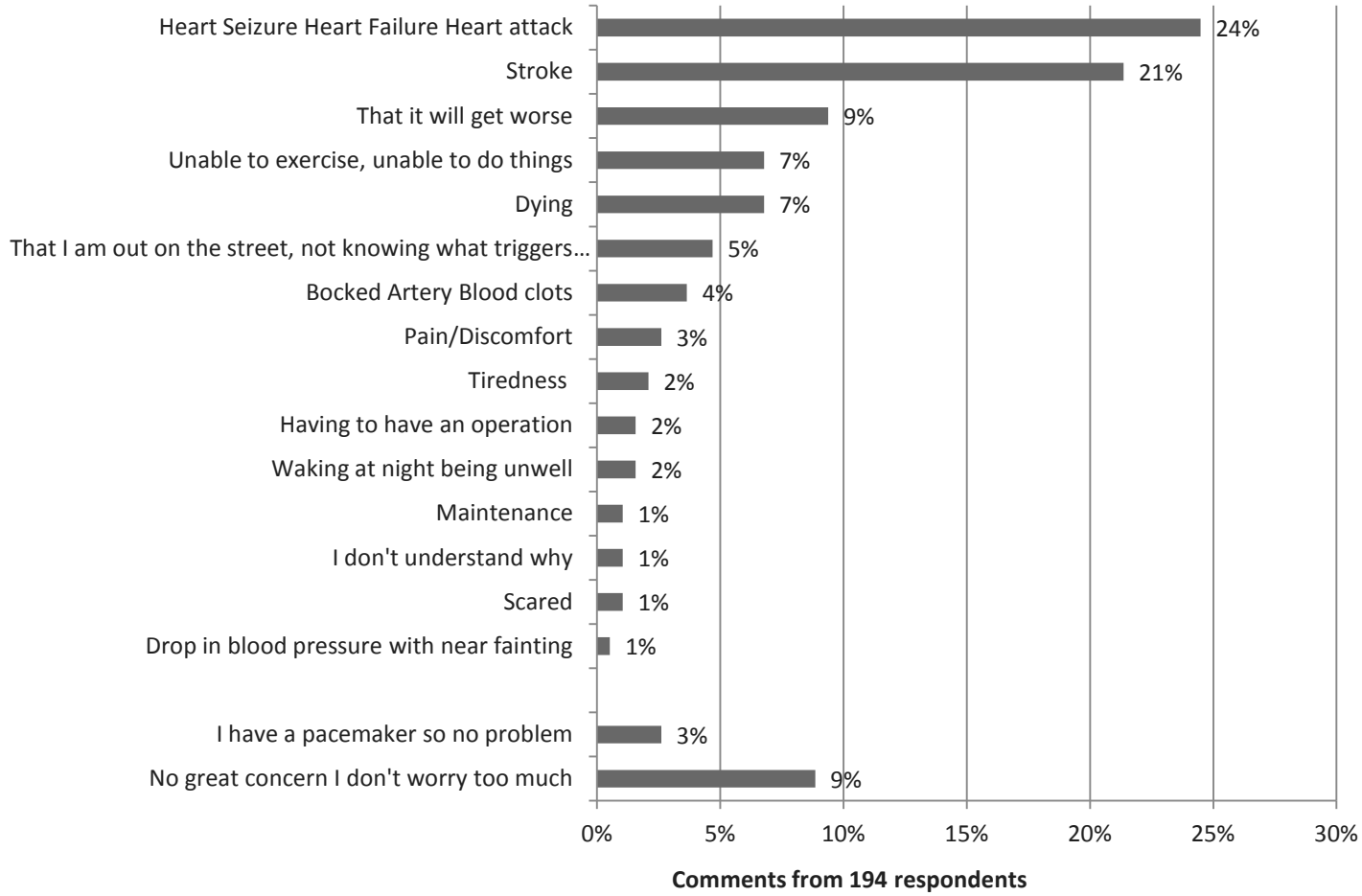


Impact and Level of Concern - Who

Category	Level of Impact *Rating scale: 1=very low, 5=very high*	Level of Concern *Rating Scale: 1=very low, 5=very high*
55 to 64	3.02	3.34
65 to 69	2.34	3.09
70 to 74	2.35	2.95
75 to 79	2.67	3.27
80 or over	2.50	2.13
Card holder	2.58	2.85
Non Card holder	2.56	3.00
Current Warfarin User	2.85	3.17
Past Warfarin User	2.93	3.70
Non Warfarin User	2.42	3.00

Impact in their words

What is your greatest concern with having Atrial Fibrillation (Irregular heartbeat/flutter)?



Impact – Quotes:

When i am out walking i feel uneasy until i arrive home

Sometimes I worry in case it does not stop and my heart will not kick back into a normal rhythm

heart attack, dying early

stroke/brain damage

Inability to do things

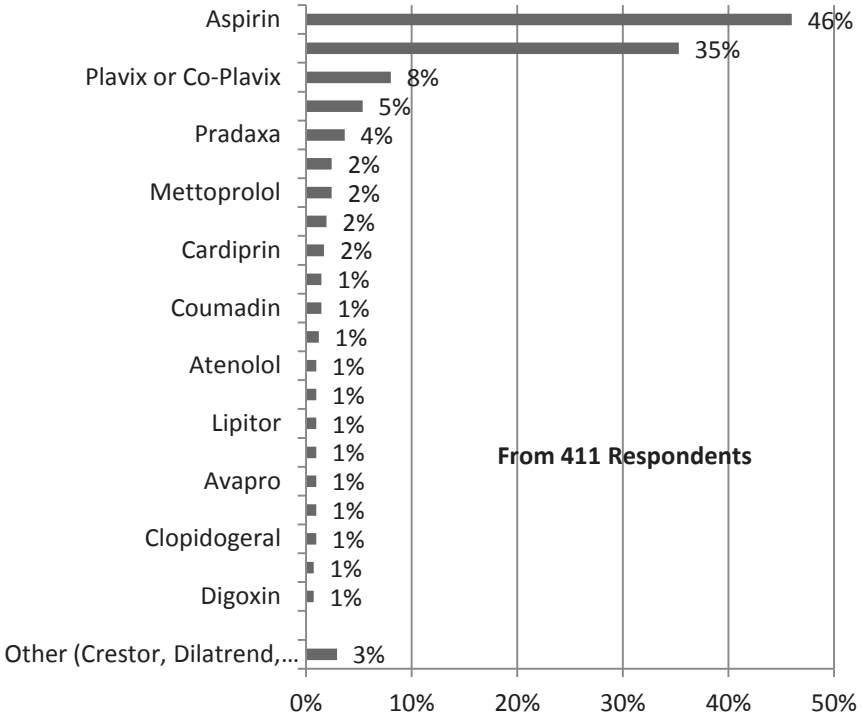
I have no great concerns . a doctor told me that a lot of people have this condition.

It restricts my day to day living and I am concerned I may have another heart attack

Awareness of treatment options
high prompted awareness for warfarin

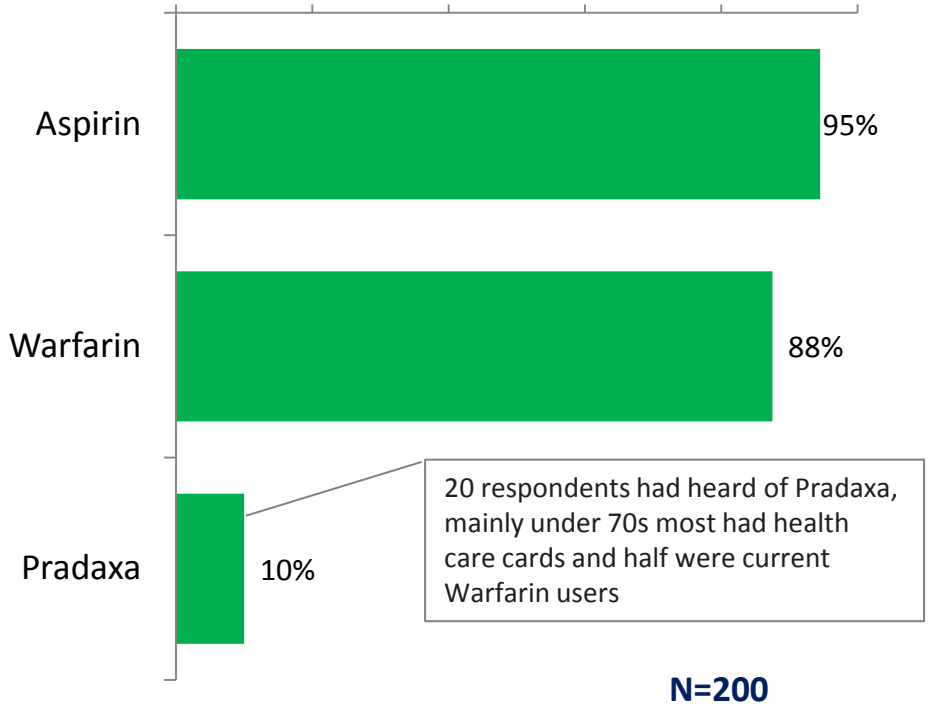
Unprompted Awareness

Thinking about blood thinning treatment options for stroke reduction in patients with Atrial Fibrillation (Irregular heartbeat/flutter), what drug treatments come to mind?



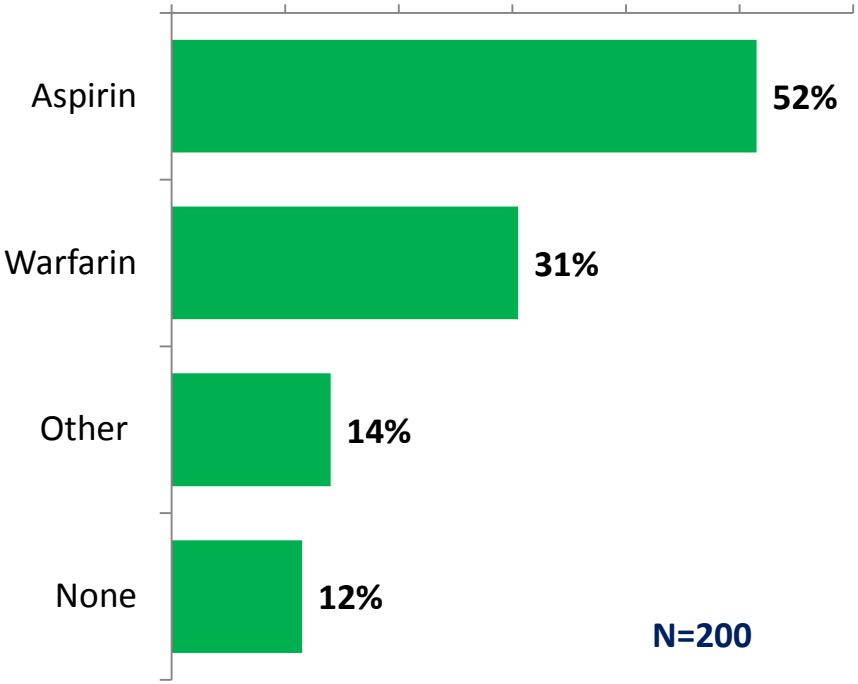
Prompted Awareness

Which of the following blood thinning treatment options for stroke reduction in patients with Atrial Fibrillation (Irregular heartbeat/flutter) have you heard of?)



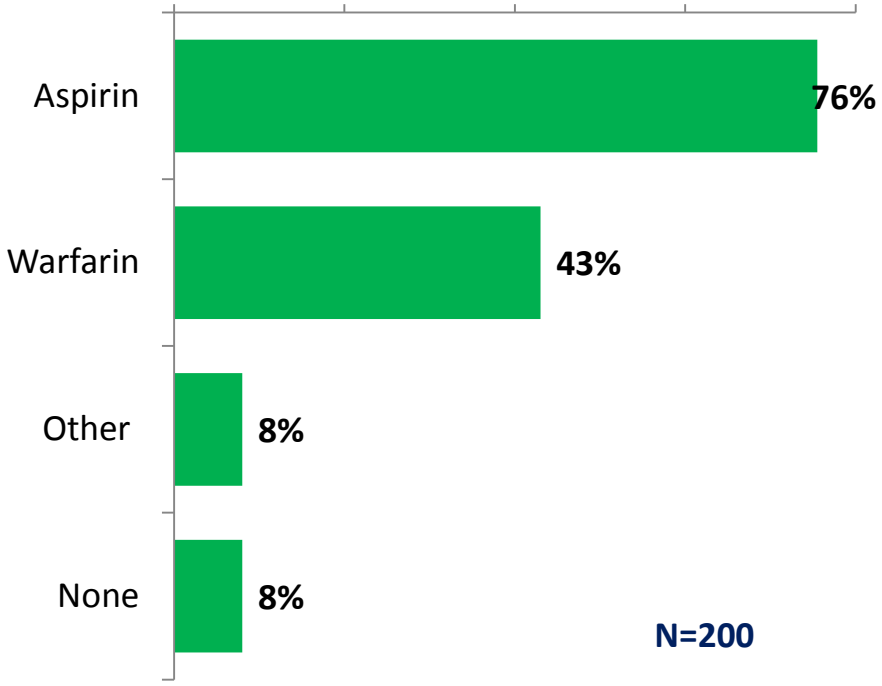
Current and Past Treatments

Which of the following blood thinning treatment options are you currently using?



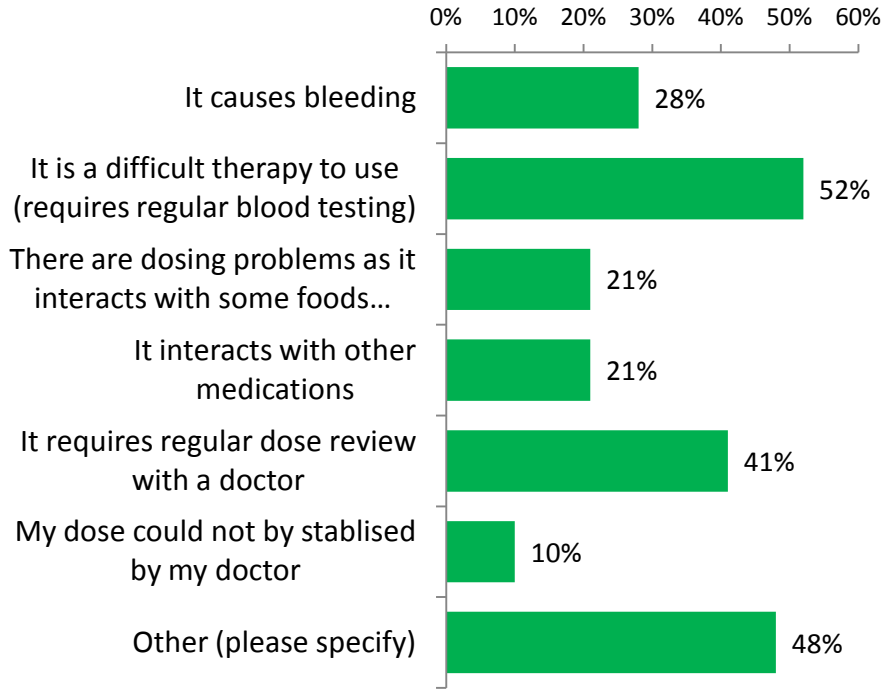
Other: Cartia, CoPlavix, Iscover, Maycardis, Metropol, Plavix, Satalol, Atanalol

Which of the following blood thinning treatment options have you ever used?



Previous Warfarin Users
Reasons for stopping

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



N=29

Other, please specify:

- *Doctor advised me to stop it.*
- *Dr. changed me to Aspirin*
- *I had an ablation and my doctor said I only need to be on Aspirin from now on.*
- *I was on it post Pulmonary embolism for approximately three months*
- *my blood clots were fixed*
- *My specialist considers me low risk and therefore aspirin is sufficient*
- *Only required for 6 months as no further atrial flutters*
- *Risk of internal bleeding*
- *Stopped due to knee replacement operation and never restarted. I have notified the specialist and he seems to think that I should be OK*
- *The doctor advised to go off it, and jump started the heart .*
- *Used for 6 months by specialist*
- *Was only required prior to surgery*

Warfarin User History

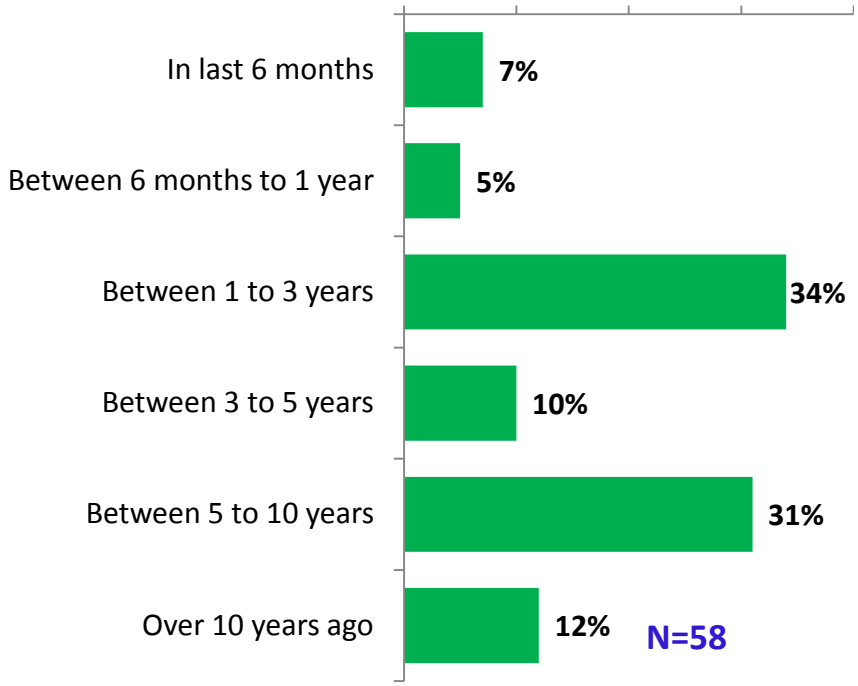
You indicated earlier that you are currently using Warfarin. Can you tell us the reason why you are using this for your Atrial Fibrillation condition?

N= 52 Current Warfarin Users

- Prescribed by cardiologist
- I was put on Warfarin to reduce the chance of having another stroke
- Cardiologist recommended –understand it is important to keep blood thin to prevent the condition creating clots
- I had a DVT in my r leg and moved to warfarin for the treatment of it. DVT is resolved now but still taking warfarin.
- Had open heart operation 6 years ago and had a artificial valve implant
- To stop blood clotting
- To thin my blood
- To maintain blood thickness at about 2.5 times normal clotting ability

When did you first started taking Warfarin?

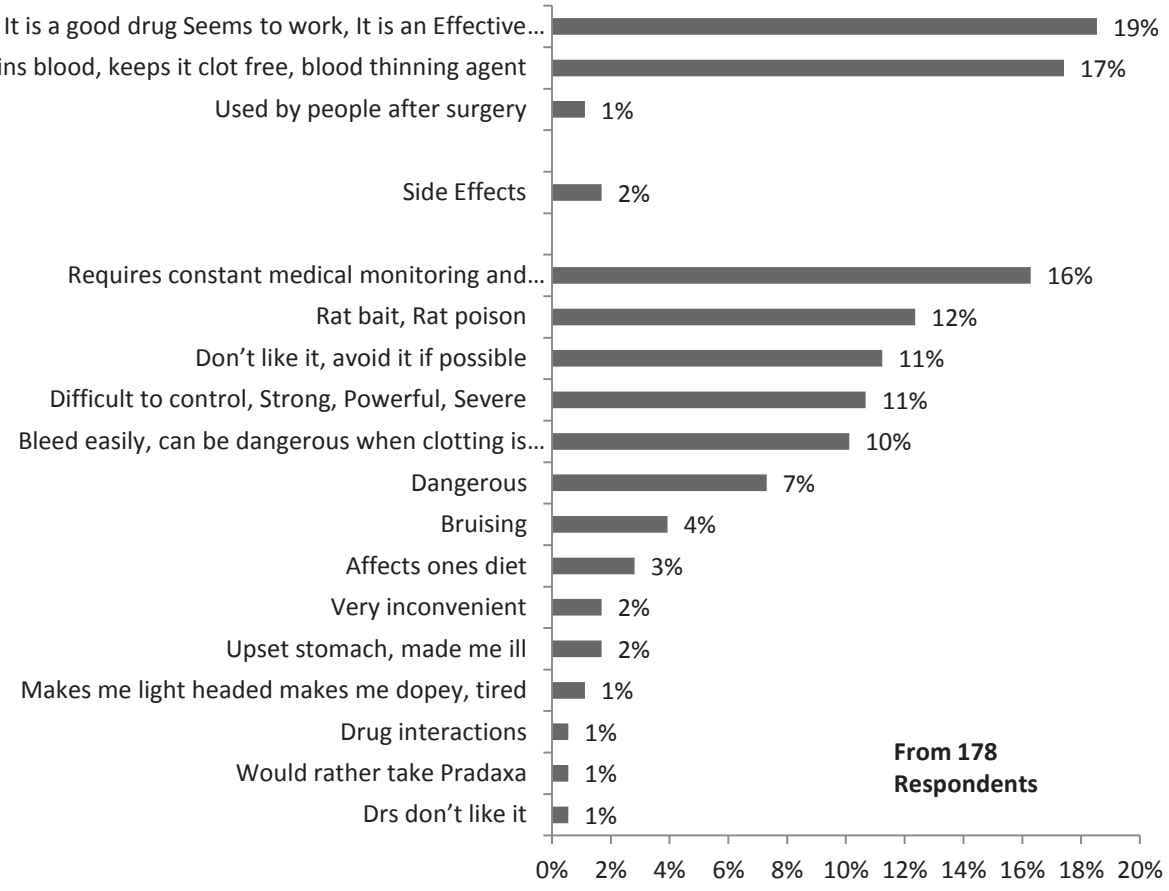
Current Warfarin Users



Warfarin - Perceptions

What are your perceptions of Warfarin?

Please comment based on your own experience or what you have heard from other sources.



Warfarin Perceptions - Quotes

I absolutely hate the very sound of the drug and would only take it briefly in absolute emergency. One's diet re green salads/vegetables, alcohol usage etc is so interrupted - I firmly believe if one has the medical knowledge and some time up one's sleeve one should attempt anything and everything before being caught up with rat poison!

Dangerous drug that needs constant monitoring

In my experience it should be restricted to Municipal Authorities to exterminate rats and similar vermin

It is a well known drug which aids heart patients.

I believe that it works well with some people but with others it causes lots of problems

It is extremely effective but can be dangerous when natural clotting is required. It also contributes to easy and extreme bruising.

Don't take it, even though my doctor wishes it. Scared of it as there are too many problems associated with it. Ie monthly tests. not being able to have regular dental work done for fear of bleeding. Also the fact that it is a product in rat poison

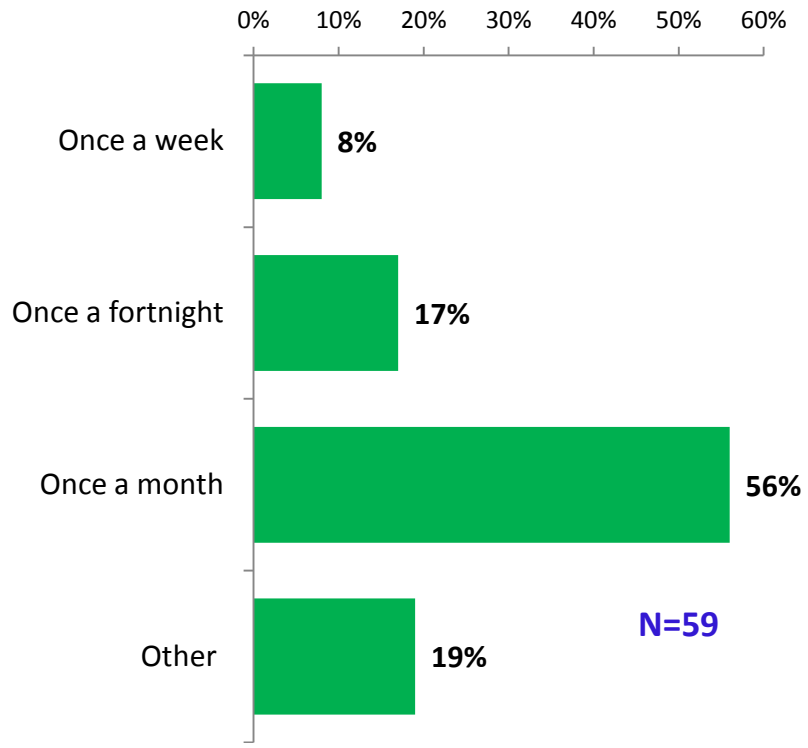
A confounded nuisance

Some people seem a bit afraid of Warfarin but it was very good for me and I had no problems at all, I only had a reaction to the red dye in Warfarin so I switched to only the blue ones and broke them into my individual dose every day.

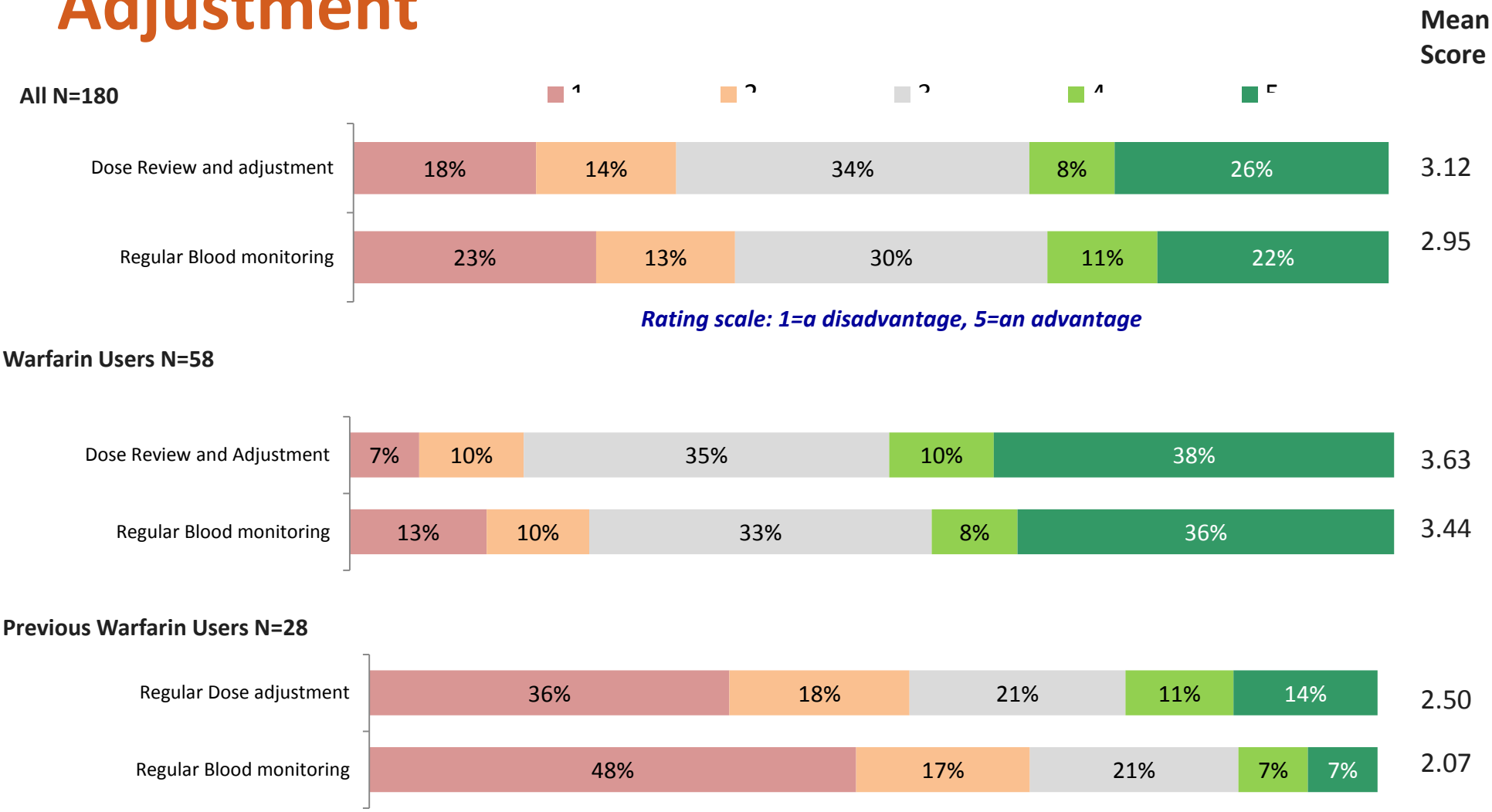
Current Warfarin Users
Blood Monitoring

How often do you have blood tests to monitor the effects of Warfarin

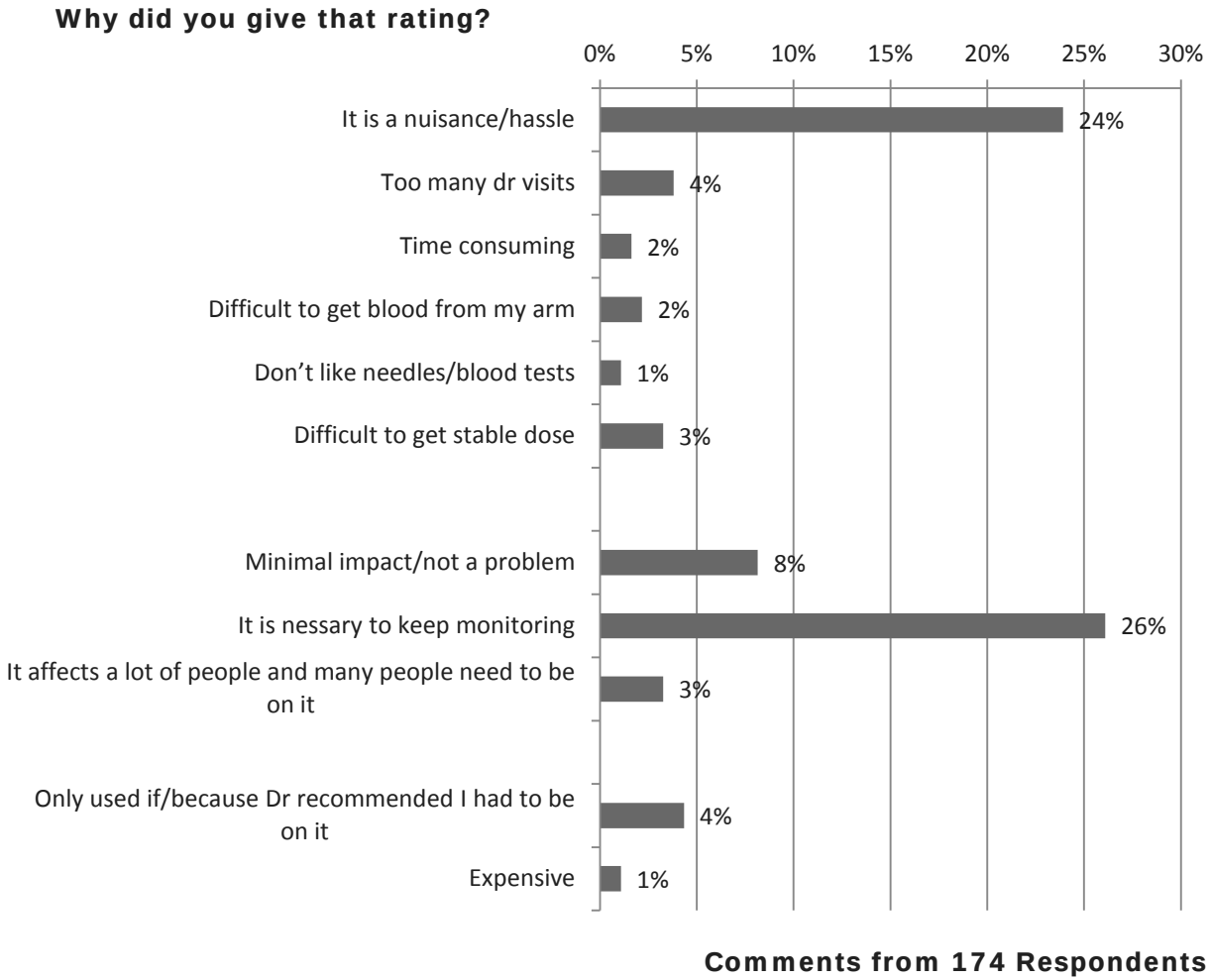
Current Warfarin Users



Views on Blood Monitoring and Dose Adjustment



Blood Monitoring – Reasons for Rating



Rating 5: ***Because it makes me feel secure***

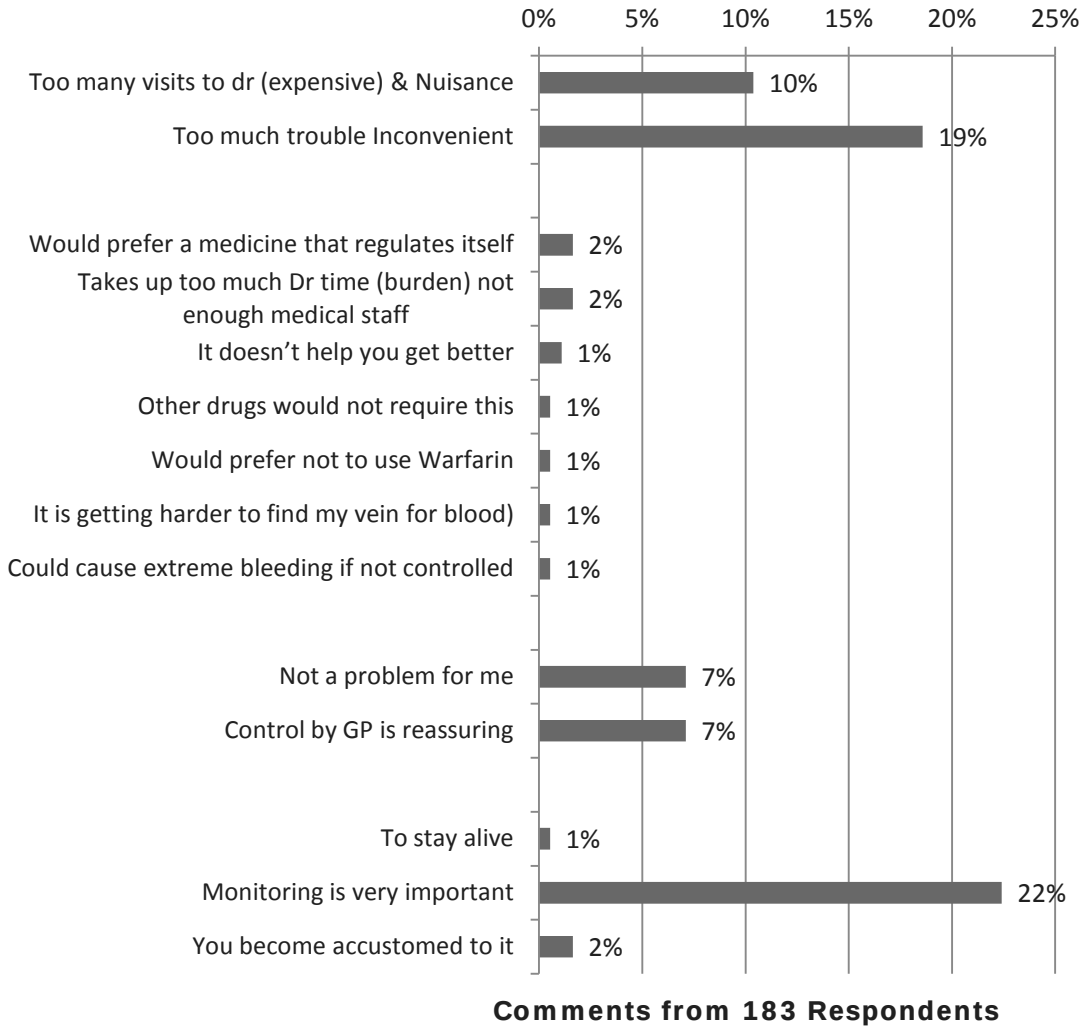
Rating 4: ***It is very comforting to know that your blood is in the right condition to avoid a stroke.***

Rating 3: ***It good to keep monitoring***

Rating 2: ***disadvantage if condition is not serious***

Rating 1: ***Because it becomes such an inconvenience and disruption of life!***

Dose Control – Reasons for Rating



Comments from 183 Respondents

Rating 5: ***Its a dangerous drug so very important***

Rating 4: ***I feel safer knowing that it is being reviewed regularly***

Rating 3: ***Does not hurt to have regular check ups***

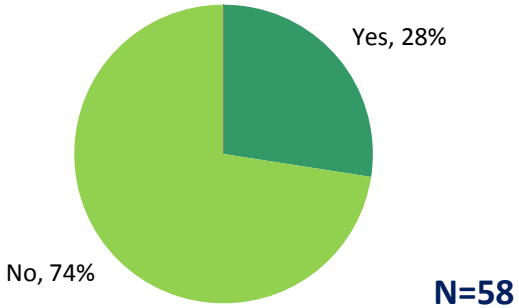
Rating 2: ***Interference with getting on with life. always at a doctor's surgery***

Rating 1: ***too much trouble***

Current Warfarin Users – One Quarter Have Interrupted Use

Have there been any times since you first started using Warfarin when you have stopped taking Warfarin

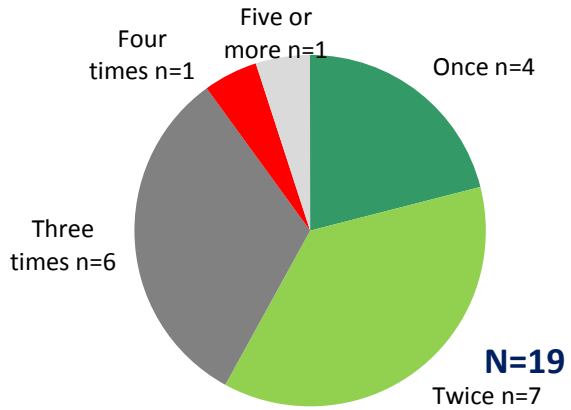
Current Warfarin Users



N=58

If so, how many times have you stopped using Warfarin since you first stated using it?

Current Warfarin Users



N=19

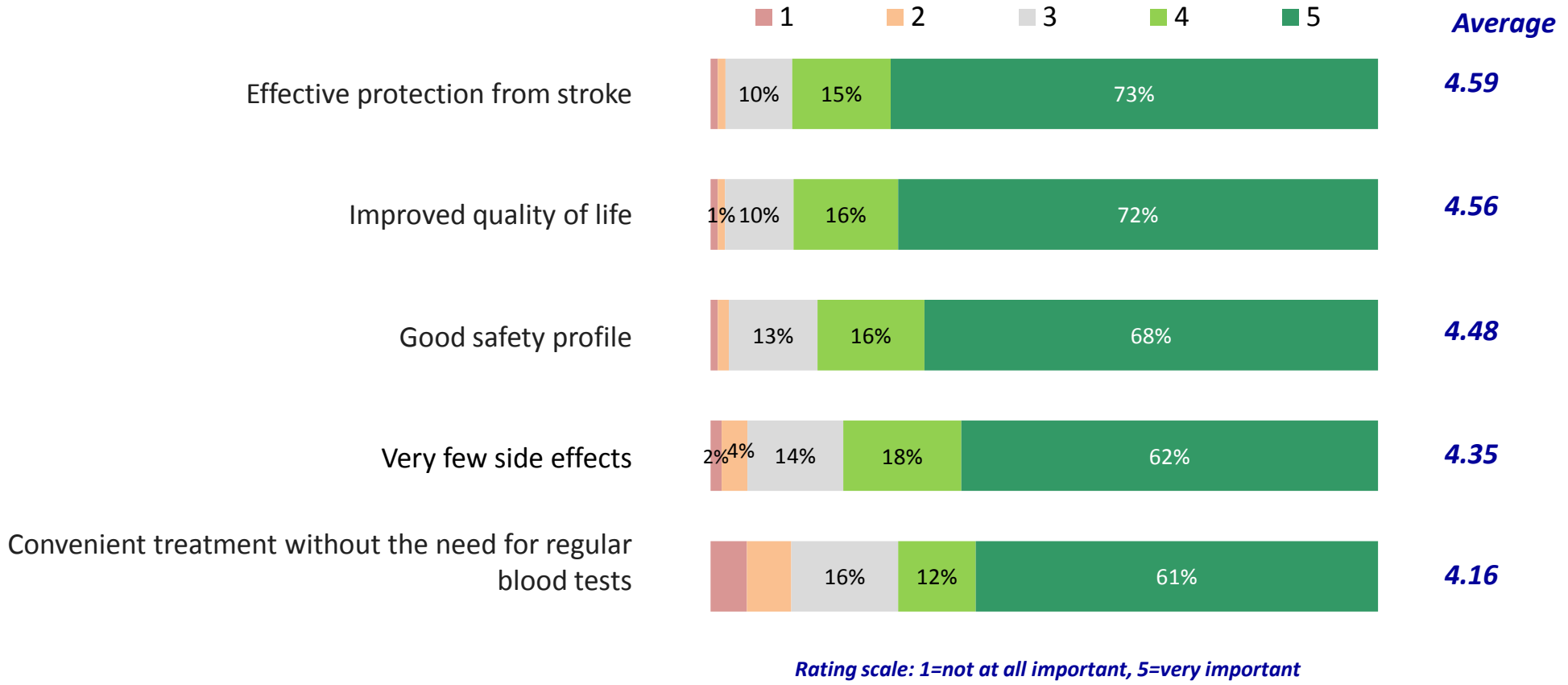
What are the reasons you have stopped using it

Current Warfarin Users

- Had surgery
- GP suggested no longer any need
- Have had operations
- Pre op trial of new drug
- Hip Replacement
- Having a angiogram

Rating of Importance of Treatment Aspects
Effective stroke prevention and QOL

Thinking of anticoagulant (stroke prevention) treatments for atrial fibrillation (irregular heartbeat/flutter), how would you rate the importance of each of the following aspects?



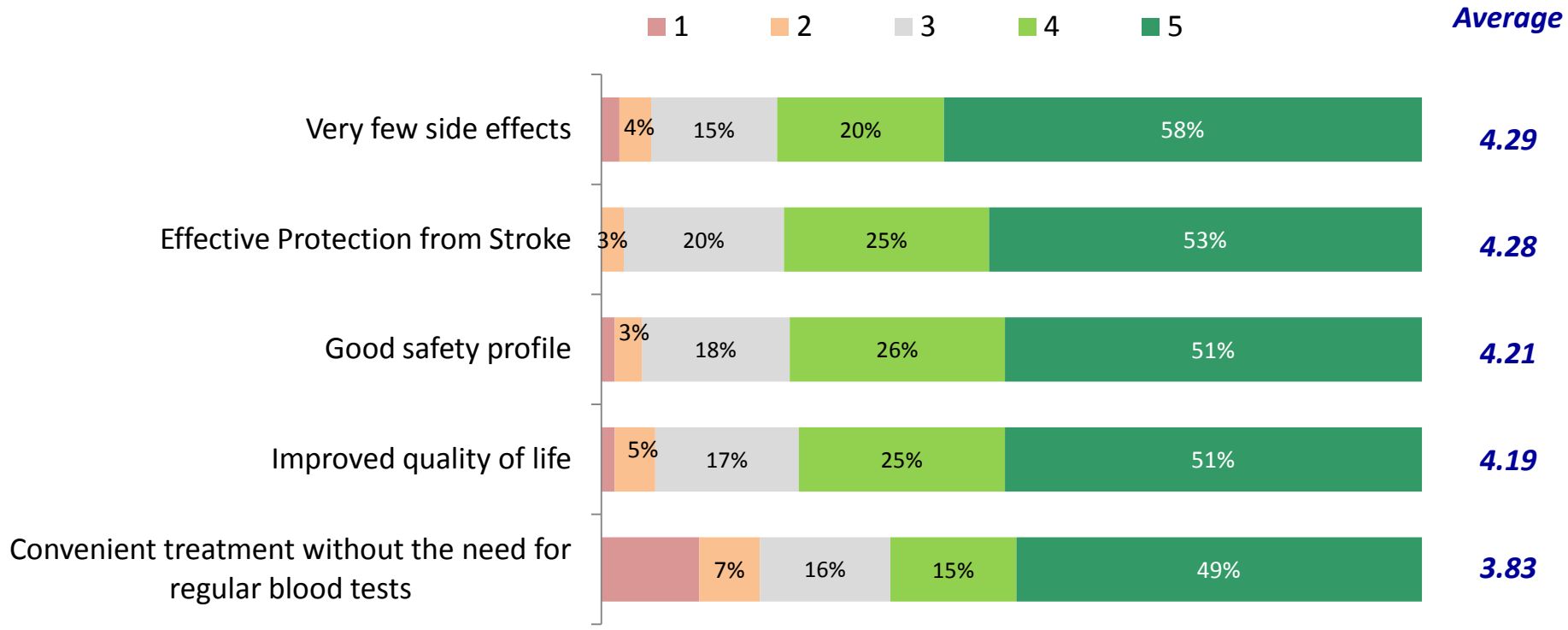
Rating scale: 1=not at all important, 5=very important

Q. respondent base: n = 192

Satisfaction with Current Treatment:

All Gaps for Convenience

How would you rate the performance of your current treatment in each of the following aspects?



Rating scale: 1=very low, 5=very high

Q. respondent base: n = 191

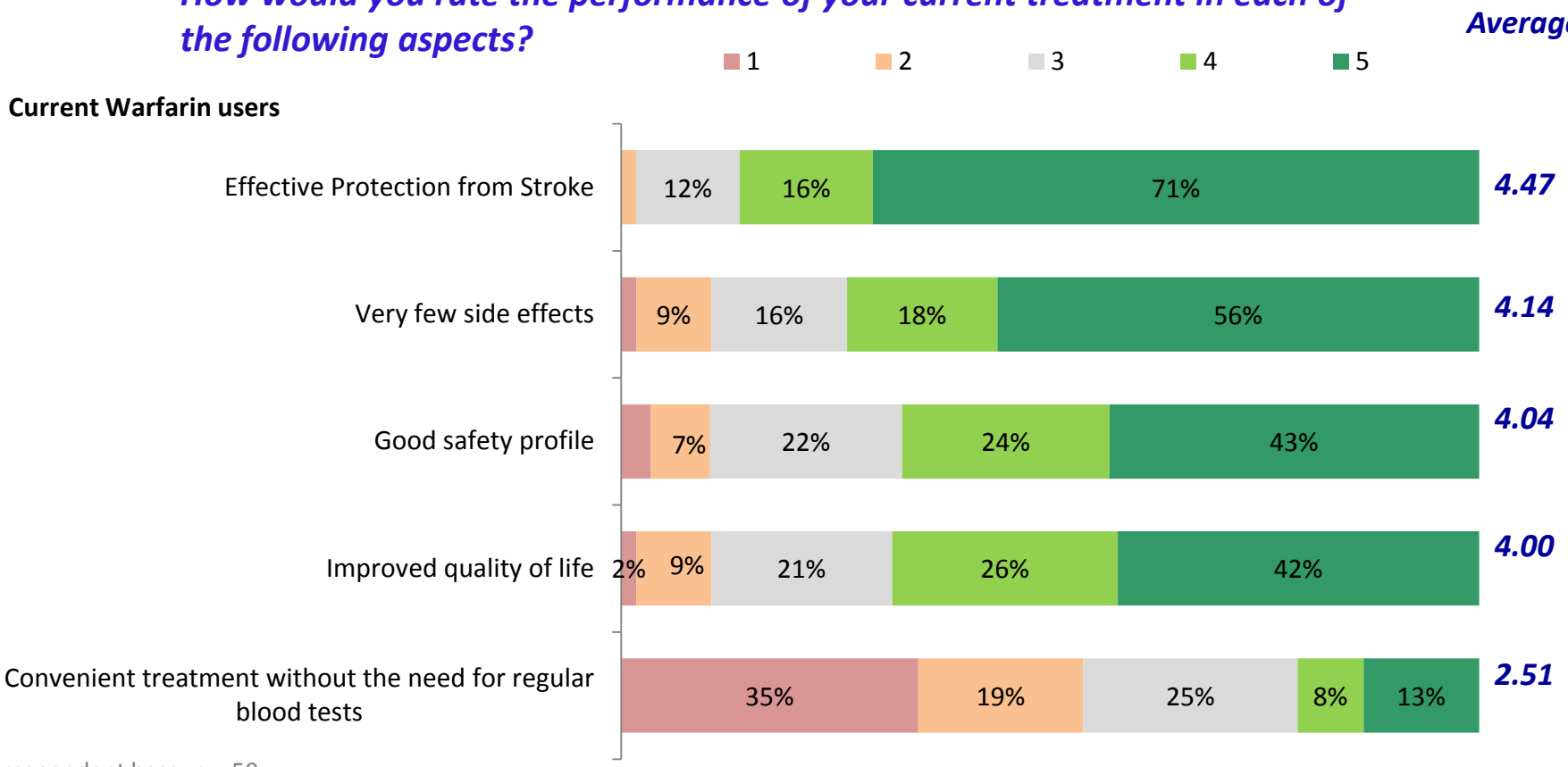
Importance and Satisfaction by different user profiles

For Current Warfarin users there is a satisfaction gap for improved quality of life and for safety profile and for convenience.

	Effective Protection from Stroke		Improved Quality of Life		Good Safety Profile		Very few side effects		Convenient treatment without the need for regular blood tests	
	Importance	Satisfaction	Importance	Satisfaction	Importance	Satisfaction	Importance	Satisfaction	Importance	Satisfaction
Current Warfarin Users N=59	4.68	4.56	4.56 →	4.00	4.52 →	3.98	4.53	4.19	3.95 →	2.51
Others N=125	4.55	4.15	4.57	4.28	4.47	4.33	4.30	4.34	4.26	4.60

Satisfaction with current treatment – Warfarin Users:
Significant gap for Convenience

How would you rate the performance of your current treatment in each of the following aspects?

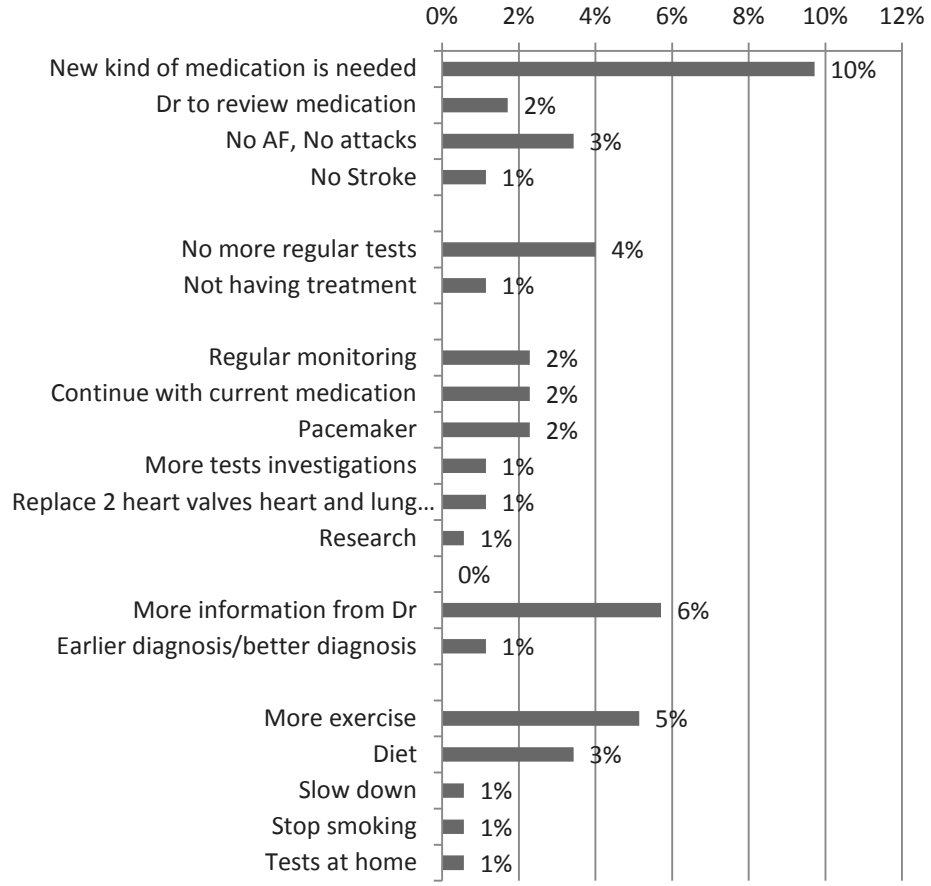


Q. respondent base: n = 59

Rating scale: 1=very low, 5=very high

Satisfaction with Current Treatment Options:
Need for Better AF Treatment

What could be done to better meet your needs in relation to Atrial Fibrillation treatment to prevent stroke



a cure rather than control

find a drug that is not intrusive and no side effects

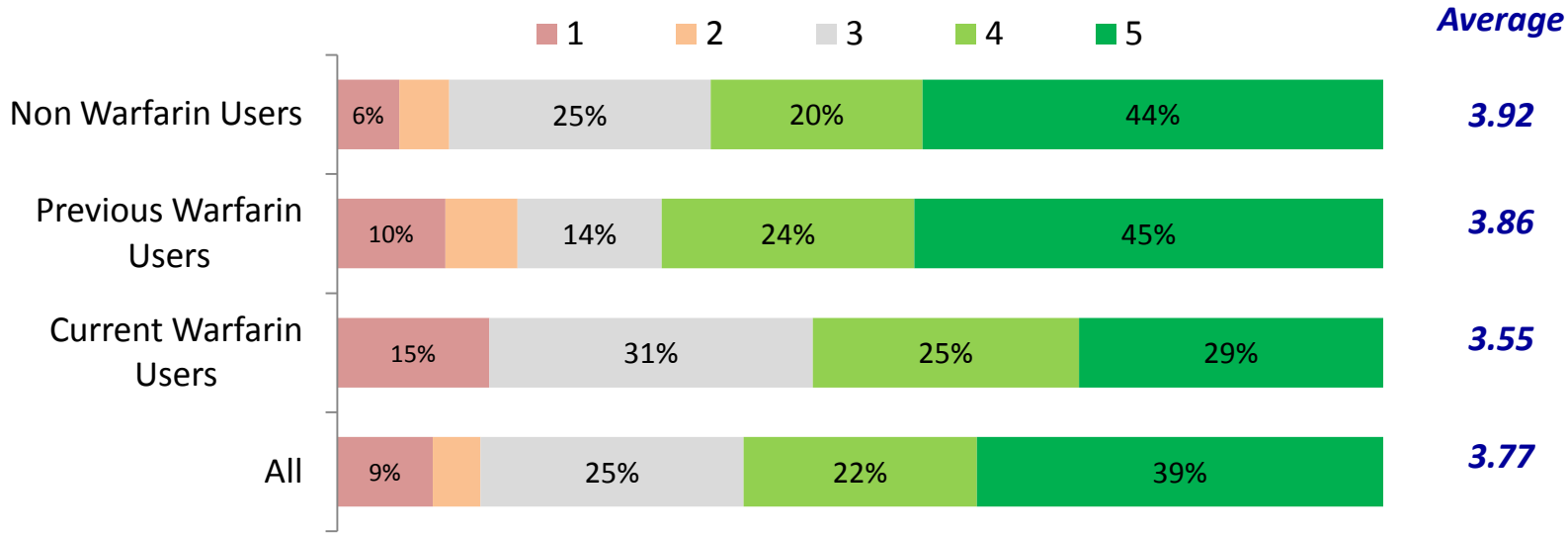
More information given by treating Drs about the condition, what to expect, possible contributing factors.

Better diet, exercise and self control

Comments from 175 respondents

Need for New Treatment Options
Moderate to High – Pre-Concept

To what extent do you see a need for new alternatives for managing the risk of stroke as a result of atrial fibrillation (irregular heartbeat/flutter)?



Rating scale: Need: 1=very low, 5=very high

Need for New Treatment Options:
Reasons – Safety and Simplicity

What are the specific reasons for your rating?

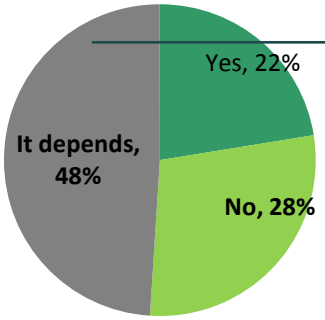
- *The safer (so) one can feel better*
- *Something far, far safer which does not need continuous monitoring or dietary changes yet gives one a chance of helping oneself*
- *Any simpler methods would be welcome*
- *Monitoring issue is the real problem*
- *Inconvenience of existing method.*

Likelihood to Try New Product – Pre-Concept

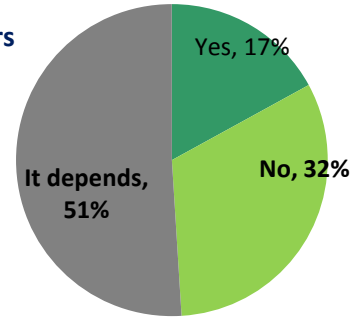
Contingent on Cost, Product Safety/Effect

Would you consider a new prescription recommended by your GP or specialist if it was not financially reimbursed by the government?

All
N=188



Warfarin users
N=59

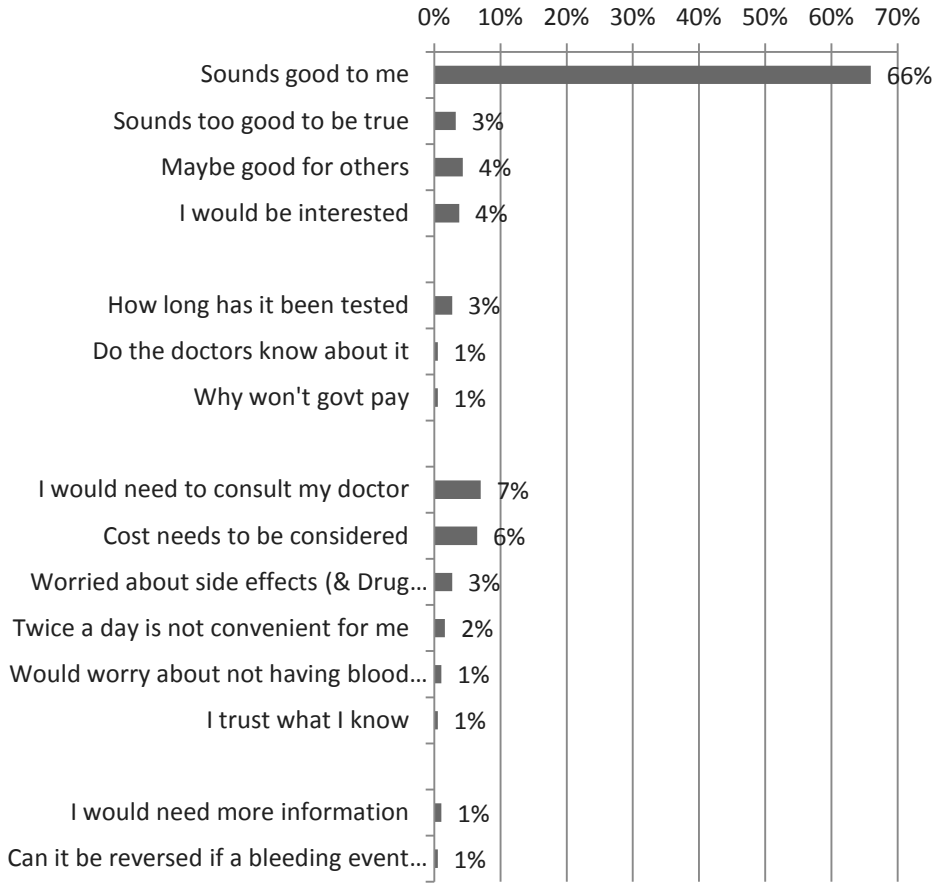


Information Needs

- *Being a Pensioner finances are limited.*
- *Cost and reasoning for change*
- *Depends on affordability*
- *Depends on cost and need for visits to GP efficacy*
- *For a specific reason*
- *How much I could afford on the pension*
- *I WOULD NEED TO KNOW THE BENEFIT OF THE SCRIPT*
- *If I could afford it*
- *If I needed it if it is better than that which is available presently maybe*
- *If it was absolutely necessary*

Response to New Product - Coded (from description – appendix)

What are your initial thoughts after reading the product description?



Comments from 185 respondents

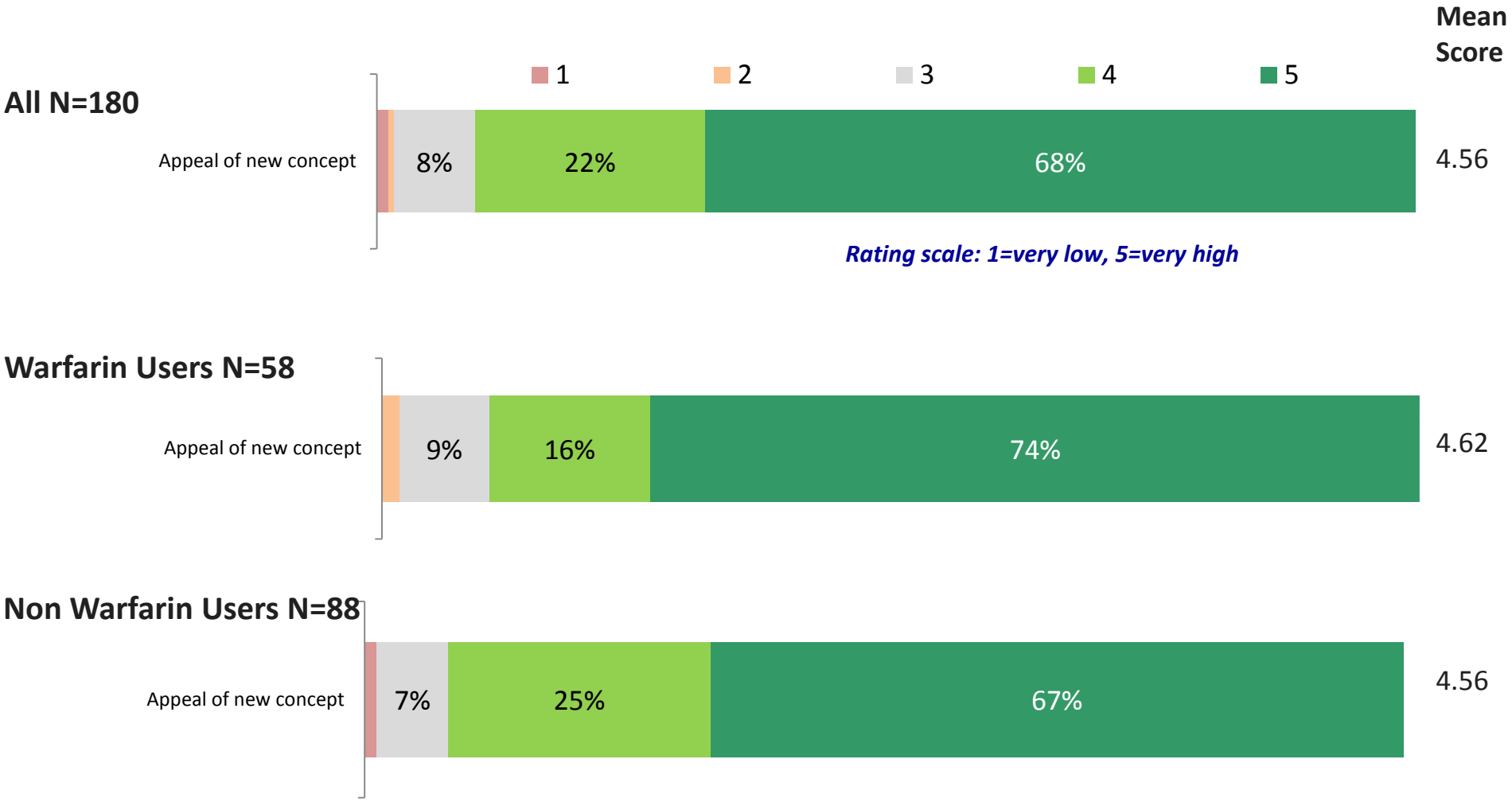
Positive but sounds too good to be true!

- *Sounds good for me/ Sounds too good to be true/ It sounds really good/ Excellent*
- *It may be of benefit to those continuing to have problems in spite of what medication they are on...*
- *A little bit of a fairytale - sorry! And how much would it cost? And why would the Govt not pay for it?*

Side effects?

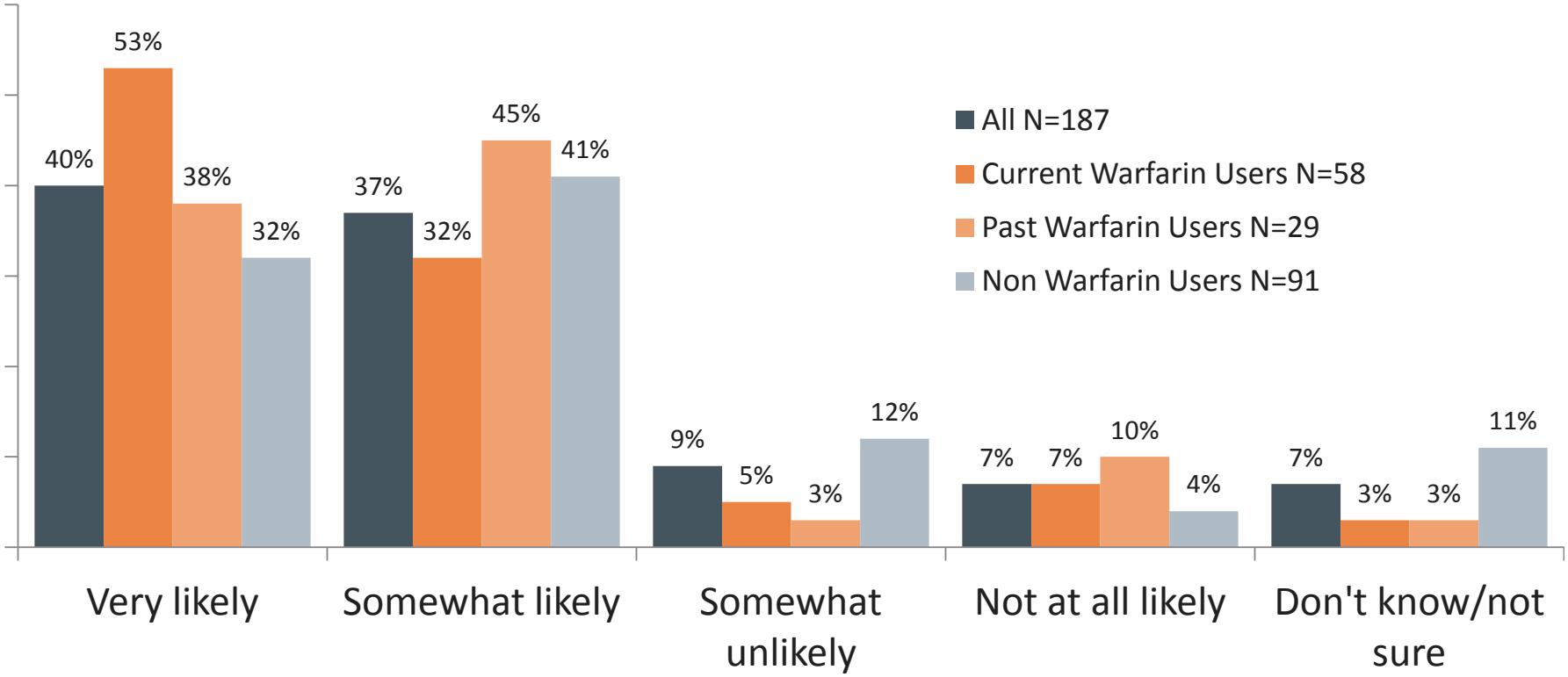
- *Seems ok, but all drugs have a side effect. How long has it been tested*
- *Very promising providing it has been well tested*
- *Sounds good but in my experience all drugs have their problems*
- *Check with my GP*

Response to New Product Concept - Significant Appeal Relative to Current Option



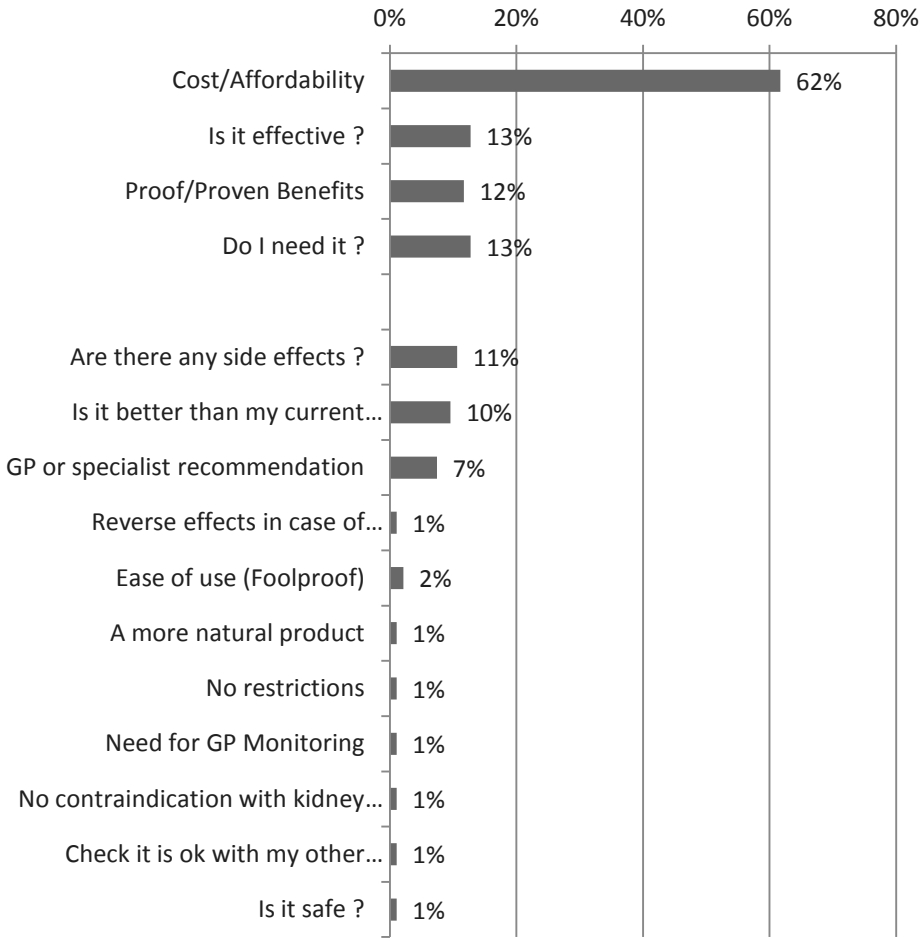
New Product – *Likelihood to Try is High*

If the product was available on the market, and not considering the price, how likely would you be to ask your GP for a prescription?



New Product – *Likelihood to Try is High – But Need GP Endorsement, Safety, Cost*

What information do you need to support your decision?



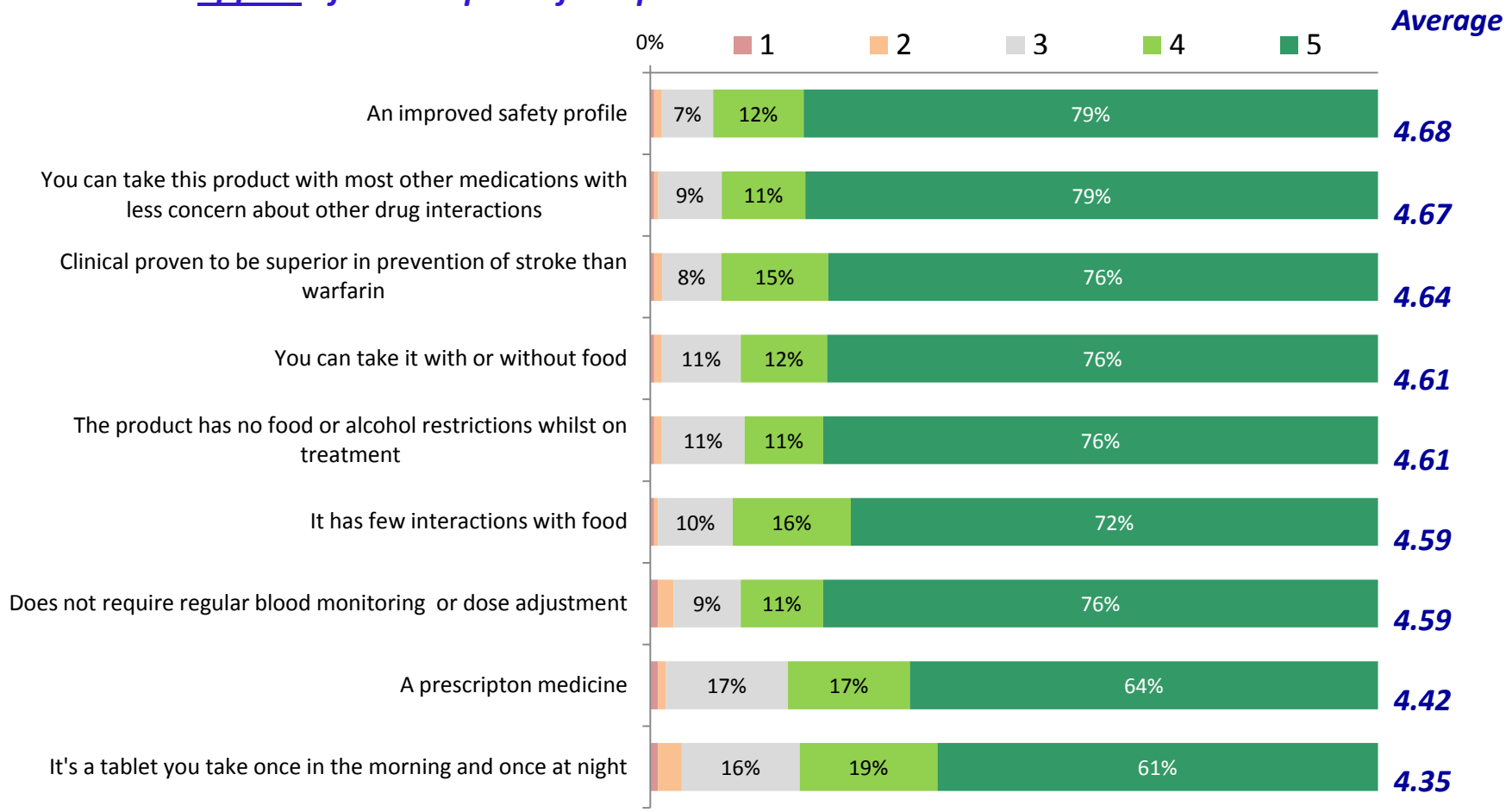
Comments from 94 respondents

- *Depends on the cost to pensioners.*
- *That it does what they say it will do and no side effects*
- *First - what 'drug' are we talking about? Secondly, what proof can be given - and I mean proof! Thirdly, how much would it cost!*
- *A strong recommendation from GP, and the possibility of medication being covered by PBS.*
- *The cost versus effectiveness.*

Response to New Product Features –

Safety profile, no blood monitor, clinical superiority, low interaction, high appeal

Please rate the appeal of each aspect of the product ?



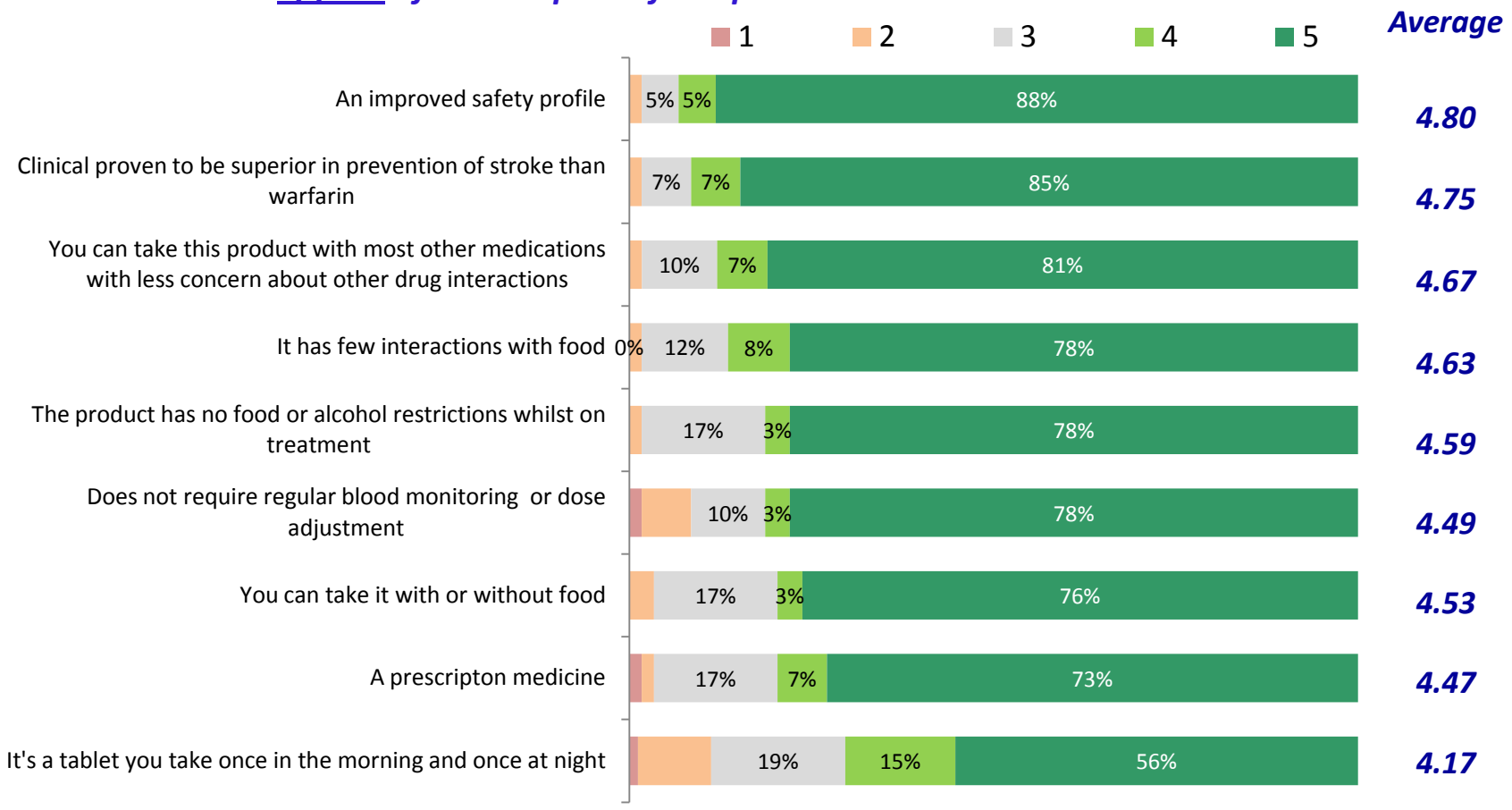
Q. respondent base: n = 170

Rating scale: 1=not at all appealing, 5=very appealing

Warfarin Users Response to New Product Features –

Safety profile, no blood monitor, clinical superiority, low interaction, extremely high appeal

Please rate the appeal of each aspect of the product ?

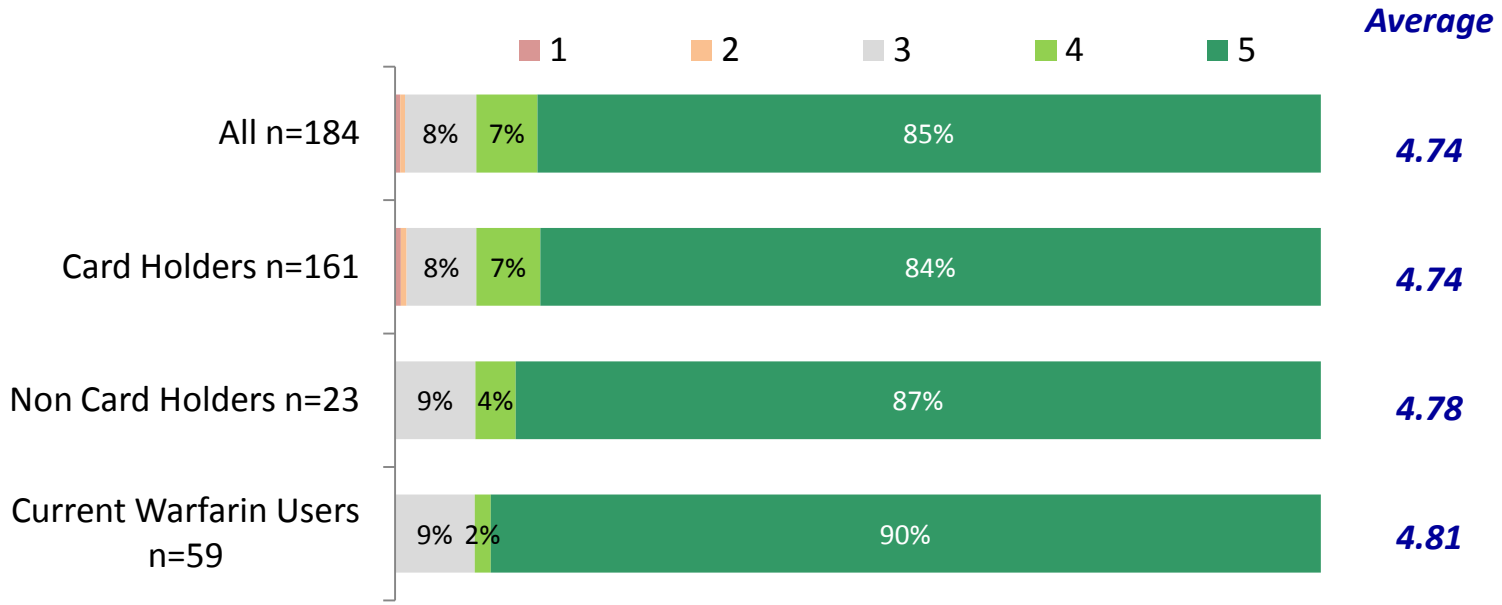


Q. respondent base: n = 51

Rating scale: 1=not at all appealing, 5=very appealing

Rating Importance of PBS Listing - Extremely High

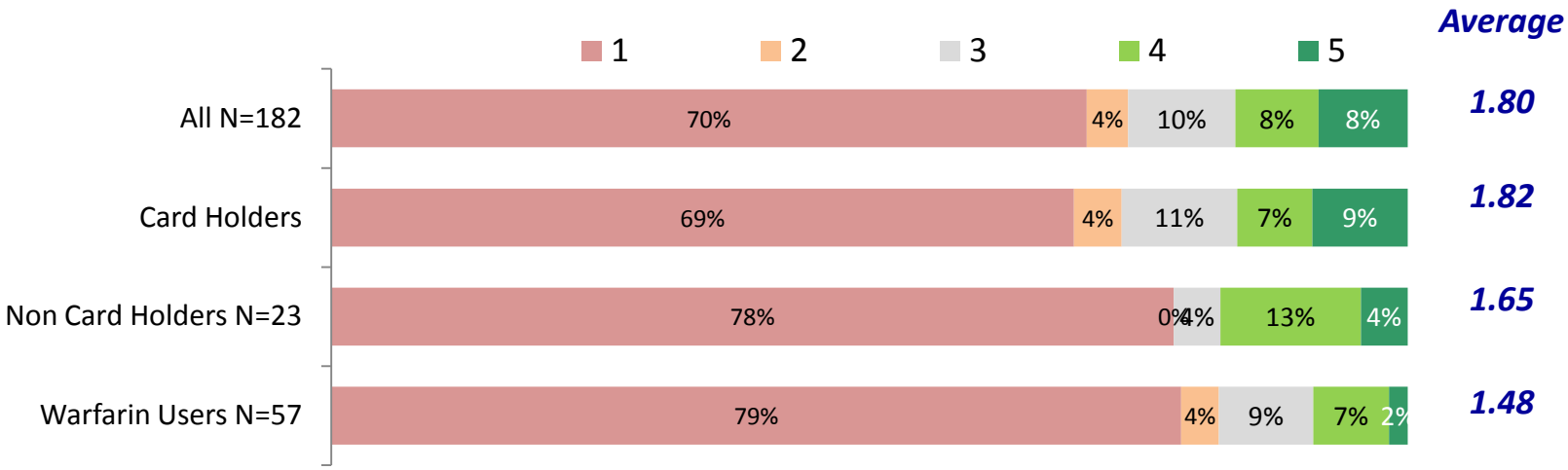
Knowing that this product has proven treatment advantages over warfarin how important would it be to you, for the government to approve access to this product through the PBS?



Rating scale:* 1=not *at all important, 5=very important

View of PBS Listing Delay – Majority Say Not Appropriate

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



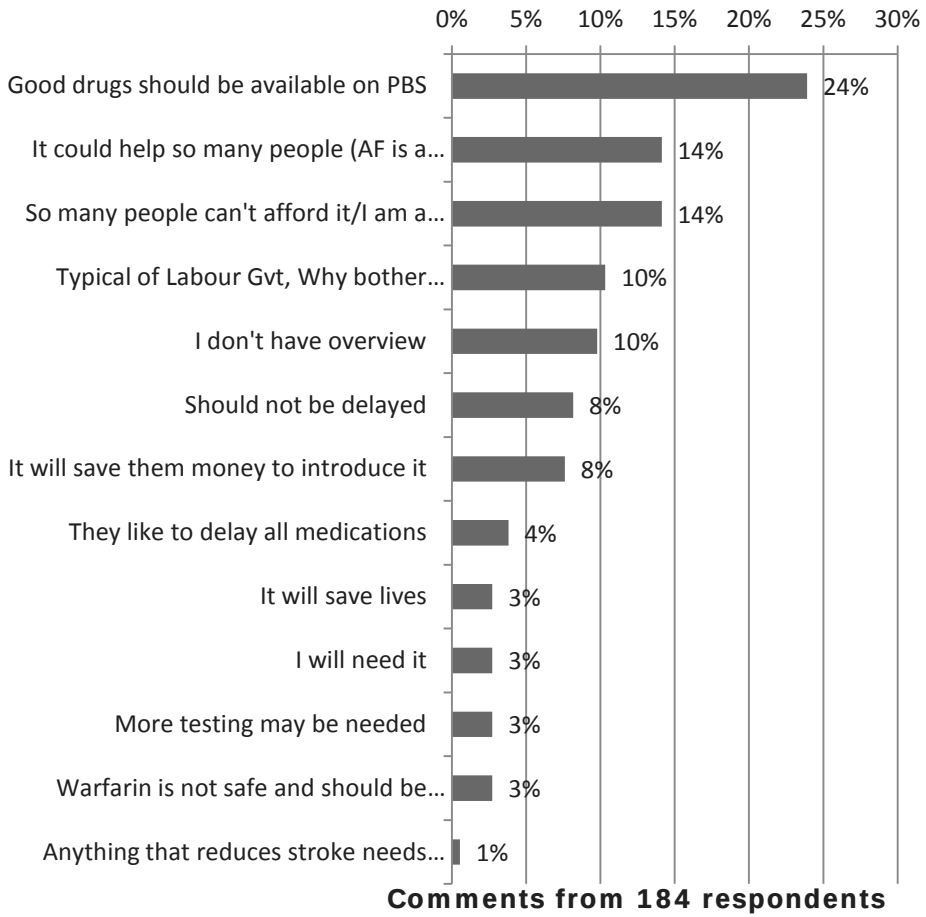
Rating scale: 1=not at all appropriate, 5=very appropriate

What is the Reason for Your Rating?

On Appropriateness of Delay:

Please rate the appropriateness of the decision by the government to delay listing given that its specialist advisory committee recommended listing the new product on the PBS?

What is the reason for your rating?



Comments from 184 respondents

Warfarin is a dangerous drug that many people use. They should be allowed to have better drugs available

The government should approve as soon as possible.

If it works as it is cracked up to be why is the government not putting it on the PBS as it will save them money on people going into hospital to get treated.

The government has a reputation of hindering new and improved medications, I know, they have blocked my pain medication upon the say so of one doctor over 2 specialists and 2 GPs! If a superior drug is available: for God's sake - people's lives are at stake every day - get on with it and leave all other matters aside; you ARE talking about LIFE!!

This is a very serious condition mainly affecting the elderly. Maybe the government thinks us oldies are not important enough to look after. I mean this is a common complaint I have 2 friends with this condition.

No data available regarding research or testing of this drug by peer review.

Do not understand reasons for government decisions on medication so really cannot comment.

They must know what they are doing.

Conclusions

- A variety of experiences for patients with Atrial Fibrillation from a low level, low concern condition to a major impact on their life with daily worry and limitations on what they can do.
- Significant interest and willingness to try a (clinician endorsed)superior new product.
- Expectations of cost are very low due to high health card carriers in the age group and patients compare with cost of existing regime.
- Reassurance of safety, testing done and no contraindications or side effects is important.
- Most patients felt the PBS delay was inappropriate.

APPENDIX D: INTERVENTIONS TO IMPROVE WARFARIN USE: LITERATURE SEARCH METHODOLOGY

A systemic literature search was conducted in order to identify all studies which aimed to improve warfarin use in the Australian clinical setting. Searches were conducted using Medline, Embase and the Cochrane Library, as well as HTA databases. The search strategies are shown in Table 61. A manual search of references was also undertaken. Overall, a total of 1,721 citations was identified.

Table 61 Details of search strategies

Database (search date)	Search string	Citations identified
Medline (10 October 2011)	#1 exp Warfarin/	12,600
	#2 "antithrombo*".m_titl.	3,444
	#3 anticoagulat$.m_titl.	5,451
	#4 warfarin.ab,ti.	12,404
	#5 1 or 2 or 3 or 4	23,756
	#6 exp Education/	557,467
	#7 exp Medication Adherence/	3,321
	#8 exp International Normalised Ratio/	2,845
	#9 exp Patient Compliance/	45,061
	#10 exp "Quality of Health Care"/	4,223,221
	#11 exp Interprofessional Relations/	47,604
	#12 exp "Delivery of Health Care"/	689,520
	#13 exp Physician's Practice Patterns/	34,043
	#14 exp Treatment Outcome/	520,115
	#15 exp Drug Utilization/	17,694
	#16 exp Education, Medical, Continuing/	19,146
	#17 exp Patient Education as Topic/	63,454
	#18 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	4,868,978
	#19 exp Australia/	85,358
	#20 (australia or aust or queensland or qld or tasmania or tas or victoria or vic or brisbane or hobart or melbourne).af.	410,271
	#21 (northern territory or western australia).af.	18,834
	#22 (northern territory or western australia or new south wales or australian capital territory or south australia).af.	69,806
	#23 (nt or wa or nsw or sa or darwin or perth or sydney or canberra or adelaide).af.	197,487
	#24 19 or 20 or 21 or 22 or 23	505,971
	#25 5 and 18 and 24	638

Database (search date)	Search string	Citations identified
Embase (10 October 2011)	#1 exp warfarin/	43,698
	#2 anticoagulat$.m_titl.	6,032
	#3 antithrombo$.m_titl.	3,855
	#4 1 or 2 or 3	50,039
	#5 exp patient satisfaction/	66,465
	#6 exp patient education/	67,629
	#7 exp patient compliance/	72,926
	#8 exp treatment outcome/	761,070
	#9 exp medication error/	8,439
	#10 exp drug monitoring/	23,176
	#11 exp quality control/	188,152
	#12 exp staff training/	7,010
	#13 exp drug utilization/	12,295
	#14 exp professional practice/	193,495
	#15 exp outcome assessment/	140,038
	#16 exp medical decision making/	57,877
	#17 exp education program/	30,306
	#18 exp Australia/	73,342
	#19 (australia or aust or queensland or new south wales or victoria or tasmania or south australia or western australia or northern territory or australian capital territory).af.	497,641
	#20 (brisbane or sydney or melbourne or hobart or adelaide or perth or darwin or canberra).af.	262,566
	#21 (nsw or vic or tas or sa or wa or nt or act).in.	402,106
	#22 18 or 19 or 20 or 21	658,447
	#23 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	1,343,148
	#25 4 and 22 and 23	790
Cochrane Library (10 October 2011)	warfarin in Title, Abstract or Keywords and program or intervention or adherence or compliance or education or training or management in Title, Abstract or Keywords in Cochrane Database of Systematic Reviews	280
National Library of Australia (TROVE) (11 November 2011)	Warfarin	2
HTA databases[3] (10 October 2011)	Warfarin	2
Manual searching	NA	9
Total		**1,721**

[3] MSAC (http://www.msac.gov.au/) and ANZHSN (http://www.horizonscanning.gov.au/)

Studies were considered eligible for inclusion if they were comparative and recruited patients receiving warfarin. The intervention must have aimed to directly improve the use of warfarin in patients, and evaluated the intervention using clinically and patient relevant outcomes. This included measures of INR, patient compliance, adverse events such as bleeds, strokes, thrombosis and clinical outcomes such as number of hospitalisations. Studies must have been conducted in Australia. This is shown in Table 62.

Table 62 Study criteria

Study design	Any comparative study design
Population	Patients receiving warfarin
Intervention	Any program which directly aims to improve warfarin use in patients
Comparator	Any
Outcomes	Clinically relevant outcomes such as measures of INR, compliance, adverse events, hospitalisations etc.
Location	Australia

Subsequently, the exclusion criteria shown in Table 63 was applied to the identified citations. Studies published prior to 2001 were excluded, as were studies not performed in Australia. Studies which were not comparative, such as letters, review articles, case reports and animal studies were also excluded. Conference abstracts were also excluded as they do not provide sufficient information on patient populations and study methodology. Studies were excluded if they did not aim to directly improve warfarin use in patients. This included studies which evaluated different warfarin dosing regimens, the relationship between of genetic variations and warfarin effectiveness, and warfarin compared with other anticoagulants. Studies which validated specific INR testing procedures were also excluded. Studies were also excluded if they did not evaluation an intervention, such as hospital chart audits which compared patients who received warfarin with patients who did not receive warfarin. Studies were also excluded if they did not evaluate a patient relevant outcome. For example, surveys which evaluated differences in clinician opinion about INR testing or perceived barriers to warfarin use were excluded.

Table 63 Exclusion criteria

Wrong study year	Not conducted in 2001 or later
Wrong study type	Not a comparative study (eg letters, case reports, review articles, single arm studies, conference abstracts)
Wrong population	Not conducted in patients receiving warfarin
Wrong intervention	Not an intervention which directly aims to improve warfarin use in patients (eg excluded interventions included warfarin protocols/dosing regimens and specific warfarin test validation)
Wrong location	Not conducted in Australia
Wrong outcome	Not a clinically relevant outcome (eg measures of satisfaction, knowledge, opinion)

The exclusion criteria shown in Table 63 was applied to the citations identified in the literature search. Of the 1,721 citations, 1,531 were non-duplicate citations. The title and abstract were reviewed, with 55 citations considered eligible for full text review. Following a review of the full text, 24 citations were included in the literature review. This is shown in Table 64.

Table 64 Summary of the literature search

Number of citations retrieved	1,721
Number of non-duplicate citations	1,531
Reasons for exclusion after review of title/abstract:	
Wong study year	452
Wrong study type	677
Wrong population	152
Wrong intervention	173
Wrong outcome	5
Wrong location	17
Total number of citations excluded	1,476
Number of full-text citations retrieved	55
Reasons for exclusion after review of full text:	
Wong study year	0
Wrong study type	4
Wrong population	2
Wrong intervention	3
Wrong outcome	0
Wrong location	22
Total number of citations excluded	31
Total number of citations identified	**24**

The full citation of the 24 citations is shown in Table 65. The publications described 19 different interventions. The Point of Care Testing (PoCT) trial reported relevant outcomes in three publications: Bubner 2009, Gialamas 2009 and Laurence 2010. Jackson 2004b,

Jackson 2004c and Peterson 2006 reported data from the same trial, as did Peterson 2010 and Stafford 2011.

Table 65 Included citations

Trial ID	Citation
Bajorek 2005	Bajorek, B. V., Krass, I., Ogle, S. J., Duguid, M. J., and Shenfield, G. M. Optimizing the use of antithrombotic therapy for atrial fibrillation in older people: a pharmacist-led multidisciplinary intervention. Journal of the American Geriatrics Society 53(11), 1912-1920. 2005
Bereznicki 2010	Bereznicki, L., Jeffrey, E. C., Peterson, G., Jackson, S., Nelson, M., Kelly, B, Gee, P, and Fitzmaurice, D. Pharmacy-based model enabling patient self-monitoring of warfarin: development and evaluation. 2010. The Pharmacy Guild of Australia
Bereznicki 2007	Bereznicki, L. R., Jackson, S. L., Morgan, S. M., Boland, C., Marsden, K. A., Jupe, D. M., Vial, J. H., and Peterson, G. M. Improving clinical outcomes for hospital patients initiated on warfarin. Journal of Pharmacy Practice and Research.37 (4) (pp 295-302), 2007.
Bubner 2009 Gialamas 2009 Laurence 2010	Bubner, T. K., Laurence, C. O., Gialamas, A., Yelland, L. N., Ryan, P., Willson, K. J., Tideman, P., Worley, P., and Beilby, J. J. Effectiveness of point-of-care testing for therapeutic control of chronic conditions: results from the PoCT in General Practice Trial. Med J Aust 2009(11), 624-626. 2009. Gialamas, A., Yelland, L. N., Ryan, P., Willson, K., Laurence, C. O., Bubner, T. K., Tideman, P., and Beilby, J. J. Does point-of-care testing lead to the same or better adherence to medication? A randomised controlled trial: the PoCT in General Practice Trial. Med J Aust 2009(9), 487-491. 2009. Laurence, C., Gialamas, A., Yelland, L., Bubner, T., Ryan, P., Willson, K., Glastonbury, B., Gill, J., Shephard, M., and Beilby, J. A pragmatic cluster randomised controlled trial to evaluate the safety, clinical effectiveness, cost effectiveness and satisfaction with point-of-care testing in a general practice setting - Rationale, design and baseline characteristics. Trials.9 , 50. 2008.
Coombes 2009	Coombes, I. D., Stowasser, D. A., Reid, C., and Mitchell, C. A. Impact of a standard medication chart on prescribing errors: a before-and-after audit. Quality & Safety in Health Care 18(6), 478-485. 2009.
Crotty 2004	Crotty, M., Whitehead, C., Rowett, D., Halbert, J., Weller, D., Finucane, P., and Esterman, A. An outreach intervention to implement evidence based practice in residential care: a randomised controlled trial. BMC Health Services Research 4(1), 6. 6-4-2004.
Duff 2010	Duff, J. and Walker, K. Improving the safety and efficacy of warfarin therapy in a metropolitan private hospital: a multidisciplinary practice improvement project. Contemporary Nurse 35(2), 234-244. 2010.
Elliott 2002	Elliott, R. A., Woodward, M. C., and Oborne, C. A. Antithrombotic prescribing in atrial fibrillation: application of a prescribing indicator and multidisciplinary feedback to improve prescribing. Age & Ageing 31(5), 391-396. 2002.
Jackson 2004a	Jackson, S. L., Peterson, G. M., and Vial, J. H. A community-based educational intervention to improve antithrombotic drug use in atrial fibrillation. Annals of Pharmacotherapy 38(11), 1794-1799. 2004.

Trial ID	Citation
Jackson 2004b Jackson 2004c Peterson 2006	Jackson, S. L., Peterson, G. M., Vial, J. H., and Jupe, D. M. Improving the outcomes of anticoagulation: an evaluation of home follow-up of warfarin initiation. Journal of Internal Medicine 256(2), 137-144. 2004. Jackson, S., Peterson, G., Vial, J., and Jupe, D. Suboptimal anticoagulant management in patients after hospital initiation of warfarin. Australian Family Physician 33(6), 477-478. 2004. Peterson, G. M., Lutrrell, D, Hughes, J., Raymond, K, Tompson, A, Jachuck, S. J., Hasan, O, Gee, P, Nash, R, Cooper, C, Fitzmaurice, D., and Roberts, B. Facilitating quality use of medicines between hospital and community. 2006. The Pharmacy Guild of Australia.
Jackson 2011	Jackson, S. L. and Peterson, G. M. Stroke risk assessment for atrial fibrillation: hospital-based stroke risk assessment and intervention program. Journal of Clinical Pharmacy & Therapeutics 36(1), 71-79. 2011.
Lubliner 2005	Lubliner, M., Cole-Sinclair, M., Kenneally, A., Street, A., Van, De, V, and Walsh, M. K. Minimising medication mishap: Introducing a warfarin safety strategy. Journal of Pharmacy Practice and Research.35 (4) (pp 266-270), 2005.
Mandryk 2008	Mandryk, J. A., Wai, A., Mackson, J. M., Patterson, C., Bhasale, A., and Weekes, L. M. Evaluating the impact of educational interventions on use of antithrombotics in Australia. Pharmacoepidemiology & Drug Safety 17(2), 160-171. 2008.
McLachlan 2005	McLachlan, A. J., Spindler, M, Fois, R. A., Krass, I., Chen, T. F., and Bajorek, B. A community based anticoagulant management service. 2005. The Pharmacy Guild of Australia.
Mullan 2005	Mullan, J. Antithrombotic prescribing in atrial fibrillation: application of a prescribing indicator and multidisciplinary feedback to improve prescribing. 2005. University of Wollongong.
Peterson 2010 Stafford 2011	Peterson, G., Jackson, S., Bereznicki, L., Nelson, M., Angley, M., Mullan, J. R., Gaetani, L., Misan, G., Marsden, K., Warbuton, K, Eaton, V., Shakib, S., Maddison, J, Doecke, C., Mangoni, A. A., Yeo, W, Potter, J, Seaton, S, Gee, P, Fitzmaurice, D., Stafford, L., van Tienen, E. C., Hill, G, DeBoos, I, Doran, C, and Jainullabudeen, T. The role of community pharmacy in post hospital management of patients initiated on warfarin. 2010. Pharmacy Guild of Australia. Stafford, L., Peterson, G. M., Bereznicki, L. R., and Jackson, S. L. A role for pharmacists in community-based post-discharge warfarin management: protocol for the 'the role of community pharmacy in post hospital management of patients initiated on warfarin' study. BMC Health Services Research 11, 16. 2011.
Roberts 2006	Roberts, G. W. and Adams, R. Impact of introducing anticoagulation-related prescribing guidelines in a hospital setting using academic detailing. Therapeutics and Clinical Risk Management. 2 (3) 309-316. 2006.
Roughead 2011	Roughead, E. E., Barratt, J. D., Ramsay, E., Pratt, N., Ryan, P., Peck, R., Killer, G., and Gilbert, A. L. Collaborative home medicines review delays time to next hospitalization for warfarin associated bleeding in Australian war veterans. Journal of Clinical Pharmacy & Therapeutics 36(1), 27-32. 2011.
Van De Vreede 2003	Van De Vreede, M. A., Kenneally, A. L., and Lubliner, M. Introducing a Multidisciplinary Medication Safety Program in a Major Hospital. Journal of Pharmacy Practice and Research. (4), Dec. 2003