

Current and Emerging Anticoagulant Agents for the Prevention and Treatment of Ischemic Stroke: Focus on Dabigatran

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Abstract: Vitamin K antagonists (VKAs) such as warfarin are the cornerstone therapy for stroke prevention in persons with atrial fibrillation. However, their inherent limitations make VKAs particularly challenging to manage safely and effectively. The resulting underutilization of this effective treatment has been well-documented. Several new oral anticoagulants are in development to address these limitations, the most advanced of which is dabigatran. The RE-LY study evaluated the safety and efficacy of 2 doses of dabigatran versus warfarin in a Phase III trial for the prevention of stroke and systemic embolism in persons with atrial fibrillation. The higher 150 mg dose demonstrated superior efficacy over warfarin, with a 34% relative risk reduction in the primary outcome ($P < 0.001$), and similar major bleeding rates. The lower 110 mg dose was similar to warfarin in efficacy but significantly reduced the risk of major bleeding. Both doses significantly reduced the risk of intracranial haemorrhage. These results provide strong evidence that dabigatran is a safe and effective alternative to warfarin with several advantages, including elimination of the requirement for routine anticoagulation monitoring.

Keywords: atrial fibrillation, stroke prophylaxis, anticoagulant, dabigatran



Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, afflicting approximately 2.5 million patients in the US and 4.5 million patients in the EU.^{1,2} Its prevalence increases substantially with age, from <1% in persons younger than 60 years up to approximately 10% in those aged 80 years and older.²⁻⁴ By 2050, the prevalence in the US is expected to surpass 10 million.⁵

AF promotes the formation of thrombus in the left atrium through the interplay of the components of Virchow's triad of stasis, endothelial dysfunction, and hypercoagulability with other risk factors such as age, gender, and hypertension.¹ Patients with AF have a 5-fold increased risk of stroke,⁶⁻⁸ such that 15%–20% of all strokes can be attributed to AF.^{6,9} The risk of stroke in AF increases notably with age.⁷ In addition, strokes in patients with AF are more severe than in those without.⁸ The objective behind long-term anticoagulant therapy in AF is to reduce the risk of stroke by preventing cerebral thromboembolism.

A risk-based approach to identifying patients who will benefit most from anticoagulant therapy is advocated by ACCP and ACC/AHA/ESC guidelines.^{1,9} Vitamin K antagonists (VKAs) such as warfarin are the only oral anticoagulants currently recommended for patients with AF at moderate to high risk of stroke. The effectiveness of VKA therapy for this indication has been well-documented in numerous studies, conferring a reduction in relative risk of 64% compared to placebo and 37% compared to antiplatelet therapy.¹⁰ Acetylsalicylic acid (ASA) is a recommended option only for those at lower risk of stroke due to its limited protection.^{1,9}

VKAs have a narrow therapeutic window, putting patients at risk of either AF-related stroke or bleeding complications if the target anticoagulant effect is not maintained. VKAs have a high degree of inter- and intra-patient variability due to the influence of genetic factors, drug-drug interactions, dietary intake of Vitamin K, and underlying medical conditions.⁹ As a result, vigilant coagulation monitoring and dose adjustment, as well as lifestyle modifications by the patient, are necessary to ensure that anticoagulant effects are within the narrow therapeutic range.

The utilization of VKA therapy in AF patients has been explored in many studies over the past decade.

These studies consistently report underutilization of oral anticoagulation therapy, with minimal improvement over time despite VKA's clearly established benefits.^{2,11-19} These findings are likely due to the unpredictable nature of VKA therapy and the resulting concerns, among patients and the medical community alike, of causing a major bleeding event such as an intracranial hemorrhage.

There is a clear need for new oral agents that provide the benefits of VKA without its limitations. Ideally, these agents should bring a balance of safety and efficacy, confer a predictable anticoagulant effect without the need for coagulation monitoring, and be free of significant food and drug interactions. To address the challenges associated with VKAs, several novel oral anticoagulants are currently in development. This paper describes those being studied for the prevention of stroke in AF with a focus on dabigatran, a novel direct thrombin inhibitor that has demonstrated significant benefits over warfarin.

Novel Oral Agents in Development for Stroke Prevention in AF

There are several potential points within the coagulation pathway for novel anticoagulants to target. Factor IIa (thrombin) plays a pivotal role in coagulation and is thus an intuitively appealing target. At the final stage of the coagulation pathway, thrombin converts fibrinogen to fibrin, the essential step in clot formation. Thrombin amplifies its own generation through feedback activation of Factors V, VIII, and XI; it is also a potent stimulus for platelet activation. Once bound to fibrin, thrombin promotes further coagulation and thrombus growth through continued local activation of clotting factors and platelets.

Direct thrombin inhibitors, such as dabigatran and AZD0837, inhibit thrombin by binding directly and exclusively to its active site. These agents are capable of inhibiting both free and fibrin-bound thrombin. This is an advantage over Vitamin K antagonists and the heparins (unfractionated and low-molecular-weight), which are ineffective against fibrin-bound thrombin.²⁰

Reversible thrombin inhibitors, such as dabigatran and AZD0837, dissociate from thrombin, thereby potentially preserving a small reservoir of free, enzymatically active thrombin available to maintain



normal haemostasis. This characteristic may contribute towards greater safety and predictability than earlier, irreversible agents such as hirudin.

Activated Factor X (FXa) is another target for novel oral anticoagulants. FXa binds with activated Factor V (FVa) to form the prothrombinase-complex, which converts prothrombin to thrombin. FXa inhibitors thus interfere with the generation of thrombin as opposed to its activity. Direct FXa inhibitors, including rivaroxaban, apixaban, edoxaban, betrixaban, and YM150, bind to the active site of the enzyme and are able to inhibit both free and prothrombinase-bound FXa. In comparison, the antithrombin-mediated action of indirect FXa inhibitors such as fondaparinux and the heparins makes them ineffective against FXa bound within the prothrombinase complex.

Direct Thrombin Inhibitors

Two oral direct thrombin inhibitors are being studied for the prevention of stroke in AF. Dabigatran etexilate is the most advanced in its clinical development program. AZD0837 is a follow-up compound of ximelagatran.

Dabigatran etexilate

Dabigatran etexilate is the prodrug of dabigatran, a reversible direct thrombin inhibitor in the later stages of clinical development. It is licensed for venous thromboembolism (VTE) prevention following elective knee or hip arthroplasty in Canada and the EU at a recommended dose of 220 or 150 mg once daily. A large Phase III trial evaluating dabigatran's safety and efficacy in preventing stroke in patients with non-valvular AF was recently published. Other trials are assessing the safety and efficacy of dabigatran for prevention of cardiac events in patients with acute coronary syndromes and the treatment and secondary prevention of VTE.

Pharmacology

Dabigatran has a predictable anticoagulant response with a linear dose-effect relationship²¹ that does not require routine monitoring. It is rapidly absorbed (T_{\max} 1.25 to 3 hours), with a correspondingly quick onset of action that is closely associated with plasma concentration (Table 1). Dabigatran has an absolute bioavailability of 6.5%. Although low bioavailability is sometimes associated with variable drug exposure, this

is not the case with dabigatran. Its pharmacokinetics are linear over a wide range of doses, demonstrating a predictable pharmacokinetic profile. Dabigatran capsules contain pellets with a tartaric acid core which enhance consistency of absorption and negate variations in gastric pH. Drug exposure is not affected by co-administration with food.

Dabigatran's half-life is 12 to 17 hours, suggesting once and twice daily dosing regimens are feasible. The primary mode of excretion is renal (80%), with the remainder predominantly excreted via the bile. Dabigatran's predictable pharmacokinetic profile is maintained in the elderly with a slightly reduced clearance rate.

VTE prophylaxis post orthopaedic surgery

A set of 3 Phase III clinical trials evaluated the safety and efficacy of dabigatran, administered as 150 or 220 mg once daily, for VTE prophylaxis following elective hip or knee arthroplasty (Table 2).^{22–24} RE-MODEL and RE-NOVATE concluded that dabigatran was as safe and effective as 40 mg of enoxaparin administered once daily following total knee replacement and total hip replacement, respectively. In RE-MOBILIZE, which compared dabigatran to 30 mg of enoxaparin administered twice daily following total knee replacement, dabigatran demonstrated a similar safety profile but did not meet its non-inferiority endpoint. The pre-specified pooled analysis concluded that 220 mg of dabigatran administered once daily is a well tolerated alternative to enoxaparin for this indication with a similar safety profile.²⁵

Post-hoc analyses of elderly patients (age >75 years) and patients with moderate renal impairment (creatinine clearance rate 30–50 ml/minute) concluded that, in each of these populations, the 150 mg once daily dose of dabigatran provided similar efficacy and a favourable bleeding profile compared with 40 mg once daily of enoxaparin.^{26,27}

VTE treatment

The Phase III trial, RE-COVER, assessed the safety and efficacy of dabigatran compared with warfarin in 2,564 patients diagnosed with acute venous thromboembolism.²⁸ Patients were initially treated with parenteral anticoagulant therapy, then were randomized to receive 6 months of therapy with either



Table 1. PK/PD characteristics.

Parameter	Dabigatran etexilate	AZD 0837	Rivaroxaban	Apixaban	Edoxaban (DU-176b)	Betrixaban
Mechanism of action	Direct thrombin inhibitor ⁵¹	Direct thrombin inhibitor ²¹	Direct FXa inhibitor ⁵⁹	Direct FXa inhibitor ⁶⁶	Direct FXa inhibitor ⁷²	Direct FXa inhibitor ⁷⁴
Oral bioavailability	6.5% ⁵¹	22%–55% ⁵⁵	~80% ⁶⁰	66% ⁶⁷	~50% in monkeys ⁷³	47% ⁷⁴
T _{max}	1.25–3 h ⁵²	1.5 h ⁵⁵	2–4 h ⁶⁰	1–3 h ^{68–70}	1.5 h ⁷²	Not reported ⁷⁴
Reversible	Yes ⁵¹	Yes ⁵⁶	Yes ⁵⁹	Yes ⁷⁰	Not reported	Yes ⁷⁴
Half-life	12–17 h ⁵³	9 h ⁵⁵	9–13 h ^{61,62}	8–15 h ^{69,70}	9–11 h ⁷²	19 h ⁷⁴
Mode of excretion	80% renal ⁵³	Hepatic ⁵⁷	66% renal, 32% fecal/biliary ⁶³	25% renal, 55% fecal ⁷⁰	Predominantly renal ⁷²	Unchanged in bile ⁷⁴
Food	Delayed absorption ⁵²	Delayed absorption ⁵⁵	Delayed absorption ⁶⁴	Not reported	Not reported	Minimal ⁷⁵
Age effect	Reduced dose advised to address age-related renal impairment ⁵⁴	Not reported	None, ⁶⁵ caution advised with moderate renal impairment ⁶³	Not reported	Not reported	Not reported
Weight effect	No ⁵⁴	Not reported	No ⁶³	Not reported	Not reported	Not reported
Gender effect	No ⁵²	Not reported	No ⁶⁵	Not reported	Not reported	Not reported
Drug-drug interactions	Strong P-gp inhibitors; contraindicated with quinidine ⁵⁴	Strong CYP3A4 inhibitors ⁵⁸	Contraindicated with strong CYP3A4 and P-gp inhibitors ⁶³	Potential with strong CYP3A4 inhibitors ⁷¹	Not known	Not known

Pharmacokinetic features of YM150 are not available.

**Table 2.** Phase III VTE results (apixaban, rivaroxaban, dabigatran).

Agent	Trial name	Enoxaparin dose	Population studied	Dose	Efficacy		Safety	
					Relative risk	P Value	Relative risk	P Value
Dabigatran	RE-NOVATE	40 mg QD	THR	150 mg QD	1.28	<0.0001 for NI	0.83	ns
				220 mg QD	0.90	<0.0001 for NI	1.29	ns
	RE-MODEL	40 mg QD	TKR	150 mg QD	1.07	0.017 for NI	0.99	ns
				220 mg QD	0.97	0.003 for NI	1.14	ns
	RE-MOBILIZE	30 mg BID	TKR	150 mg QD	1.33	NI not met	0.42	ns
				220 mg QD	1.23	NI not met	0.42	ns
Rivaroxaban	RECORD 1	40 mg QD	THR	10 mg QD	0.30	<0.001	3.02	0.18
	RECORD 2	40 mg QD	THR	10 mg QD	0.21	<0.001	1.19	ns
	RECORD 3	40 mg QD	TKR	10 mg QD	0.51	<0.001	1.18	0.77
	RECORD 4	30 mg BID	TKR	10 mg QD	0.69	0.012	2.47	0.11
Apixaban	ADVANCE 1	30 mg BID	TKR	2.5 mg BID	1.02	0.064 for NI	0.67	0.03
	ADVANCE 2	40 mg QD	TKR	2.5 mg BID	0.62	<0.001 for NI	0.73	0.09

Abbreviations: THR, total hip replacement; TKR, total knee replacement; QD, once daily; BID, twice daily; NI, non-inferiority; ns, not significant. *P*-values are for superiority unless otherwise noted.

dabigatran at 150 mg twice daily or dose-adjusted warfarin (INR 2.0–3.0). Results demonstrated that this dose of dabigatran was as safe and effective as warfarin for this indication.

Stroke prevention in atrial fibrillation

Phase II

PETRO, a 12-week dose-finding and safety trial of dabigatran in AF, was conducted to identify doses that achieved the desired level of anticoagulant effect for further study in Phase III.²⁹ Three blinded twice-daily doses of dabigatran (50, 150, and 300 mg) were compared with open-label dose-adjusted warfarin (INR 2.0–3.0) in 502 patients. Those receiving dabigatran were also randomized to receive ASA (0, 81, or 325 mg/day). Endpoints included major and minor bleeding episodes, evaluated by an independent adjudicated committee blinded to treatment, and thromboembolic events.

A linear dose-response relationship was observed (Fig. 1). The 150 mg twice-daily dose provided the appropriate level of anticoagulant effect for further evaluation in Phase III testing. Co-administration with ASA at this dose did not increase major or clinically relevant bleeding.

Phase III

Design

In RE-LY, the largest outcomes trial ever performed in this population, 18,113 patients with non-valvular AF and at least one additional risk factor for stroke were randomized to one of 2 blinded twice-daily doses of dabigatran (110 and 150 mg) or open-label dose-adjusted warfarin (INR 2.0–3.0).³⁰ Enrollment was balanced between patients experienced with VKA therapy and those who were VKA-naïve. Patients were followed for a minimum of 12 months; the mean follow-up period was 2 years. RE-LY followed a

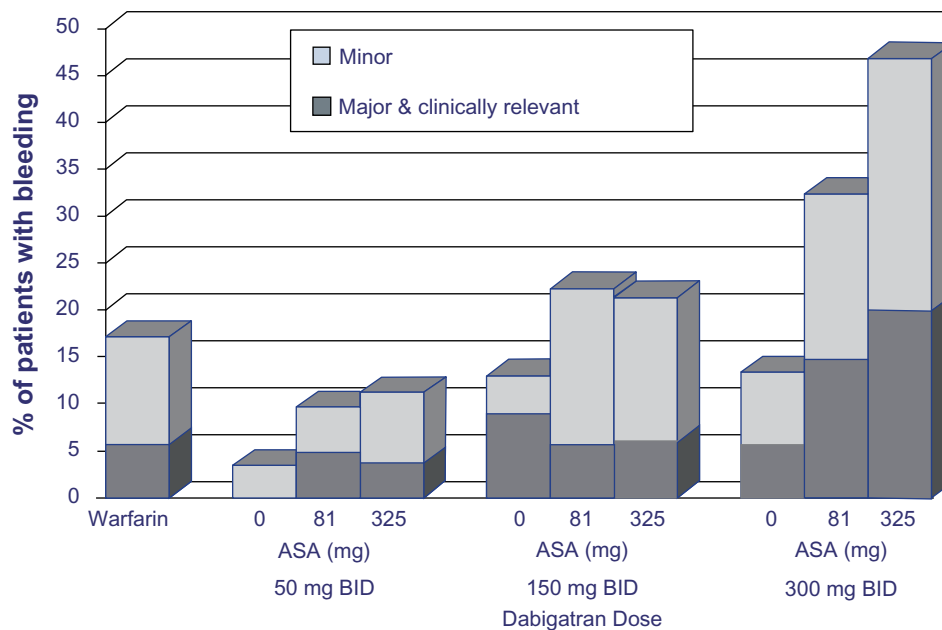


Figure 1. Results from PETRO: Major and minor bleeding.

non-inferiority design, with pre-specified superiority comparisons on all subsequent P-values once both doses demonstrated non-inferiority.

The primary study outcome was a composite of stroke, including haemorrhagic, and systemic embolism. Major bleeding was the primary safety outcome. Additional outcomes assessed included stroke, systemic embolism, death, myocardial infarction (MI), pulmonary embolism (PE), transient ischemic attack, and hospitalization. The primary net clinical benefit outcome was a composite of stroke, systemic embolism, PE, MI, death, or major bleeding. An international team of adjudicators performed blinded assessment of all outcomes. Several measures were taken to maximize treatment benefits for patients assigned to warfarin, including INR testing at least once every 4 weeks and close monitoring of time in therapeutic range with support measures provided as appropriate.

Results

Comparison of baseline characteristics revealed that the three groups were well balanced. The mean age of the patients was 71 years; 63.6% were men. The mean CHADS₂ score was 2.1. Patients treated with warfarin experienced a mean time within the therapeutic range of 64%.

Both doses of dabigatran demonstrated non-inferiority over warfarin with respect to the primary efficacy outcome of stroke or systemic embolism ($P < 0.001$ for both doses; Table 3, Fig. 2). The 150 mg dose demonstrated superiority over warfarin, with a relative risk reduction (RRR) of 34% ($P < 0.001$). Vascular mortality was reduced by 15% with the 150 mg dose ($P = 0.04$).

Safety results were also favourable for dabigatran. The 110 mg dose reduced the risk of major bleeding by 20% over warfarin; the 150 mg dose was similar to warfarin. The rate of gastrointestinal (GI) bleeding, a subset of major bleeding, was increased by about 0.5% with the 150 mg dose ($P < 0.001$); this increase was offset by a reduction in bleeding at other sites. Both doses reduced the risk of life threatening bleeding (RRR 32% and 19% for 110 mg and 150 mg doses, respectively; $P < 0.001$ and $P = 0.037$). Importantly, the devastating complication of intracranial haemorrhage was significantly reduced with both doses of dabigatran over warfarin (RRR 69% and 60% for 110 and 150 mg doses, respectively; $P < 0.001$ for both), benefits that appeared to be consistent over the study period (Fig. 3).

The overall net clinical benefit was significantly improved with the 150 mg dose of dabigatran over warfarin (RRR of 9%; $P = 0.04$). One of the



Table 3. RE-LY: Efficacy and safety outcomes.

Event	Dabigatran, 110 mg (N = 6015)		Dabigatran, 150 mg (N = 6076)		Warfarin (N = 6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin	
	# of patients	%/yr	# of patients	%/yr	# of patients	%/yr	Relative Risk (95% CI)	P Value†	Relative Risk (95% CI)	P Value†
Stroke or systemic embolism**†	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	0.34	0.66 (0.53–0.82)	<0.001
Stroke	171	1.44	122	1.01	185	1.57	0.92 (0.74–1.13)	0.41	0.64 (0.51–0.81)	<0.001
Haemorrhagic	14	0.12	12	0.10	45	0.38	0.31 (0.17–0.56)	<0.001	0.26 (0.14–0.49)	<0.001
Disabling/fatal‡	112	0.94	80	0.66	118	1.00	0.94 (0.73–1.22)	0.65	0.66 (0.50–0.88)	0.005
Myocardial infarction	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048
Death from vascular causes	289	2.43	274	2.28	317	2.69	0.90 (0.77–1.06)	0.21	0.85 (0.72–0.99)	0.04
Death from any cause	446	3.75	438	3.64	487	4.13	0.91 (0.80–1.03)	0.13	0.88 (0.77–1.00)	0.051
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04
Gastrointestinal	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001
Net clinical benefit outcome	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001

All analyses were based on the time to first event.

*Data are shown for all patients who had at least one event.

†P-value for non-inferiority <0.001 for both doses of dabigatran compared with warfarin.

#P values are for superiority.

‡A score of 3 to 6 on the modified Rankin scale was classified as disabling or fatal stroke.

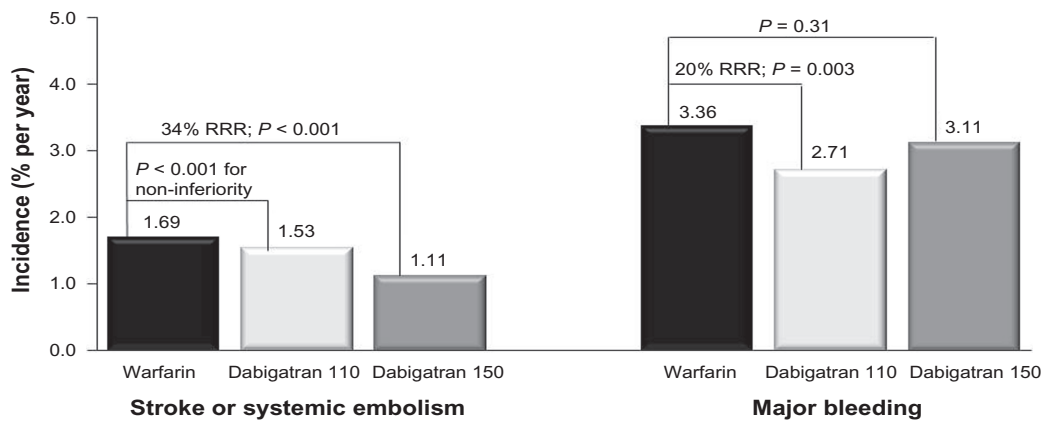


Figure 2. RE-LY: Primary efficacy and safety outcomes. *P*-values are for superiority unless otherwise noted. **Abbreviation:** RRR, relative risk reduction.

components of this endpoint, MI, was more frequent with the 150 mg dose of dabigatran compared with warfarin (0.74% and 0.53% per year, respectively, *P* = 0.048). There was no evidence of hepatotoxicity. No significant interactions were observed in any of the subgroup analyses, including prior VKA experience, CHADS₂ score, gender, BMI, weight, baseline calculated creatinine clearance rate (severe renal impairment was an exclusion criterion), and baseline use of ASA, amiodarone, and proton-pump inhibitors.

The only adverse event occurring more frequently with dabigatran was dyspepsia (11.8%, 11.3%, and 5.8% in the 110 mg and 150 mg doses, and warfarin, respectively; *P* < 0.001 for both doses), perhaps due to the tartaric acid core within the capsules. GI issues contributed to the observed higher discontinuation rates with dabigatran compared with warfarin (21% at 2 years for both doses of dabigatran and 17% at 2 years for warfarin, *P* < 0.001). The differential discontinuation rates may also be partially due to the

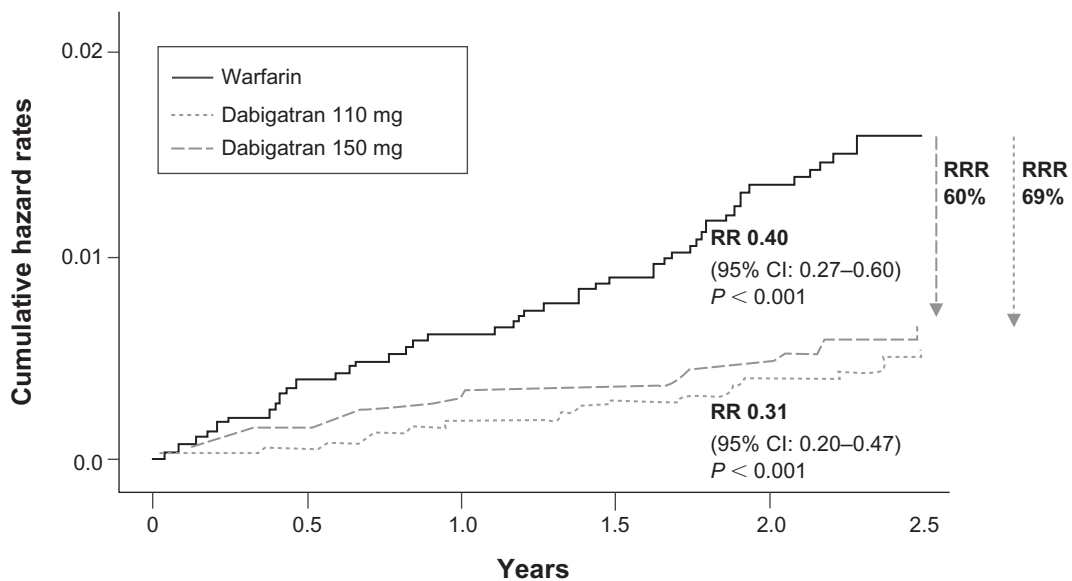


Figure 3. Time to first intracranial bleed. *P*-values are for superiority unless otherwise noted. **Abbreviation:** RR, relative risk; RRR, relative risk reduction; CI, confidence interval.



open-label nature of the design, whereby patients and physicians may be more cautious with an unevaluated treatment than they would with a well-known agent such as warfarin. Importantly, all analyses were performed on an intention-to-treat basis, thus dabigatran demonstrated the benefits described above despite higher discontinuation rates.

A post-hoc analysis of RE-LY results explored whether the benefits observed with dabigatran varied depending on the level of INR control at individual sites.³¹ Results from this analysis were consistent with the overall study results, showing benefits in the primary efficacy and safety outcomes irrespective of the level of site-based INR control.

Summary

Both doses of dabigatran demonstrated significant benefits over warfarin. The 150 mg twice-daily dose was superior to warfarin in prevention of stroke and systemic embolism with a similar safety profile. The 110 mg twice-daily dose was similar to warfarin in efficacy with a superior safety profile. These results enable the potential tailoring of dose to individual patients. Importantly, both doses of dabigatran reduced the risk of intracranial haemorrhage to approximately one third that of warfarin without a reduction in protection from stroke. These study results demonstrate that the direct thrombin inhibitor dabigatran has the potential to offer patients with AF a simple, convenient option that brings significant benefits over warfarin.

Further information surrounding the longer term effects of dabigatran therapy will be available from RELY-ABLE, an extension study of the patients receiving dabigatran who completed RE-LY.

AZD0837

AZD0837 is the pro-drug of AR-H067637, a reversible direct thrombin inhibitor in development for stroke prevention in AF. Results of a Phase II trial have been recently published.³² An extension study of the patients enrolled into that trial has been completed, as well as another Phase II trial using ASA as the comparator; results for these studies are not available. Further development of this compound has been postponed indefinitely; at present, it is unknown whether Phase III studies will be initiated.

AZD0837 appears to be well-tolerated, with no increased liver risk observed. Its bioavailability ranges between 22 and 55%. AZD0837 is rapidly absorbed (T_{\max} 1.5 hours), has a half-life of 9 hours, and is excreted via the liver. An extended release formulation has been developed that provides a smoother plasma concentration profile, enabling a potential once-daily dose.

Stroke prevention in atrial fibrillation

Phase II

In a dose-guiding trial, 955 patients were randomized to receive one of 4 blinded doses of extended release AZD0837 (150, 300, or 450 mg once daily or 200 mg twice daily) or open-label dose-adjusted warfarin (INR 2.0–3.0) for a period of 3 to 9 months. Endpoints studied include bleeding events (classified as major, clinically relevant minor, or minimal), D-dimer concentration, activated partial thromboplastin time, and ecarin clotting time.

AZD0837 was generally well tolerated at each of the doses tested. The 300 mg once daily dose, which provided similar suppression of thrombogenesis with potentially less bleeding in comparison to warfarin, was considered the most favourable. No clinically relevant liver signal was observed; this result, combined with results from studies of dabigatran, support the concept that the hepatotoxicity observed with ximelagatran is not a class effect of oral direct thrombin inhibitors.

FXa inhibitors

There are several oral direct FXa inhibitors at varying stages of development for the prevention of stroke in AF. Rivaroxaban, apixaban, and edoxaban currently have Phase III studies ongoing for this indication. Betrixaban and YM150 are in earlier stages of development.

Rivaroxaban

Rivaroxaban is a reversible direct FXa inhibitor approved in Canada and the EU for VTE prophylaxis in patients undergoing elective knee or hip arthroplasty at a recommended dose of 10 mg once daily. Phase III evaluation of rivaroxaban in AF is ongoing. Phase II studies in AF were not performed. Rivaroxaban is also being studied for prevention of cardiac events



in patients with acute coronary syndromes and the treatment and secondary prevention of VTE.

Rivaroxaban is well tolerated, with a predictable, dose-dependent anticoagulant response that does not require routine monitoring.²¹ It has a high relative bioavailability (~80%) and is rapidly absorbed (T_{max} 2 to 4 hours). Rivaroxaban's half-life ranges from 9 to 13 hours. It has a dual mechanism of excretion that is 66% renal (30% to 40% of which is unchanged drug) and 32% faecal/biliary.

VTE prophylaxis post orthopaedic surgery

Rivaroxaban was evaluated in a series of 4 Phase III clinical trials, RECORD 1–4, for VTE prevention in patients following elective hip or knee arthroplasty.^{33–36} In RECORD 1 and 2, patients undergoing total hip replacement were given rivaroxaban for 31–39 days. Enoxaparin was given for 31–39 days in RECORD 1 or 10–14 days in RECORD 2. In RECORD 3 and 4, patients undergoing total knee replacement received prophylaxis for 10–14 days. All patients were followed up for 30–35 days after the last dose of study medication. In these studies, 10 mg of rivaroxaban administered once daily demonstrated superior efficacy over enoxaparin. In RECORD 1, 2, and 3, the dose of enoxaparin used as the comparator was 40 mg once daily; in RECORD 4, it was 30 mg twice daily. There were no significant differences in major bleeding.

VTE treatment

The Phase III trial Einstein-Extension evaluated rivaroxaban for continued anticoagulant therapy following completion of 6 or 12 months of initial anticoagulant treatment for confirmed symptomatic DVT or PE.³⁷ Patients were initially treated with either rivaroxaban or warfarin, then randomized to receive either 20 mg of rivaroxaban administered once daily or placebo for a further 6 or 12 months. Results demonstrated that continued therapy with this dose of rivaroxaban was superior to placebo in reducing the risk of VTE recurrence.

Stroke prevention in atrial fibrillation

ROCKET-AF is a large Phase III study comparing a 20 mg once daily dose of rivaroxaban with dose-adjusted warfarin (INR 2.0–3.0) in patients with non-valvular AF and a CHADS₂ score of at least 2,

a patient population at greater risk of stroke than was studied in RE-LY. Patients with moderate renal impairment (calculated creatinine clearance 30 to 49 ml/minute inclusive) randomized to rivaroxaban receive a reduced dose of 15 mg. Results from ROCKET-AF are anticipated late 2010. A small Phase III study, Japan-ROCKET-AF, is concurrently ongoing in Japan to evaluate a lower dose of rivaroxaban (10 mg once daily) for this indication.

Apixaban

Apixaban is a well-tolerated reversible direct FXa inhibitor in clinical development for stroke prevention in AF, prevention of cardiac events in patients with acute coronary syndromes, and VTE treatment and prevention.

In the Phase III studies ADVANCE 1, 2, and 3, a 2.5 mg dose of apixaban administered twice daily was compared with enoxaparin for VTE prophylaxis in elective knee or hip arthroplasty patients. In ADVANCE 2 and 3, the enoxaparin dose was 40 mg once daily; in ADVANCE 1, a twice daily dose of 30 mg was used. Based on published results from ADVANCE 1 and ADVANCE 2, apixaban demonstrated a favourable safety profile.^{38,39} Statistical criteria for non-inferiority were met only in ADVANCE 2. Results from ADVANCE 3 are not yet available.

Phase II studies were not performed in the setting of stroke prevention in AF. A pair of Phase III studies for this indication is ongoing. The larger, ARISTOTLE, is a double-blind non-inferiority trial comparing 5 mg of apixaban administered twice daily with dose-adjusted warfarin (INR 2.0–3.0) in approximately 18,000 patients with non-valvular AF and at least one other risk factor for stroke. The primary endpoint is the occurrence of stroke or systemic embolism. Results are expected in 2011. The other is AVERROES, a double-blind superiority study comparing the same dose of apixaban with ASA (81–324 mg) in approximately 5600 patients who are unsuitable for warfarin therapy. The primary endpoint is occurrence of stroke (including hemorrhagic) or systemic embolism. Results from AVERROES are expected in 2010.

Edoxaban

Edoxaban is a direct FXa inhibitor being studied for stroke prevention in AF and the treatment and



prevention of VTE. Data from a Phase II study in patients with non-valvular AF have been presented.⁴⁰ In this study, 1146 patients were randomized to receive one of 4 blinded doses of edoxaban (30 or 60 mg, administered once or twice daily) or open-label dose-adjusted warfarin (INR 2.0–3.0) for 12 weeks. Patients receiving one of the twice-daily regimens experienced higher rates of major and clinically relevant bleeding. The 2 once-daily dosing regimens were well-tolerated and demonstrated a similar safety profile to warfarin.

ENGAGE—AF TIMI—48 is a Phase III, double-blind, double-dummy trial comparing two doses of edoxaban (30 or 60 mg administered once daily) with dose-adjusted warfarin in approximately 16,500 patients with non-valvular AF and a CHADS₂ score of at least 2. The treatment period is 24 months. The primary endpoint is a composite of stroke and systemic embolic events. Results from this trial are expected in 2011.

Betrixaban

Betrixaban is a reversible direct FXa inhibitor in Phase II development for stroke prevention in AF. Development in other indications, such as acute coronary syndromes and prevention and treatment of VTE, may be initiated as well. It is excreted almost unchanged in the bile, and thus may prove to be an option for patients with severe renal impairment.

Results are not yet available from the recently completed Phase II trial EXPLORE-Xa, in which three blinded once-daily doses of betrixaban (30, 60, and 80 mg) were compared with open-label dose-adjusted warfarin (INR 2.0–3.0) in 500 patients with non-valvular AF and at least one additional risk factor for stroke. Patients were treated for at least 3 months. The primary endpoint was major or clinically relevant non-major bleeding.

YM150

YM150 is a direct FXa inhibitor in the early stages of development for stroke prevention in AF and VTE prevention in orthopaedic surgery patients. Initial Phase II results assessing YM150 in AF are not yet available. A second Phase II study, OPAL-2, is ongoing. In this double-blind, double-dummy dose-finding trial, 1280 patients will be randomized

to one of 6 groups receiving YM150 (3 twice-daily, 3 once-daily) or warfarin. The primary outcome is major and clinically relevant non-major bleeding events. The estimated completion of this study is in 2010.

Discussion

Results from RE-LY, a landmark trial in AF, demonstrate that the oral direct thrombin inhibitor dabigatran has the potential to offer patients a simple, convenient option with significant benefits over warfarin. The 64% reduction in risk of stroke conferred by warfarin was established almost 20 years ago.⁴¹ RE-LY is the first trial since then to demonstrate statistical superiority of a new agent over warfarin, representing a significant milestone in the history of anticoagulation therapy (Fig. 4).

The clinical relevance of the results observed in RE-LY is noteworthy. The primary event of stroke or systemic embolism is infrequent in the trial population, but devastating. It is important to recognize that the low annual primary event rate of 1.69% observed for warfarin is expected and consistent with rates recorded in other trials.^{42,43} The observed infrequency is a function of the underlying low rate of the primary event, the clinical trial population itself, and the effectiveness of the two active therapies studied. Achieving an absolute risk reduction of 0.58% per year over warfarin's baseline rate of 1.69% is an important result that translates to a relative risk reduction of 34% and a clinically relevant benefit to the large population at risk.

Within RE-LY, the mean duration of time patients receiving warfarin were within therapeutic range was 64%, a finding consistent with controlled clinical trials and reproduced in many dedicated anticoagulation clinics.⁹ Unfortunately, many patients outside of clinical trials do not have access to this level of specialized care and are thus not as well controlled as the RE-LY study population.¹⁹ In a recent Canadian report, only 36% of AF patients receiving warfarin were within therapeutic range.⁴⁴ One would therefore anticipate, notwithstanding other unanticipated untoward developments, that the anticoagulation benefits observed with dabigatran over warfarin in RE-LY may be more pronounced once broadened into routine clinical practice.

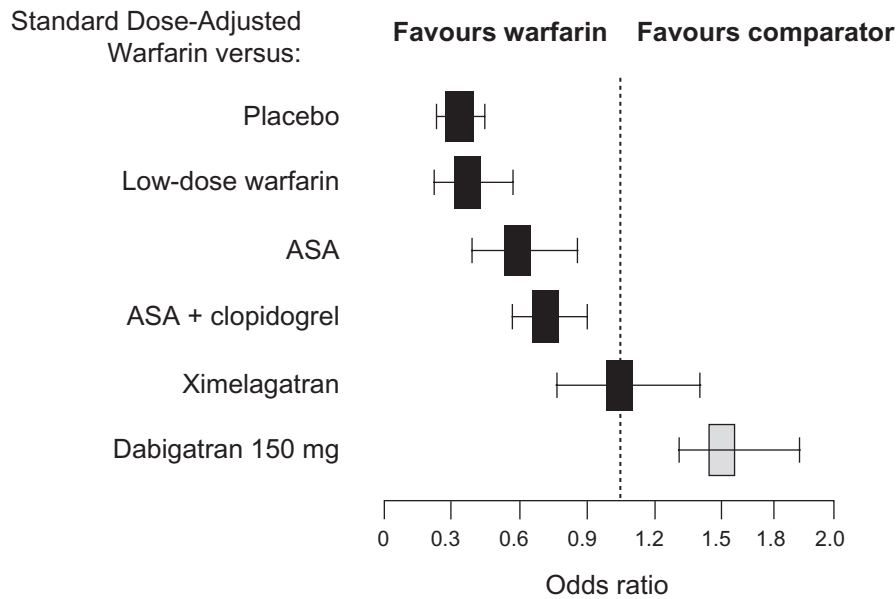


Figure 4. Meta-analysis of ischaemic stroke or systemic embolism.

The opportunity dabigatran provides to tailor dosing to individual patients is a considerable additional benefit. A dose that offers superior efficacy over warfarin may be the obvious choice for patients at high risk of stroke and without increased risk of major bleeding. For patients in whom bleeding is a greater concern, the lower dose provides just as much protection from stroke as warfarin with a significantly reduced risk of major bleeding. This is particularly appealing given that both doses reduced the risk of intracranial haemorrhage to approximately one third that of warfarin. With respect to adverse effects, dabigatran is associated with higher rates of dyspepsia compared to warfarin. However, given that past studies have confirmed many patients view stroke as a worse outcome than death, the risk of dyspepsia will likely be considered by most as relatively trivial in comparison to the risk of stroke.

The increased MI rate observed with dabigatran in RE-LY is worthy of further exploration. Interestingly, the MI rate observed in the warfarin arm is consistent with results from past studies (Fig. 5) (ACTIVE-W, SPORTIF III and V, SPAF III, SPINAF).^{42,43,45-47} Similarly, the MI rates observed in the dabigatran arms are similar to rates observed for other treatments (ximelagatran in SPORTIF III and V, ASA + clopidogrel in ACTIVE-A and ACTIVE-W, ASA in ACTIVE-A, EAFT, and SPAF 1) and lower than with placebo (SPINAF, EAFT, SPAF 1).^{42,43,45,48-50} These

studies are suggestive of a potential protective effect against MI with warfarin. Additional studies of dabigatran are ongoing and are expected to shed further light on this finding.

Additional topics to be explored regarding therapy with dabigatran include co-administration with other drugs frequently prescribed in this patient population. Reassuringly, RE-LY demonstrated no significant interactions with baseline use of ASA, amiodarone, and proton-pump inhibitors. Focused assessments will be required to facilitate the establishment of appropriate treatment paradigms for patients requiring concomitant therapies. Excretion of dabigatran is primarily renal; thus it is contraindicated in patients with a creatinine clearance of less than 30 ml per minute. Supplemental information regarding treatment in patients with moderate renal impairment will be forthcoming. There will be occasions where clinical treatment decisions for an individual patient will be influenced by the specific level of anticoagulant effect present. Given dabigatran's predictable response and linear dose-effect relationship, establishment of a defined therapeutic range and a means to quantify the level of anticoagulant effect will be useful enhancements to the information currently available. Finally, until an antidote is available, healthcare providers will require guidance regarding appropriate clinical management in cases of excess anticoagulant effect.

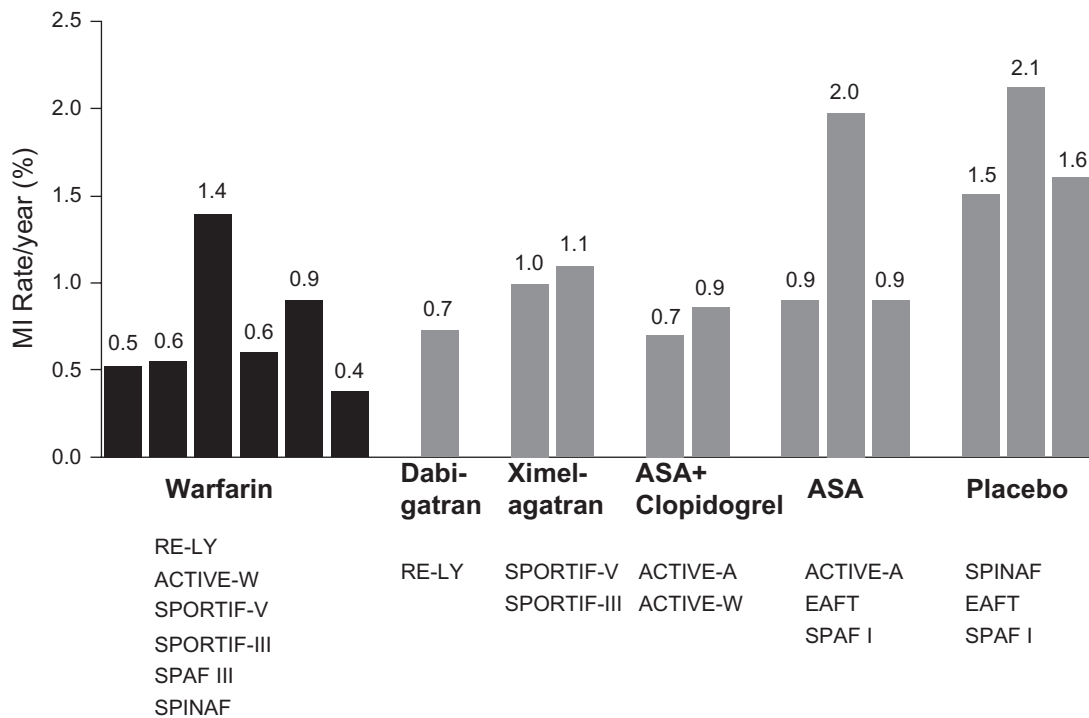


Figure 5. Myocardial infarction rates in previous atrial fibrillation studies.

The population of patients with AF is large and increasing. Many of these patients are at increased risk of stroke due to underutilization of anticoagulant therapy, a situation that has arisen due to a fear of bleeding, a lack of resources to effectively monitor INR levels, and the inconvenience to patients of warfarin therapy. As a result, patients at moderate to high risk of stroke are all too often treated with ASA rather than warfarin, despite its modest benefits. An anticoagulant agent that is both safe and effective will resolve both the fears associated with warfarin therapy as well as the inconveniences. The opportunity with dabigatran to tailor dosing to optimally address individual patient needs may facilitate a decline in the proportion of patients on ASA who would be better served by an agent offering greater protection from stroke. Further, removing the need for INR monitoring will enable anticoagulant clinics to re-focus on their original mandate—the diagnosis and management of VTE—a far more effective use of the expertise and resources associated with these specialized clinics.

By resolving today's hurdles of underutilization and sub-therapeutic anticoagulation, the number of patients who experience stroke will be reduced,

which will have an important impact on society by reducing the burden on patients, their families, and overloaded health care systems. The availability of a safe, effective, and convenient anticoagulant therapy to replace warfarin will trigger a welcome evolution of the treatment paradigm.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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