

Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran

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Vitamin K antagonists (VKAs) are effective for stroke prevention in patients with atrial fibrillation (AF) but are difficult to use. Dabigatran etexilate is a prodrug that is rapidly converted to the active direct thrombin inhibitor dabigatran. It is administered in a fixed dose without laboratory monitoring and is being compared with warfarin (international normalized ratio 2-3) in the RE-LY trial. Two doses of dabigatran (110 and 150 mg BID) are being evaluated. RE-LY is a phase 3, prospective, randomized, open-label multinational (44 countries) trial of patients with nonvalvular AF and at least 1 risk factor for stroke.

Recruitment concluded with a total of 18,113 patients. Patients who were VKA-naive and experienced are included in balanced proportions. The primary outcome is stroke (including hemorrhagic) or systemic embolism. Safety outcomes are bleeding, liver function abnormalities, and other adverse events. Adjudication of end points is blinded to drug assignment. The trial is expected to accrue a minimum of 450 events with a minimum 1-year of follow-up.

RE-LY is the largest AF stroke prevention trial yet undertaken. It is unique because it includes equal numbers of VKA-experienced and naive patients and evaluates 2 different dosages of dabigatran, which may allow tailoring of dosing to individual patient needs. The worldwide site distribution and broad range of stroke risk further increase the general applicability of the trial. Results are expected in 2009. (Am Heart J 2009;157:805-810.e2.)

Vitamin K antagonists (VKAs) reduce strokes in patients with nonvalvular AF (NVAf) by 68%.¹ Vitamin K antagonists have major limitations, including multiple drug and dietary interactions which lead to high variability in dose. Genetic variants of the enzyme that metabolizes warfarin, cytochrome P-450 2C9 (CYP2C9), and variants of the gene encoding vitamin K epoxide reductase (*VKORC1*), partly explain the differences in patient doses and variability.² The narrow therapeutic window leads to frequent monitoring of the international normalized ratio (INR) and is a major challenge to patients and physicians. Consequently, only about half of elderly patients with appropriate indications for VKAs are

prescribed oral anticoagulation.³ Furthermore, in well-monitored clinical trials, patients remain in the therapeutic window only between about 60% and 68% of the time.^{4,6} In the general population, the time in therapeutic range (TTR) is worse.⁷ Thus, there is a search for alternative orally effective antithrombotic treatments which include the combination of aspirin and clopidogrel,⁶ oral thrombin inhibitors^{4,5} and oral factor Xa inhibitors.⁸

Dabigatran

Dabigatran etexilate is the prodrug of dabigatran, a direct thrombin (factor IIa) inhibitor. Dabigatran etexilate does not have antithrombin activity. After administration it is rapidly converted by serum esterase to the active moiety, dabigatran, which is a nonpeptide, potent, competitive, and reversible inhibitor of thrombin.⁹ Peak dabigatran plasma concentrations occur 0.5 to 2 hours after oral administration. There is a biexponential distribution phase with a terminal half-life of 12 to 17 hours. About 80% of the drug is excreted unchanged by the kidneys. The average absolute bioavailability of dabigatran is 6.5%. The pharmacokinetics and pharmacodynamics of dabigatran allow fixed dose administration without coagulation monitoring.

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Table I. RE-LY inclusion criteria

- 1.) AF documented as follows:
There is ECG documented AF on the day of screening or randomization
The patient has had a symptomatic episode of paroxysmal or persistent AF documented by 12-lead ECG within 6 m before randomization
There is documentation of symptomatic or asymptomatic paroxysmal or persistent AF on 2 separate occasions, at least 1 day apart, one of which is within 6 m before randomization. In this case, AF may be documented by 12 lead ECG, rhythm strip, pacemaker/ICD electrogram, or Holter ECG. The duration of AF should be at least 30 s. Electrograms (not marker channels or mode switch episodes) from pacemakers and defibrillators can be used to document only 1 episode of paroxysmal or persistent AF
- 2.) In addition to documented AF, patients must have one of the following:
 - a. History of previous stroke, TIA, or systemic embolism
 - b. Ejection fraction <40% documented by echocardiogram, radionuclide or contrast angiogram in the last 6 m
 - c. Symptomatic heart failure, New York Heart Association class 2 or higher in the last 6 m
 - d. Age ≥ 75 y
 - e. Age ≥ 65 y and one of the following:
 - i) Diabetes mellitus on treatment
 - ii) Documented coronary artery disease (any of: prior myocardial infarction, positive stress test, positive nuclear perfusion study, prior CABG surgery or PCI, angiogram showing $\geq 75\%$ stenosis in a major coronary artery
 - iii) Hypertension requiring medical treatment
- 3.) Age >18 y at entry
- 4.) Written, informed consent

ICD, Implantable cardiac defibrillator.

Dabigatran etexilate has undergone phase 2 trial evaluation in 502 AF patients^{10,11} and in approximately 8,000 patients undergoing orthopedic surgery for deep venous thrombosis prevention.^{12,13} These studies demonstrated adequate safety and identified dabigatran doses for evaluation in further large studies. Based on phase 2 clinical and pharmacokinetic data, 2 different doses of dabigatran, 150 mg and 110 mg twice a day, were chosen for comparison against VKA in the Randomized evaluation of long-term anticoagulant therapy warfarin, compared with dabigatran (RE-LY). The identification of 2 doses with similar efficacy as adjusted dose warfarin might provide an opportunity to tailor the dose to individual patients to maximize the benefit against risk.

Study design

RE-LY is a phase 3, multicenter, prospective, open-label, randomized trial with blinded evaluation of all outcomes (PROBE design). Two doses of dabigatran are compared with warfarin for stroke prevention in patients with NVAF and at least 1 risk factor for stroke. The dose of dabigatran is blinded. The primary objective is to demonstrate that at least 1 dose of dabigatran etexilate is noninferior to warfarin (INR 2-3). The inclusion and exclusion criteria are outlined in Tables I and II. The RE-LY protocol required a balanced representation of anticoagulant naive (defined as patients who previously

Table II. RE-LY exclusion criteria

1. History of heart valve disorders (ie, prosthetic valve or hemodynamically relevant valve disease)
2. Severe, disabling stroke within the previous 6 m, or any stroke within the previous 14 d
3. Conditions associated with an increased risk of bleeding:
 - a. Major surgery in the previous month
 - b. Planned surgery or intervention in the next 3 m
 - c. History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding
 - d. Gastrointestinal hemorrhage within the past year
 - e. Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 d
 - f. Hemorrhagic disorder or bleeding diathesis
 - g. Need for anticoagulant treatment of disorders other than AF
 - h. Fibrinolytic agents within 48 h of study entry
 - i. Uncontrolled hypertension (systolic blood pressure >180 mm Hg and/or diastolic blood pressure >100 mm Hg)
 - j. Recent malignancy or radiation therapy (≤ 6 m) and not expected to survive 3 y
4. Contraindication to warfarin treatment
5. Reversible causes of atrial fibrillation (eg, cardiac surgery, pulmonary embolism, untreated hyperthyroidism).
6. Plan to perform a pulmonary vein ablation or surgery for cure of the AF
7. Severe renal impairment (estimated creatinine clearance ≤ 30 mL/min)
8. Active infective endocarditis
9. Active liver disease, including but not limited to
 - a. Persistent ALT, AST, Alk Phos $>2 \times$ ULN
 - b. Known active hepatitis C (positive HCV RNA)
 - c. Active hepatitis B (HBs antigen +, anti HBc IgM+)
 - d. Active hepatitis A
10. Women who are pregnant or of childbearing potential who refuse to use a medically acceptable form of contraception throughout the study
11. Anemia (hemoglobin level <100g/L) or thrombocytopenia (platelet count <100 $\times 10^9$ /L)
12. Patients who have developed transaminase elevations upon exposure to ximelagatran.
13. Patients who have received an investigational drug in the past 30 d
14. Patients considered unreliable by the investigator or have a life expectancy less than the expected duration of the trial because of concomitant disease, or has any condition which in the opinion of the investigator, would not allow safe participation in the study (eg, drug addiction, alcohol abuse).

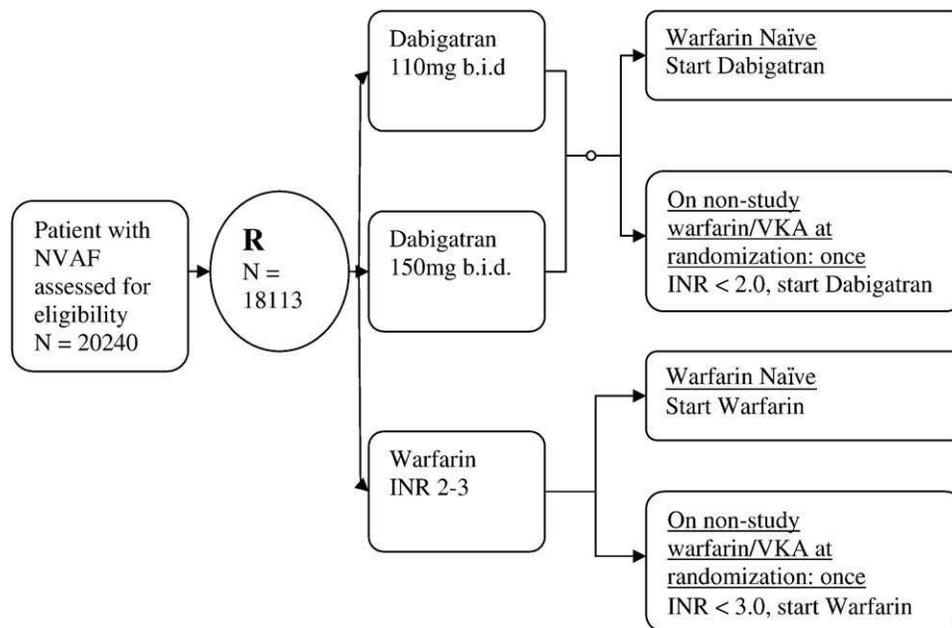
ALT, alanine aminotransferase; AST, aspartame aminotransferase; Alk phos, alkaline phosphatase; HCV, hepatitis C virus; HBs, hepatitis B surface; HBc, hepatitis B core; IgM, immunoglobulin M.

had received a total of ≤ 2 months of VKA therapy) and VKA experienced patients.

Randomization and follow-up

18,113 patients were recruited from 967 centers in 44 countries as of December 2007. The patients were randomized by a central randomization service, through an interactive voice response system (IVRS) located at the Coordinating Centre at Population Health Research Institute (PHRI) in Hamilton, Canada (Figure 1). After randomization, patients had study visits scheduled at 14 days (via telephone), at 1 month, 3 months and then at 3 monthly intervals during the first year and 4-monthly intervals thereafter. The enrollment period was 24 months with a planned minimum follow-up period of 12 months.

Figure 1



Design of the RE-LY trial. R, Randomization.

Drug administration and initiation

Dabigatran etexilate was supplied as identical capsules containing either 110 mg or 150 mg. Patients randomized to warfarin were dispensed tablets containing 1 mg, 3 mg and 5 mg warfarin. Patients taking VKAs at the time of randomization stopped their VKA drug on the day of randomization and began the assigned drug when the INR fell <2.0 (if randomized to dabigatran) or <3.0 (if randomized to warfarin). Patients not on VKA at the time of randomization began study medication on the day of randomization. For patients on warfarin, the dose adjustments required to maintain INR 2-3, were made by the local investigator. A warfarin dose-adjustment algorithm was provided to centers but the protocol did not mandate its use (Appendix 1, available online). Patients assigned to a dose of dabigatran remained on that dose for the duration of the study.

Safety monitoring

Patients randomized to warfarin underwent INR testing at least once every 4 weeks. The TTR for warfarin, calculated by the Rosendaal method,¹⁴ was monitored closely throughout the study, and several measures were adopted to maximize the TTR. All study participants had monthly laboratory evaluation of hepatic function during the first year using a central laboratory to eliminate inter and intrasite variation. Hepatic function abnormalities that occur during the trial for all patients either on warfarin or dabigatran were

classified as alert status 1, 2, or 3, depending on the severity of the changes. The extent of follow-up was mandated based on the alert status (Appendix 2, available online). An interim safety analysis after 6,000 patients had completed at least 6 months of dabigatran exposure was planned and prespecified in the protocol.

Statistical considerations

The primary efficacy variable is the time to the first occurrence of stroke (including hemorrhagic) or systemic embolism (Appendix 3, available online). The primary efficacy analysis will use the Cox proportional hazard model including treatment as a factor in the model. The hazard ratio (risk ratio) and its confidence limits will be determined for evaluating the noninferiority of dabigatran compared with warfarin. The null hypothesis is that the hazard ratio of dabigatran versus warfarin is larger than or equal to the specified noninferiority margin $\delta = 1.46$. The alternative hypothesis is that the hazard ratio of dabigatran versus warfarin is <1.46. The noninferiority margin was calculated based on the risk reduction observed in the 6 placebo-controlled warfarin trials.² It preserves 50% of the benefits of VKA versus control therapy, based on the lower boundary of the 95% confidence interval (CI) of the VKA effect. The upper bound of the 95% CI of the hazard ratio of dabigatran versus warfarin will be compared with the noninferiority margin for the noninferiority testing.

The number of patients required in RE-LY is driven by the noninferiority margin, the primary event rate, the

duration of exposure, the required power of the primary comparison (type II error) and the significance level (type I error). Because there are 2 doses to be compared with warfarin, we adopted the Hochberg procedure¹⁵ to account for multiple comparisons. Assuming a 2-year recruitment period and at least 1 year of follow-up and a primary event rate of 1.6% per year, it was determined that at least 15,000 patients would be needed to achieve a minimum of 450 events. The study would have approximately 84% power to conclude noninferiority of dabigatran over warfarin at α of .025 (1-sided) level.

Secondary outcomes include a composite of all stroke (including hemorrhagic), systemic embolism, and death as well as a composite of all stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, and vascular death (including death from bleeding). The other end points include the individual occurrence of the components of the primary and secondary end points, as well as transient ischemic attacks (TIAs) and hospitalizations and a net clinical benefit as measured by the composite of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, all-cause death, and major bleeds (Appendix 3).

The identification of patient factors that determine bleeding and stroke risk will be an important aspect in determining the risk-benefit profile of both warfarin and dabigatran. In RE-LY, it is expected that patients who were previously treated with VKAs represent a selected population (survivor bias) and may differ in their efficacy and safety response compared with those who are VKA-naive. A subgroup analysis comparing dabigatran versus warfarin in these 2 groups of patients will be performed for the primary outcome and for major hemorrhage.

The safety of each dose of dabigatran will be compared with warfarin. The proportions of patients experiencing fatal or life-threatening bleeds, major bleeds, minor bleeds, or bleeds leading to permanent discontinuation will be determined for each treatment group (Appendix 3). The laboratory assessment of liver function will be closely followed up during the first year of exposure for all treatment groups.

To avoid bias, a prospective, blinded end point methodology was adopted. Outcomes are objective, clearly defined, and clinically relevant. The outcome events including strokes, non-central nervous system systemic emboli, deaths, myocardial infarctions, pulmonary embolism, major bleeds, and some minor bleeds are adjudicated by a blinded adjudication committee. The TIAs are also adjudicated to capture potential strokes. To ensure that all events are captured, there will be a review of all hospitalizations, events suggesting loss of neurologic function, or indicators of bleeding such as hemoglobin level decrease >2 g/dL. Furthermore, at every visit, a questionnaire to detect signs and symptoms of bleeding or stroke is administered to identify potential end points.

The trial is unblinded with respect to dabigatran or warfarin assignment. However, all investigators, members of the coordinating center, the operations committee, the steering committee, the event adjudication committee, and the sponsor remain blinded to treatment level analyses of efficacy and safety. Only the data and safety monitoring board (DSMB) and the DSMB-associated statistician have access to the randomization code and by-treatment event rates.

Study organization

The study organization is outlined in Appendix 4, available online.

Use of concomitant drugs

The trial allows acetylsalicylic acid (ASA) (≤ 100 mg/day), clopidogrel, ticlopidine, dipyridamole, or ASA/dipyridamole. The use of nonstudy warfarin or other VKAs is only permitted if patients are withdrawn from study medication. ASA-containing over-the-counter medications, long-term use of corticosteroids, nonsteroidal anti-inflammatory drugs or heparin, and fibrinolytic agents are discouraged.

P-glycoprotein inhibitors may interact with dabigatran. Quinidine doubles the concentration of dabigatran. The use of quinidine was not allowed in RE-LY as of the second quarter of 2008. The most common P-glycoprotein inhibitors in chronic use in the AF population are verapamil and amiodarone. The DSMB have not reported an elevated bleeding risk with their concurrent use with dabigatran.

Anticoagulation interruption for elective surgical procedure

In the preoperative phase, patients randomized to warfarin can be managed with or without bridging anticoagulant therapy.¹⁶ The recommendation is to stop warfarin 5 days before the procedure. In patients at high risk for thromboembolism, low-molecular-weight heparin or unfractionated heparin can be used to bridge the patient. Postoperatively, resumption of anticoagulant therapy was encouraged as soon as clinically feasible with or without bridging therapy. Patients randomized to dabigatran required discontinuation of anticoagulant therapy at least 24 hours before the procedure and resumption of therapy, post procedure, as soon as clinically feasible.

Cardioversion

If there was a need for cardioversion (electric or pharmacologic) during the study, the protocol recommends that patients be maintained on the study drug (warfarin or dabigatran) unless, in the judgment of the investigator, another approach was deemed necessary. As a safety measure, transesophageal echocardiographs were encouraged but not mandated in patients assigned to dabigatran, who required cardioversion. If cardioversion was planned within 60 days of randomization, a transesophageal echocardiograph was recommended

Table III. Substudy program of RE-LY

Substudy	Goals
Dabigatran plasma concentrations and APTT levels	Pharmacokinetic and pharmacodynamic profile of dabigatran and relations to efficacy and safety outcome events
Interruption for surgery	Management and outcome events in patients requiring temporary discontinuation of treatment of an invasive procedure
Risk and coagulation plasma biomarkers	Accumulation and analyses of plasma biomarkers to enhance understanding of the pathobiology of AF and the effects of dabigatran and VKA treatments through analysis of markers of coagulation, inflammation, endothelium, metabolism, myocardial function and damage, and renal function
Platelet function	Measurement of platelet activation and aggregation and comparison of influence of dabigatran vs warfarin treatment
Genomic	Identify genetic variants related to pharmacokinetics, pharmacodynamics, efficacy and safety of dabigatran and warfarin
Quality of life	Evaluation of quality of life by standardized form comparing the results between dabigatran and warfarin treated patients

APTT, Activated partial thromboplastin time.

before the procedure, to exclude the presence of a left atrial thrombus.

Substudy program

Several substudies are incorporated as additions to the main study (Table III).

Patient recruitment

After approximately 12 months of patient recruitment, it appeared that the target enrollment of 15,000 patients could be achieved well before the projected 2-year recruitment duration. To protect the study against the possibility of low event rates and the need for increased follow-up, the operations committee, in consultation with the steering committee and the sponsor, decided to continue enrolment as originally planned with the goal of reaching 18,000 patients, thus increasing the statistical power of the analyses from approximately 84% to 90%. At the conclusion of recruitment on December 15, 2007, 18,113 patients had been randomized—approximately 50% naive to anticoagulation. After review of 6,000 patients treated for at least 6 months, the DSMB recommended that the frequency of liver function testing could be reduced.

Discussion

The RE-LY trial is a large phase 3 evaluation of dabigatran, a novel oral direct thrombin inhibitor in comparison with warfarin for prevention of stroke in patients with NVAF. The choice of an open-label design with blinded event ascertainment instead of a conven-

tional double-blind trial was based on several factors. Four of the early placebo-controlled trials against warfarin were open-label trials.¹⁷⁻²⁰ The drug effects in the open-label trials were comparable with the SPINAF trial, the only completed double-blind AF stroke trial²¹ and the double-blind CAFA study,²² which was prematurely terminated. An open-label design is more likely to be representative of true differences in the management of warfarin and dabigatran in daily practice. In addition, an open design would also allow management of intercurrent events based on the characteristics of the anticoagulant agent rather than manage all patients as if they were on warfarin. A double-blind methodology is complex, requiring dummy INRs and management assuming that patients are assigned to warfarin. The operations committee made the decision to conduct a large open trial but included safeguards to avoid potential biases.

The decision to test 2 doses of dabigatran in a large phase 3 trial is unusual. Identifying the correct dose was considered critical. The dose of 150 mg BID was tested in the phase 2 PETRO study, whereas 110 mg twice a day had not been directly tested.¹⁰ The choice of this lower dose was based on interpolations of phase 2 data, considerations of the peak and time course of anticoagulant effect of dabigatran, and the observation that a total daily dose of 220 mg was effective in orthopedic surgery patients for deep venous thrombosis prevention.^{23,24} The identification of a lower dabigatran etexilate dose that might potentially have similar efficacy to adjusted-dose warfarin with less bleeding was considered important. Having 2 doses might allow tailoring of dosing to optimize the benefit against risk.

Previous trials have mainly included VKA experienced patients. In the SPORTIF III, SPORTIF V, and the ACTIVE W trials, 73%, 84%, and 77% of patients recruited were on a VKA at time of entry into the study.^{4,6} Thus, the study populations were enriched with patients tolerating warfarin, who accept regular INR monitoring and have “survived the warfarin stress test” of a major bleed or other side-effects. Bias in favor of warfarin might lead to a study of “switchers,” that is, warfarin-treated patients who in the future might switch from warfarin to dabigatran treatment and not reflect “starters,” that is, patients with AF and a newly developed indication for antithrombotic treatment. In ACTIVE W, patients who were already receiving a VKA at study entry (anticoagulant-experienced) had a greater reduction in vascular events (relative risk 1.50, 95% CI 1.9-1.80) and a significantly ($P = .03$) lower risk of major bleeding with oral anticoagulation therapy (1.30; 0.94-1.79) than patients not on this treatment (VKA naive) at study entry (1.27, 0.85-1.89 and 0.59, 0.32-1.08, respectively).⁶ RE-LY has enrolled the highest number of anticoagulant naive patients. It will therefore be more widely applicable than published trials.^{4,6}

Ximelagatran was the first direct thrombin (factor IIa) inhibitor to undergo phase 3 evaluation for stroke

prevention in patients with AF. In SPORTIF III and V,^{4,5} ximelagatran was similar to warfarin therapy in preventing stroke and systemic embolic events. However, the hepatotoxicity of the drug led to cessation of its development.²⁵⁻²⁷ In RE-LY, a comprehensive liver monitoring plan was embedded in the protocol. The experience with ximelagatran suggested that the greatest likelihood of a hepatotoxic effect would manifest during the first 6 months of therapy. The relaxation of liver function monitoring by DSMB after reviewing the results of 6 months of treatment of the first 6,000 patients provides hope that dabigatran is not toxic to the liver.

In conclusion, RE-LY is a large international trial of stroke prevention in NVAF and will provide reliable information on the long-term safety and efficacy of dabigatran in comparison with warfarin. Results are expected in 2009.

Disclosures

The authors, Ezekowitz, Connolly, Parekh, Oldgren, Themeles, Wallentin and Yusuf have all received grant support from the sponsor of RE-LY, Boehringer-Ingelheim Pharmaceuticals inc (Ridgefield, CT). In addition, the authors, Ezekowitz, Connolly, Wallentin and Yusuf have been consultants for Boehringer-Ingelheim Pharmaceuticals inc. The authors, Reilly, Varrone, and Wang are employees of Boehringer-Ingelheim Pharmaceuticals inc.

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Appendix 1. Warfarin INR Nomogram

Table I. Initiating Warfarin

Day	INR	Warfarin dose (mg)
1	–	5
2	–	5
3	<1.5	10
	1.5-1.9	5
	2.0-3.0	2-3*
4	>3.0	0
	<1.5	10
	1.5-1.9	7-8*
	2.0-3.0	5
5	>3.0	0
	<2.0	10
	2.0-3.0	5
6	>3.0	0
	<1.5	12-13*
	1.5-1.9	10
	2.0-3.0	7-8*
	>3.0	0

Lower doses: age >75 years, weight <60 kg, interacting medications known to potentiate warfarin, hepatic dysfunction, hypoproteinemia, hyperthyroid, impaired nutritional intake, increased baseline INR.

Higher doses: hypothyroid, interacting medications known to inhibit warfarin, diet rich in vitamin K.

* At discretion of physician.

Table II. After warfarin initiated (maintenance)

INR	Action
≤1.5	Increase weekly dose by 15%; repeat INR in 7-10 d.
1.51-1.99	If unexplained, increase weekly dose by 10%; repeat INR in 7-10 d.
2.00-3.00**	No change
3.01-4.99	If INR 3.01-3.99 do not hold warfarin. If high on 2 consecutive occasions, decrease weekly dose by 10%; If INR 4.00-4.99 hold for 1 day; repeat INR in 7-10 d.
5.00-8.99	Hold warfarin. Consider vitamin K 2-4 mg PO if at increased risk of bleeding. If INR still high 24 h later, consider giving 1-2 mg additional vitamin K PO and restart at lower dose (decrease weekly dose by 15%) when INR therapeutic. Check INR weekly until stable.
≥9.0	Hold warfarin and give vitamin K 5.0-10 mg PO. Monitor more frequently and repeat vitamin K if necessary.
Serious bleeding regardless of INR	Hold dose and give vitamin K 10 mg IV and fresh frozen plasma, recombinant factor VIIa, or prothrombin complex concentrates depending on urgency of situation.

** If INR is between 1.80 and 2.00 or 3.00 and 3.20, consider no change in repeat INR in 7 to 10 days, for first occurrence ONLY.

Appendix 2. Algorithm for hepatic monitoring

Alert status 1: sGPT/ALT, sGOT/AST, or Alk Phos >2x ULN: repeat LFTs weekly until enzymes fall <2x ULN.

Alert status 2: sGPT/ALT or sGOT/AST >3x ULN, or bilirubin >2 x ULN: weekly LFTs until liver enzymes are <2x ULN. Abdominal ultrasound imaging and further laboratory testing are encouraged to exclude alternative cause of liver dysfunction.

Alert status 3: sGPT/ALT or sGOT/AST >5x ULN or SGPT/ALT or SGOT/AST >3 x ULN associated with total bilirubin >2 x ULN or development of signs and symptoms of hepatic disease.

Dabigatran is discontinued immediately. If the investigator and the sponsor agree, study medication may be restarted if no evidence of liver disease is found and the abnormality resolves.

Appendix 3. Study definitions

A). Definition of outcome events:

- Stroke is an acute onset of a focal neurologic deficit of presumed vascular origin lasting for ≥24 hours or resulting in death. Stroke is categorized as ischemic or hemorrhagic or cause unknown (based on computed tomographic or magnetic resonance scanning or autopsy). Fatal stroke is defined as death from any cause within 30 days of stroke. Severity of stroke will be assessed by modified Rankin score at discharge from hospital and at 3 to 6 months later.
- Systemic embolism is an acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina or grafts) and must be documented by angiography, surgery, scintigraphy, or autopsy.
- Myocardial infarction: depending on whether percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) has been performed, a myocardial infarction end point is defined as follows:
 - In patients not undergoing PCI or CABG, a patient had to fulfill at least 2 of the following 3 criteria:
 - Typical prolonged severe chest pain or related symptoms or signs (eg, ST changes of T-wave inversion in the electrocardiogram [ECG]) suggestive of myocardial infarction.
 - Elevation of troponin or creatine kinase-MB (CK-MB) to more than upper limit of normal (ULN) or, if CK-MB was elevated at baseline, re-elevation to >50% increase above the previous level.
 - Development of significant Q waves in at least 2 adjacent ECG leads.
 - After percutaneous coronary intervention (within 24 hours), elevation of troponin or CK-MB to > 3x ULN or, if CK-MB was elevated at baseline, re-elevation to >3x ULN and a >50% increase above the previous level, and/or development of significant Q waves in at least 2 adjacent ECG leads.
 - After coronary artery bypass grafting (within 72 hours), elevation of CK-MB to >5x ULN or, if CK-

MB was elevated at baseline, re-elevation to $>5\times$ ULN and a $>50\%$ increase above the previous level, and/or development of significant Q waves in at least 2 adjacent ECG leads.

- Silent myocardial infarction will be retrospectively diagnosed by the appearance of significant new Q waves between study visits. In such cases, the date of the event is recorded as the midpoint between the 2 study visits.
 - Myocardial infarction may also be demonstrated at autopsy.
4. Deaths will be classified as being vascular (including bleeding) or nonvascular due to other specified causes (eg, malignancy) or of unknown etiology.

B). Major and minor bleeding events:

- i. Major bleeding is defined by ≥ 1 of the following criteria:
- bleeding associated with reduction in hemoglobin level of at least 2.0 g/L;
 - leading to transfusion of at least 2 U of blood or packed cells; or
 - symptomatic bleeding in a critical area or organ such as intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding.

Furthermore, major bleed is classified as life-threatening if they met ≥ 1 of the following criteria:

- fatal, symptomatic intracranial bleed;
- reduction in hemoglobin level of at least 5.0 g/L;
- transfusion of at least 4 U of blood or packed cells;
- associated with hypotension requiring the use of intravenous inotropic agents; or
- necessitated surgical intervention.

- ii. Minor bleeds are defined as clinical bleeds that do not fulfill the criteria for major bleeds.

Appendix 4. Study Organization

Steering committee: Michael Ezekowitz (co-principal investigator), Stuart Connolly (co-principal investigator), Lars Wallentin (cochair), Salim Yusuf (cochair), Jeanne Varrone (clinical trial monitor), Ralf Bilke (clinical trial

monitor until March 2008), representatives of Boehringer-Ingelheim Pharmaceuticals Inc Paul Reilly and Lars-Eric Lins, Susan Wang (trial statistician) and Ellison Themeles (PHRI Project Manager), and national coordinators Rafael Diaz (Argentina), John Amerena, (Australia), Kurt Huber (Austria), Hein Heidbuchel (Belgium), Alvaro Avezum (Brazil), Dimitar Raev (Bulgaria), Stuart J. Connolly and Mario Talajic (Canada), Liu Lishen (China), Velasco Caicedo (Columbia), Petr Jansky (Czech Republic), Knud Eric Pedersen (Denmark), Lauri Toivonen (Finland), Jean-Yves LeHeuzey (France), Harald Darius and Stefan Hohnloser (Germany), John Nanas (Greece), Chu-Pak Lau (Hong-Kong), Keltai Matyas (Hungary), Prem Pais and Denis Xavier (India), David Halon and Basil S. Lewis (Israel), Guiseppe DiPasquale and Maria Grazia Franzosi (Italy), Masatsugu Hori (Japan), Sung Soon Kim (Korea), Razali Omar (Malaysia), Jesus Antonio Gonzalez-Hermosillo (Mexico), Marco Alings and Timothy Simmers (Netherlands), Pal Smith (Norway), Raul Gamboa (Peru), Antonio L. Dans (Philippines), Andrzej Budaj (Poland), Jorge Ferreira (Portugal), Patrick Commerford (South Africa), Dragos Vinereanu (Romania), Sergey Golitsyn (Russia), Ru San Tan (Singapore), Gabriel Kamensky (Slovakia), Josep Brugada (Spain), Jonas Oldgren and Lars Wallentin (Sweden), Iris Baumgartner (Switzerland), Jyh-Hong Chen (Taiwan), Supachai Tanomsup (Thailand), Cetin Erol (Turkey), Marcus Flather (United Kingdom), Michael Ezekowitz and Greg Flaker (United States), Alexander Parkhomenko (Ukraine)

Operations committee: Lars Wallentin, Salim Yusuf, Michael Ezekowitz, Stuart Connolly, Paul Reilly, Lars-Eric Lins, (replaced by Manfred Haehl), Jeanne Varrone, Ellison Themeles, Elizabeth Palmcrantz-Graf, Jonas Oldgren, John Eikelboom, Amit Parekh

Data safety monitoring board: Peter Sleight (chair), George Wyse (cochair), Lars Ryden, Peter Sandercock, Jane Collier, Emmanuel Lesaffre, David DeMets, Jack Hirsh

Central Adjudication Core Committee: Cam Joyner (cochair), Hans-Christoph Diener (cochair), Anke Diehl, Gary Ford, Marlene Robinson