A New Anticoagulant for a New Era: Review of Recent Data on Dabigatran Etexilate

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Abstract: Dabigatran etexilate is an oral direct thrombin inhibitor that could be administered in fixed doses and does not require laboratory monitoring. It is currently being evaluated through the RE-VOLUTION clinical trials program, which will involve more than 38,000 patients by the time it is completed. These clinical trials will evaluate the efficacy and safety of dabigatran etexilate for several indications. This article will review the clinical development of dabigatran, the published trial data, and the potential indications for this promising oral anticoagulant.

The Need for a New Anticoagulant

Warfarin is the anticoagulant of choice in most countries for long-term anticoagulation.[1] Despite its major disadvantages, mainly its narrow therapeutic range and high interaction potential, it has remained largely unchallenged for the last few decades. However, in the last few years, numerous novel anticoagulants have been developed. Among these agents, oral direct thrombin inhibitors and factor Xa inhibitors are furthest in clinical development.[2] This review will mainly focus on dabigatran etexilate (Boehringer Ingelheim), a promising oral direct thrombin inhibitor.

Thrombin as a Target in the Coagulation Cascade

The serine protease thrombin is the final mediator in the coagulation cascade that leads to the production of fibrin and the formation of blood clots; thrombin is also a potent activator of platelets.[3] Because of its central role in the coagulation cascade, thrombin is an attractive target for inhibition.[4] Thrombin-inhibiting drugs can block the action of thrombin by binding to 3 domains: the active site, the catalytic site, and 2 exosites. Bivalent direct thrombin inhibitors block thrombin at both the active site and exosite 1, whereas univalent inhibitors bind only to the active site.[5] Several peptidic direct thrombin inhibitors, such as desirudin, have been approved. However, these agents still require parenteral administra-

tion, limiting their chronic use.[3] Dabigatran etexilate is a novel oral direct thrombin inhibitor approved for clinical use that is already licensed for prevention of venous thromboembolism (VTE) after hip replacement surgery in Europe and Canada.[2,3]

Pharmacokinetics and Pharmacodynamics

Dabigatran etexilate is an orally administered prodrug, which is rapidly absorbed and metabolized to its active form, dabigatran. It selectively targets thrombin in a dose-dependent and reversible manner (Ki=4.5 nM). Dabigatran also inhibits thrombin-induced platelet aggregation. It is mainly eliminated by renal excretion.[6] Dabigatran metabolism is not affected by the P450 system; therefore, the potential for interactions with drugs that are metabolized by this system is low.[6,7] Dabigatran etexilate has been found to act as a substrate of P-glycoprotein (P-gp), hence potent P-gp inhibitors or inducers can affect the bioavailability of dabigatran.[2] Age and gender have no clinically relevant effects on the pharmacodynamics or pharmacokinetics of dabigatran.[8] There is limited clinical experience in patients with a body weight less than 50 kg or more than 110 kg.[9]

Clinical Development

Dabigatran etexilate has been successfully tested in randomized controlled trials for several indications that were traditionally treated by warfarin. The development of dabigatran etexilate followed what has now become a well established paradigm for development of new oral anticoagulants. The first phase usually comprises trials to evaluate the new drug versus warfarin in VTE prevention after major orthopedic surgery. Such studies are more feasible to perform because of the short-term nature of this indication. The use of surrogate venographic markers produces relatively high event rates even with existing anticoagulants, thus requiring smaller numbers of patients to show an effect. Moreover, bleeding complications can be easily monitored and controlled in a hospital setting. The next phase involves VTE treatment studies where long-term safety data can be acquired.[10] These studies can be used as dose-finding studies for stroke prevention in patients with atrial fibrillation, meaning that these drugs can go straight into phase III development in this indication without requiring specific phase II stroke prevention studies in patients with atrial fibrillation.[11] Finally, studies examining prevention of arterial thromboembolic events in high-risk patients, such as those with acute coronary syndromes, are performed.[10] Boehringer Ingelheim, the manufacturer of dabigatran, has initiated a large clinical trial program that mirrors the above-mentioned paradigm. The RE-VOLUTION clinical trial program will include more than 38,000 patients by the time it is completed.[12]

Clinical Indications

Deep Venous Thromboembolism Prophylaxis After Knee and Hip Arthroplasty

The rates of deep venous thrombosis (DVT) following major orthopedic surgery in patients who received no prophylaxis are approximately 40–60%. The standard of care according to the current American College of Chest Physicians (ACCP) guidelines is routine prophylaxis with low-molecular-weight heparin (Grade IA).[13,14] Three large, noninferiority, phase III, prospective, randomized, double-blind studies were done to evaluate the safety and efficacy of dabigatran etexilate versus enoxaparin after total knee replacement (RE-MODEL and RE-MOBI-

Table 1. RE-VOLUTION Clinical Trial Program

Indication	Phase II Study	Phase III Study
Primary venous thromboembolism prevention after major orthopedic surgery	BISTRO I	RE-MODEL, RE-NOVATE, RE-MOBILIZE
Secondary venous thromboembolism prevention		RE-MEDY, RE-SONATE
Acute venous thromboembolism treatment		RE-COVER
Stroke prevention in atrial fibrillation	PETRO	RE-LY
Secondary prevention of acute coronary syndrome		RE-DEEM

BISTRO=Boehringer Ingelheim Studying Thrombosis; PETRO=Prevention of Embolic and Thrombotic Events in Patients with Persistent Atrial Fibrillation; RE-DEEM=Randomized Dabigatran Etexilate Dose Finding Study in Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel; RE-LY=Randomized Evaluation of Long-Term Coagulation Therapy.

LIZE trials)[15,16] and total hip replacement (RE-NOVATE trial).[17] In the 2 trials conducted in Europe (RE-MODEL and RE-NOVATE), dabigatran etexilate was initiated 1–4 hours postoperatively and compared to enoxaparin 40 mg given on the evening before surgery and once daily afterwards for the duration of the trial. In the RE-MOBILIZE trial, dabigatran etexilate was started 6–12 hours postoperatively, and enoxaparin 30 mg twice daily was started 12–24 hours after surgery (the US-approved dosing regimen). In the RE-NOVATE trial, prophylaxis was administered for 28–35 days according to the current VTE prevention guidelines for hip arthroplasty and for 6–15 days in the 2 knee arthroplasty trials (RE-MODEL and RE-MOBILIZE). Dabigatran etexilate was investigated at 2 doses: 150 mg and 220 mg once daily.[18,19] The primary endpoint for all 3 trials was a composite of total VTE (venographic or symptomatic) and all-cause mortality during treatment. Secondary endpoints included major VTE and VTE-related mortality. The primary safety outcome was bleeding events, classified as major, clinically relevant, or minor events according to standard definitions.

The RE-NOVATE trial enrolled 3,494 patients undergoing hip arthroplasty in 115 centers. The noninferiority of both doses of dabigatran etexilate was established for the primary endpoint (6.0% and 8.6% for dabigatran etexilate 220 mg and 150 mg doses, respectively, vs 6.7% for enoxaparin; $P<.0001$ for each dose vs enoxaparin). Rates of bleeding were similar between the 2 doses of dabigatran and enoxaparin for both major bleeding (2.0% and 1.3%, vs 1.6%, respectively) and clinically relevant nonmajor bleeding (predominantly wound and skin hematoma and hematuria; 4.2% and 4.7% vs 3.5%, respectively).[17,19] Previously, liver toxicity was the main reason ximelagatran, another oral direct thrombin inhibitor, was withdrawn from the market. In the RE-NOVATE study, the incidence of liver enzyme elevations (>3 times upper limit of normal) did not differ significantly between groups.[17,19]

In the RE-MODEL trial, both doses of dabigatran etexilate were noninferior to enoxaparin for the primary outcome (36.4% and 40.5% for 220 mg and 150 mg doses, respectively, vs 37.7% for enoxaparin; $P<.0003$ and $P<.017$). Major bleeding rates were similar across groups (1.5% with 220 mg, 1.3% with 150 mg, and 1.3% with enoxaparin).[16,19]

The RE-MOBILIZE trial failed to show noninferiority between dabigatran etexilate and enoxaparin for the primary outcome (31.1% and 33.7% for the 220 mg and 150 mg doses, respectively, vs 25.3% for enoxaparin); however, this was mostly due to a higher number of asymptomatic distal DVT in both dabigatran etexilate groups. Major bleeding rates were not different, with a trend favoring dabigatran etexilate (0.6% in each dose group vs 1.4% in the enoxaparin group; $P=.14$ for 220 mg and $P=.09$ for 150 mg vs enoxaparin).[15,19]

A pooled analysis of these studies, which included a combined total of 8,210 patients, showed no statistically significant differences between dabigatran etexilate and enoxaparin for the primary efficacy outcomes of total VTE and all-cause mortality (relative risk [RR], 1.06; 95% confidence interval [CI], 0.94–1.18) or for the secondary efficacy outcome of major VTE, a composite of pulmonary embolism, proximal DVT, and VTE-related mortality (RR, 0.92; 95% CI, 0.66–1.29). Also, no significant differences were found in safety outcomes between dabigatran etexilate and enoxaparin, including major bleeding (RR, 0.99; 95% CI, 0.63–1.54) and clinically relevant bleeding (RR, 1.15; 95% CI, 0.88–1.50).[20] A meta-analysis of all 3 trials found no significant differences between dabigatran etexilate and enoxaparin either in the 2-trial analysis (all $P>.15$), or when all 3 trials were combined (all $P>.30$). Relative risk (random effects model) for the composite endpoints of total VTE and all-cause mortality were 0.95 (95% CI, 0.82–1.10) and 1.05 (95% CI, 0.87–1.26) in the 2- and 3-trial analyses, respectively. However, heterogeneity between the trials could not be excluded.[18]

Deep Venous Thromboembolism Treatment

Venous thromboembolism affects up to 2 adults per 1,000 annually.[21] The standard of care is administration of rapid-acting parenteral anticoagulation for 5–7 days followed by at least 3 months of treatment with warfarin.[22] The RE-COVER study was a double-blind trial that randomized 2,539 patients diagnosed with acute, symptomatic, proximal lower extremity DVT or pulmonary embolism to receive either oral dabigatran at a dose of 150 mg twice daily or dose-adjusted warfarin to achieve an international normalized ratio of 2–3 for 6 months. Dabigatran was noninferior to warfarin in preventing recurrent VTE (2.4% vs 2.1%, hazard ratio [HR], 1.10; 95% CI, 0.65–1.84; $P<.001$ for pre-specified noninferiority margin). The noninferiority margins were designed to correspond to preservation of 57% (for hazard ratios) and 75% (for differences in risk) of the lower boundary of the 95% confidence interval for the efficacy of warfarin compared with no anticoagulation, as assessed in 4 previous studies. Major bleeding was comparable between the dabigatran group (1.6%) and the warfarin group (1.9%; HR, 0.82; 95% CI, 0.45–1.48). For any bleeds, dabigatran etexilate showed a significant 29% reduction ($P=.0002$) compared to warfarin. As in previous studies, there was no evidence of significant hepatotoxic events with dabigatran. The results of this trial support the use of dabigatran as a fixed-dose oral treatment for acute

DVT and pulmonary embolism. The results, however, do not provide sufficient support for the use of dabigatran as monotherapy for acute symptomatic DVT because dabigatran was only started after initial parenteral anticoagulation therapy had been administered for a median of 9 days.[21]

Atrial Fibrillation

It is estimated that in the United States, approximately 2.8 million patients have atrial fibrillation, nearly 40% of whom receive oral anticoagulation with warfarin to minimize risks of stroke and death.[23] The phase II PETRO (Prevention of Embolic and Thrombotic Events in Patients with Persistent Atrial Fibrillation) study randomized 502 patients to dabigatran, dabigatran plus acetylsalicylic acid, or warfarin. The PETRO-Ex study was an open-label extension of PETRO, in which 361 patients receiving dabigatran were followed for an average of 29 months. Both studies showed thromboembolic event rates that were lowest with dabigatran etexilate 150 and 300 mg twice daily; major bleeding was most frequent with the 300 mg twice-daily dose compared with other doses.[9,24]

These studies paved the road for the pivotal phase III RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, which included 18,113 patients who had atrial fibrillation and risk factors for stroke. Patients were randomized to receive 1 of 2 fixed-dose regimens of dabigatran (110 mg twice daily or 150 mg twice daily) administered in a blinded fashion, with adjusted-dose warfarin administered in an unblinded fashion. The primary outcome was a composite of stroke and systemic embolism. The primary outcome rates were 1.69% per year in the warfarin group, as compared with 1.53% per year in the dabigatran 110 mg group (RR with dabigatran, 0.91; 95% CI, 0.74–0.11; $P<.001$ for noninferiority) and 1.11% per year in the dabigatran 150 mg group (RR, 0.66; 95% CI, 0.53–0.82; $P<.001$ for superiority). Concurrent use of antiplatelet agents was permitted, and median follow-up was 2 years. The rate of major bleeding was 3.36% per year in the warfarin group compared with 2.71% per year in the 110 mg dabigatran group (RR with dabigatran, 0.80; 95% CI, 0.69–0.93; $P=.003$) and 3.11% per year in the 150 mg dabigatran group (RR, 0.93; 95% CI, 0.81–1.07; $P=.31$). The rates of a life-threatening bleeding event, intracranial bleeding event, and major or minor bleeding event were higher with warfarin than with either dabigatran dose. Major gastrointestinal bleeding occurred more frequently with dabigatran at the 150 mg dose than with warfarin (RR, 1.50; 95% CI, 1.10–1.89; $P<.001$). Unexpectedly, the rates of acute myocardial infarction (MI) were also higher (0.74% for 150 mg dabigatran vs 0.53% for warfarin; RR, 1.38; 95% CI, 1.00–1.91; $P<.05$). A potential explanation might be that warfarin provided better protection against MI than dabigatran. Mortality rates were similar between warfarin and the 110 mg dabigatran group; the difference in mortality between 150 mg dabigatran (3.64%) and warfarin (3.75%) was borderline significant ($P=.051$).[25] Similar to previous studies, there was no significant hepatotoxicity with dabigatran. When the rates of major vascular events, major bleeding, and death were combined to produce the net clinical benefit, the rates were 7.64% per year with warfarin and 7.09% per year with 110 mg dabigatran (RR with dabigatran, 0.92; 95% CI, 0.84–1.02; $P=.10$) and 6.91% per year with 150 mg dabigatran (RR, 0.91; 95% CI, 0.82–1.00; $P=.04$).[26]

Secondary Prevention of Coronary Events

The RE-DEEM (Randomized Dabigatran Etexilate Dose Finding Study In Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors For Cardiovascular Complications Also Receiving Aspirin And Clopidogrel) trial is a phase II randomized, double-blind, placebo-controlled, dose-escalation study designed to evaluate the safety of 4 doses of dabigatran etexilate: 50, 75, 110, or 150 mg twice daily. Inclusion criteria were ST elevation or non-ST elevation acute coronary syndrome within the last 14 days, treatment with aspirin and clopidogrel, and at least 1 additional risk factor for cardiovascular complications. The primary endpoint was a composite of major and clinically relevant minor bleeding events during 26 weeks of treatment. Secondary endpoints included death, MI, severe recurrent ischemia, stroke, and changes in D-dimer used as a surrogate of anticoagulation efficacy. The trial recruited 1,878 subjects at a mean (standard deviation) of 7.4 (3.9) days from the index event. Inclusion diagnosis was ST elevation in 60% and non-ST elevation acute coronary syndrome in 40% of the patients; 54% of the patients underwent percutaneous coronary intervention for the index event at the time of randomization. The initial results were presented at the American Heart Association meeting in 2009. Major and clinically relevant minor bleeding events were seen in 2.4% of patients in the placebo group compared with 3.5%, 4.3%, 7.9%, and 7.8% in the 50, 75, 110, and 150 mg twice daily groups, respectively. Rates of cardiovascular death, non-fatal MI, or stroke were 3.8% in the placebo group compared with 4.6%, 4.9%, 3.0%, and 3.5% in the 50, 75, 110, and 150 mg twice daily groups, respectively. Final results will be published in the near future.[27]

Potential Indications

The list of potential indications is expanding, as more clinical data on the efficacy and safety of dabigatran

etexilate become available. Because of the ease of oral administration and the lack of need for monitoring, this new agent would be an attractive option for ambulatory cancer patients receiving chemotherapy who require treatment for cancer-associated DVT and also as a preventive treatment for central vein catheter–associated thrombosis. However, there are currently no trials exploring its role under these circumstances.[28]

Recent robust data show persistence of post-operative VTE risk for up to 12 weeks from orthopedic surgery and up to 1 year from cancer surgery.[29] If a more extended prophylaxis proves to be necessary in these populations, the advantages of dabigatran etexilate will make it ideal for this indication, and it could help both physicians and patients to adhere to optimal preventive strategies.[30]

Potential Limitations

One of the main limitations of dabigatran is the lack of an approved antidote. Dabigatran etexilate requires twice-daily dosing in contrast to warfarin, which requires only once-daily dosing.[31] Dyspepsia appears to be a significant side effect of dabigatran, the mechanism of which remains unknown.[21,26] The unexpected slight increase in MI rates with dabigatran as compared to warfarin needs to be investigated further. Cost-benefit will need to be established, but considering the lack of need for monitoring, it is likely that the cost-effectiveness of dabigatran will be favorable when compared with warfarin in the long term, even if dabigatran is more costly than warfarin.[32]

Conclusions

Dabigatran etexilate is a novel oral direct thrombin inhibitor with several advantages. It can be administered in fixed doses and does not require laboratory monitoring. Favorable data from randomized controlled trials provided basis for approval for prevention of VTE after hip replacement surgery in Europe and Canada. It is hoped that recent data on the use of dabigatran etexilate in treatment of acute DVT and in prevention of arterial thromboembolism in patients with atrial fibrillation will pave the way for regulatory approval for these important indications. Trial data in high-risk indications, such as in patients with acute coronary syndromes, will be reported in the near future. It is expected that the list of potential indications will expand, as more clinical data on the efficacy and safety of dabigatran etexilate will become available. The US Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee unanimously voted on September 20, 2010 in favor of approving dabigatran etexilate for stroke prevention in patients with atrial fibrillation.[33]

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