Oral Dabigatran Etxilate: an Emerging Alternative to Conventional Anticoagulation Therapy

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Oral Dabigatran Etxilate: an Emerging Alternative to Conventional Anticoagulation Therapy

Abstract

Background: Thromboembolic events are a substantial healthcare concern, both in hospital and community settings. The current standards of anticoagulation, heparin and warfarin, have well-demonstrated efficacy, but come with sizeable drawbacks. Heparin requires parenteral administration, and carries the risk of osteoporosis and severe thrombocytopenia. Warfarin, the only oral anticoagulant available, gives inconsistent results, and thus requires frequent laboratory monitoring and adjustment. A fixed-dose oral anticoagulant would ease the burden of anticoagulation both for patients and prescribers, and would likely increase adherence to prophylactic guidelines. Dabigatran etexilate, an oral direct thrombin inhibitor, is poised to offer this advantage, and has been appraised in several diverse settings of thromboembolic risk. While authorized for use in Europe, it awaits FDA approval in the United States.

Methods: An exhaustive search of available medical literature was performed on five databases: MEDLINE, CINAHL, ISI World of Science, the National Clinical Trials Registry and the Boehringer Ingelheim Clinical Trials database, looking for studies comparing this new drug to conventional anticoagulation therapy. Using the keywords dabigatran, warfarin, heparin, enoxaparin, BIBR 1048 and Pradaxa resulted in 327 entries. Included for review were original, randomized controlled trials, comparing dabigatran to warfarin or heparin therapy. Exclusion criteria were: animal studies, non-English language publications, and studies without an active control.

Results: Of the studies reviewed, seven showed dabigatran to have equal or superior efficacy to various heparin and warfarin protocols. One study showed dabigatran have inferior efficacy, when compared to enoxaparin for perioperative anticoagulation. Bleeding rates varied between the trials, but were generally comparable to control therapy. Among all the trials, two issues arose concerning safety and tolerability; patients taking dabigatran had a higher rate of dyspepsia in several trials, and one trial demonstrated an increased rate of myocardial infarction.

Conclusion: Dabigatran stands to offer crucial improvements in anticoagulation therapy. Current studies show promise, but firm conclusions are limited by several factors in trial design, including variations in control therapy, minimal long-term studies and a lack of independent investigation. For dabigatran to be established as an alternative short-term therapy in hospitalized patients, further data is needed comparing it to varying intensities of parenteral anticoagulation. In regards to its outpatient indications, the ongoing studies of long-term dabigatran therapy will help to define its safety profile and fortify the efficacy picture demonstrated thus far.

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A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies

Pacific University
Hillsboro, OR

For the Masters of Science Degree, August 2010

Faculty Advisor: James Ferguson, MS PA-C
Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD
Biography

Megan Merritt grew up in the Seattle area, and was reportedly dispensing medical advice as early as the first grade. Looking for a change of pace and scenery after high school, she attended New York University, where she toiled away as a pre-med student and simultaneously earned a bachelor’s degree in English Literature. In order to catch her breath after that endeavor, she returned to Seattle and worked as an Emergency Room Technician for two years. During that time she was exposed the kindness, wit and practicality of several local Physician Assistants, and committed herself to a slight deviation in her long-held career trajectory. She was accepted to the Pacific University PA Program in 2008 and became engaged shortly thereafter. Since starting PA school, she and her trusty suitcase have been in constant motion across a variety of Northwest locales. Now that graduation is here, she is excited to return to Seattle, retire the suitcase, find her dream job… and finally see to getting married.
Abstract

Background: Thromboembolic events are a substantial healthcare concern, both in hospital and community settings. The current standards of anticoagulation, heparin and warfarin, have well-demonstrated efficacy, but come with sizeable drawbacks. Heparin requires parenteral administration, and carries the risk of osteoporosis and severe thrombocytopenia. Warfarin, the only oral anticoagulant available, gives inconsistent results, and thus requires frequent laboratory monitoring and adjustment. A fixed-dose oral anticoagulant would ease the burden of anticoagulation both for patients and prescribers, and would likely increase adherence to prophylactic guidelines. Dabigatran etexilate, an oral direct thrombin inhibitor, is poised to offer this advantage, and has been appraised in several diverse settings of thromboembolic risk. While authorized for use in Europe, it awaits FDA approval in the United States.

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Results: Of the studies reviewed, seven showed dabigatran to have equal or superior efficacy to various heparin and warfarin protocols. One study showed dabigatran have inferior efficacy, when compared to enoxaparin for perioperative anticoagulation. Bleeding rates varied between the trials, but were generally comparable to control therapy. Among all the trials, two issues arose concerning safety and tolerability; patients taking dabigatran had a higher rate of dyspepsia in several trials, and one trial demonstrated an increased rate of myocardial infarction.

Conclusion: Dabigatran stands to offer crucial improvements in anticoagulation therapy. Current studies show promise, but firm conclusions are limited by several factors in trial design, including variations in control therapy, minimal long-term studies and a lack of independent investigation. For dabigatran to be established as an alternative short-term therapy in hospitalized patients, further data is needed comparing it to varying intensities of parenteral anticoagulation. In regards to its outpatient indications, the ongoing studies of long-term dabigatran therapy will help to define its safety profile and fortify the efficacy picture demonstrated thus far.

Keywords: dabigatran, enoxaparin, heparin, warfarin, venous thromboembolism, atrial fibrillation
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List of Abbreviations

ACCP……………………………………………American College of Chest Physicians
ADR…………………………………………….Adverse drug reaction
ALT…………………………………………….Alanine aminotransferase
AST…………………………………………….Aspartate aminotransferase
ARR………………………………………Absolute risk reduction
CI…………………………………………..Confidence interval
COX-2……………………………………Cyclo-oxygenase-2
DTI……………………………………….Direct thrombin inhibitor
DVT…………………………………………Deep vein thrombosis
FDA………………………………………Food and Drug Administration
HIT………………………………………..Heparin-induced thrombocytopenia
INR………………………………………..International normalized ratio
LMWH……………………………………Low-molecular-weight heparin
NIH……………………………………….National Institutes of Health
NNT………………………………………..Number needed to treat
NSAID……………………………………Non-steroidal anti-inflammatory drug
PE.........................................................................................Pulmonary embolism
RCT..............................................................Randomized controlled trial
SPAF.................................................................Stroke prevention in atrial fibrillation
TIA.................................................................Transient ischemic attack
TKR.................................................................Total knee replacement
UFH.................................................................Unfractionated heparin
ULN.................................................................Upper limit of normal
VKA.................................................................Vitamin K Antagonist
VTE.................................................................Venous thromboembolism
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BACKGROUND

Across a variety of healthcare settings, thromboembolic events contribute to significant morbidity and mortality worldwide. Among hospitalized patients, venous thromboembolism (VTE) has been identified as the most frequent cause of preventable death. Meanwhile, outpatients with hypercoagulability face a lifelong threat of recurrent deep vein thrombosis (DVT), pulmonary embolism (PE) and ischemic stroke. In each context, pharmacologic anticoagulation has been proven to reduce these risks substantially; however, available therapeutic interventions remain far from ideal. Inherent risks and requisite monitoring, closely tied to any anticoagulation plan, place a significant burden on patient and practitioner alike, and as a result many patients are undertreated. Surgical patients are discharged with only a few days of VTE prophylaxis, despite guidelines recommending at least 7-10 days, and recent studies showing the benefits of even longer therapy. Among outpatients at high risk of stroke (those with atrial fibrillation and one or more additional stroke risk factor), less than 50% of are prescribed the appropriate anticoagulant therapy. This group of patients is predicted to grow precipitously in the next 50 years, as the population ages in developed countries. Given the spectrum and volume of persons at risk, it is clear that a new approach in thromboembolism prophylaxis is needed.

For the last 50 years, vitamin-K antagonists (VKAs) and heparins have functioned as the gold standard of anticoagulation. Warfarin, an oral vitamin-K antagonist, was approved for use in humans in 1954, after functioning successfully for several years as a
rat poison. Its mechanism of anticoagulation is broad and indirect; warfarin acts by
decreasing biologically available vitamin K, which in turn prevents the formation of
coaulation factor II (prothrombin), along with factors VII, IX and X, and regulatory
proteins C and S. This non-selective inhibition of four separate clotting factors has
been postulated to contribute to warfarin’s notoriously steep dose-response curve. In its
favor, warfarin is inexpensive and widely available, with well-demonstrated efficacy.
However, warfarin therapy carries a multitude of drawbacks and limitations. Its sharp
response curve creates a narrow therapeutic index; prescribers must walk a fine line
between embolic and hemorrhagic events. Amplifying this danger is the extreme
unpredictability of anticoagulation response, both between patients and in the same
patients over time, as weight, health, and metabolism changes occur. Multiple dietary
interactions alter warfarin’s therapeutic activity, including alcohol use and vitamin K
intake. Its metabolism through cytochrome P450 creates a myriad of drug-drug
interactions. To compensate for this instability, warfarin therapy entails continual
laboratory monitoring using international normalized ratio (INR) measurements, which
adds cost, time and inconvenience for its users. Lastly, warfarin can take as many as five
days of therapy to reach an appropriate degree of anticoagulation, and a faster-acting
parenteral agent must be given as bridge-therapy on initiation.

Heparin, also an indirect thrombin inhibitor, was discovered early in the 20th
century, and has been in clinical use since the 1940s. Heparin molecules enhance the
function of antithrombin, a plasma protein which acts through several mechanisms to
inhibit active thrombin. Heparin is effective, fast-acting and widely available. However,
unfractionated heparin (UFH) demonstrates non-specific protein binding and
unpredictable distribution, necessitating laboratory monitoring to determine a safe
dose.14,17,19,20 Additionally, UFH therapy is associated with the serious complication of
heparin-induced thrombocytopenia (HIT).14,19 Its refined derivative, low-molecular-
weight heparin (LMWH) has the benefit of increased predictability and decreased HIT
risk,17 but is still difficult to dose in patients with obesity or renal insufficiency.19,20
Moreover, all heparins require parenteral administration and carry a risk of
osteoporosis,14 thus decreasing their desirability as long-term therapy.17

In the search for a new anticoagulant, several authors have proposed a list of ideal
properties for such a drug’s kinetics and administration. Cited qualities include: (1) oral
and parenteral formulations available, (2) a small number of daily administrations
needed, (3) rapid onset and offset of action, (4) safe and reversible mechanism (5)
predictable kinetics, (6) wide therapeutic window, (7) minimal interaction with
concomitant food or drugs, and (8) minimal need for individual monitoring and dose
adjustment.13,14,17,21

Several potential targets for therapy have emerged. Factor Xa and Factor IIa
(thrombin) are among the most frequently discussed options. Factor Xa inhibitors in
development include oral rivaroxaban, oral apixaban and parenteral idraparinux.13,14,21 In
other research laboratories, drugs targeting Factor IIa (thrombin) have shown great
promise.17 Four intravenous direct thrombin inhibitors (DTIs) have been developed, three
of which have already been put into use during percutaneous coronary interventions, and
in the treatment of HIT.22 Ximelagatran, an oral DTI, was developed by AstraZeneca, and
demonstrated utility in the settings of orthopedic surgery,23 acute VTE therapy,24 stroke
prevention in atrial fibrillation25,26 and cardioprotection following acute myocardial
infarction. However, concerns regarding hepatotoxicity and cardiac events during clinical trials prompted the FDA to deny approval for the use or marketing of ximelagatran in the United States in 2004, and it was subsequently withdrawn from all markets in February of 2006. Since then, dabigatran etexilate, a new oral DTI, has entered the later stages of Phase III trials, and is already approved in Europe for VTE prophylaxis with orthopedic surgery.

Dabigatran etexilate (hereafter referred to as dabigatran) is an enterally absorbed prodrug, which is quickly converted to its active form and widely distributed through the body, reaching therapeutic effect within 0.5-2.0 hours after administration. Dose-finding studies have demonstrated a serum half-life of 12 to 17 hours and a therapeutic effect for 12 to 24 hours following administration. Cytochrome P450 is not involved in the metabolism of dabigatran, and approximately 80% of the unaltered drug is excreted by the kidneys. A review of dabigatran administration in seven early trials found it to exhibit reliable pharmacokinetics and anticoagulant effect, with no clinically significant food or drug interactions evident. With this exciting potential for a less cumbersome option in oral anticoagulation, Phase III trials were undertaken to study the use of dabigatran in several applications.

Patients requiring long-term anticoagulation therapy, for indications such as secondary VTE prophylaxis and stroke prevention, stand to benefit most from a new oral anticoagulant. However, Phase III studies in these arenas necessitate large, lengthy trials because the overall rate of embolic events is relatively low. On the other hand, a short-term setting such as perioperative VTE prophylaxis, where thrombus formation rates are fairly high and clinical endpoints are more clearly defined, provides a better setting for
therapeutic investigation.\textsuperscript{13,31} Thus, the initial studies on dabigatran focused on its potential following knee and hip replacements, where the rate of VTE ranges from 40-80\%,\textsuperscript{2,11} and a time frame of risk is clearly established.\textsuperscript{31} Although they focus on a specific setting of anticoagulation, these studies have implications for a broad spectrum of patients, as Alexander Turpie points out, since the pathophysiology underlying thrombus formation is similar between the venous system of surgical patients and the left atrium of atrial fibrillation patients.\textsuperscript{13} On top of the evidence from these initial orthopedic surgery trials, in the last six months the results of two major long-term studies were released suggesting dabigatran to be effective for acute VTE therapy\textsuperscript{32} and for stroke prevention in atrial fibrillation (SPAF).\textsuperscript{33} With the extent of information that now exists on dabigatran, a thorough review of studies is warranted to synthesize the available evidence regarding both the efficacy and safety of this new drug in various anticoagulation settings.

**METHODS**

An exhaustive search of the literature was conducted on three databases: MEDLINE, CINAHL, and ISI World of Science, using the following sets of terms: “dabigatran and warfarin” and “dabigatran and heparin or enoxaparin.” This resulted in approximately 327 entries, including seven original research articles. Adding two alternative names for the drug, “BIBR 1048” and “Pradaxa,” yielded several additional studies. Further searches were then conducted on the National Institutes of Health (NIH) Clinical Trials database and the Boehringer Ingelheim Research & Development website, using the keyword “dabigatran,” to uncover any unpublished studies on this new drug. This contributed another four completed trials, three of which had posted results. A
screening of bibliographic material was then performed for selected works, to provide both pertinent background information and evidence of any additional studies that might have been missed.

For selected articles, inclusion criteria were: original, randomized controlled trials (RCTs), comparing dabigatran to either warfarin or heparin therapy. Excluded were non-English language publications, animal studies, and studies without an active control.

RESULTS

In total, this search produced eight studies, looking at dabigatran therapy in three different contexts (see Table 1). Given the involved nature of warfarin therapy as a comparator, several of the included studies were not double-blinded. For this reason, a modified JADAD score was implemented to rate the methodological strength of each study (see Table 2). It should be noted that, as these studies involve a drug under development, all were sponsored by grants from the manufacturer Boehringer Ingelheim. Seven were published articles, and one was an unpublished clinical trial report.

Four studies examined dabigatran’s application as VTE prophylaxis following joint replacement surgery, comparing it to enoxaparin over a perioperative anticoagulation period lasting 6-35 days.34-37 The size of these trials ranged from 1949 to 3463 patients, with VTE occurrence ranging from 6.7% to 40.5%.34-37 These studies were all double-blinded, using a combination of identical appearing pills and subcutaneous injections in each therapy group. All studies allowed concomitant therapy with low-dose aspirin (<160 mg per day) and selective cyclo-oxygenase-2 (COX-2) inhibitors. A specified method of venography evaluation, outlined by Rabinov and Paulin,38 was used in all trials to assess for DVT at the end of therapy. Changes in liver enzymes were
closely monitored in each trial, given dabigatran’s relation to the discontinued ximelagatran, as were bleeding rates and other adverse events. All bleeding events in these trials were defined as major, clinically significant or minor, based on the criteria established by the European Agency for the Evaluation of Medicinal Products and the investigators of the initial dabigatran study (see Table 3.)

The other four studies reviewed compare dabigatran to adjusted-dose warfarin therapy; one looked at the treatment of acute VTE and three looked at SPAF. Warfarin was prescribed in each study towards a goal INR of 2.0-3.0. The population in these trials ranged from 166 to 18,113 patients, and thromboembolic event rates ranged from 0% to 2.7%. Two studies followed outcomes over 12 weeks of therapy, one over six months, and one over a median of two years treatment. One study was double-blinded, while the other three employed open-label warfarin. In addition to embolic events, each study looked at bleeding rates, adverse reactions and changes in liver enzymes. Definitions of bleeding events in these trials were similar to those in the orthopedic surgery trials, but were not based on a single set of guidelines.

The earliest controlled trial of dabigatran, the Boehringer Ingelheim Study in ThROmbosis II (BISTRO II Study), earned a modified-JADAD score of six out of seven. This European study compared oral dabigatran, in several different dosing strategies, to a standard of 40 mg daily subcutaneous enoxaparin following total hip or knee replacement surgery. In order to refine the initial pharmacokinetic data and determine the appropriate dosing of this new drug, dabigatran groups received 50 mg, 150 mg or 225 mg twice daily, or 300 mg once daily, and plasma drug concentrations were measured over time. Among the 1949 treated subjects, the average age was 65.9
years, the average weight was 79 kg, and 79% were female. The mean duration of surgery was 1.4 hours, 27% of these using general anesthesia, and 73% using neuraxial anesthesia (epidural, spinal, or both). Patients randomized to dabigatran therapy were scheduled to begin treatment 1-4 hours post-operatively, with actual delay of 2.6 hours on average. Meanwhile, patients randomized to enoxaparin were scheduled to begin treatment 12 hours prior to surgery. However, in some countries where the study was conducted, standard practice dictates that enoxaparin be started post-operatively, and this variation was allowed. The primary outcome used for efficacy analysis was the total incidence of VTE, based both on symptomatic events and bilateral screening venography.

The BISTRO II study found that dabigatran, in all dose groups higher than 50 mg, showed statistically superior VTE prophylaxis over enoxaparin (for 150 mg bid, ARR of 17.4%, NNT 9; for 225 mg bid, ARR of 15.4%, NNT 7). With only one major bleeding event (0.3%), dabigatran 50 mg twice daily showed significantly lower rates than all other groups in this respect, including enoxaparin ($P = .047$). The major bleeding rate increased with each escalation in dabigatran dose (4.1% in the 150 mg twice daily group, 3.8% in the 225 mg twice daily group, and 4.7% in the 300 mg once daily group), but this did not reach statistical significance when compared to the rate of 2.0% among enoxaparin users ($P = .10, .15, and .051$, respectively). Clinically significant bleeding occurred in 2.3% to 5.1% of dabigatran users, compared to 2.6% of enoxaparin users. Minor bleeding occurred in 4.6% to 9.7% of dabigatran users, compared to 6.4% of enoxaparin users.
The authors make it evident that aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were checked at baseline in every participant, and at unspecified intervals thereafter. From this data, ALT increases greater than three times the upper limit of normal (3 X ULN), occurred in 1.5%-3.1% of the dabigatran groups, compared to 7.4% in the enoxaparin group. In regards to other adverse events, the authors state that 160 serious adverse events reported during the treatment period, but only 24 of these were deemed a potential adverse drug reaction (ADR) by the investigators (0.5% of enoxaparin patients, versus 0%, 1.0%, 3.1% and 1.5% of dabigatran 50 mg, 150 mg, 300 mg and 225 mg, respectively). The specific nature of these events was not commented upon.

Two years after publishing BISTRO II, Eriksson and several of the same investigators published the RE-MODEL trial, which also meets six of the seven modified-JADAD criteria. Examining dabigatran as a perioperative anticoagulant in 2076 knee arthroplasty patients, the trial was conducted in Europe, Australia and South Africa, and focused on two doses of dabigatran (150 or 220 mg once daily) compared to 40 mg daily subcutaneous enoxaparin. The mean age among participants was 67.6 years, the average weight was 82.3 kg, and 66.0% were female. For the surgical procedure, which lasted an average of 91 minutes, general anesthesia was used in 23%, neuraxial anesthesia was used in 48%, and a combination of both was used in 29% of cases. Dabigatran dosing began 1-4 hours post-operatively, and was initiated with a half-dose; the mean time to this starting dose was 3.5 hours. For the control group, enoxaparin began either the evening prior to surgery or post-operatively, depending on the local standard. Treatment continued 6-10 days until bilateral venography, after which the need
for continued anticoagulation was decided by the investigator. For this study, the primary efficacy outcome was defined as total VTE events combined with all-cause mortality during the treatment period (from the first dose to three days after the last dose).  

The primary outcome of interest occurred in 40.5%, 36.4% and 37.7% of the dabigatran 150 mg, 220 mg and enoxaparin groups, respectively. Per the authors’ preset criteria for non-inferiority (a 9.2% margin), both doses of dabigatran proved non-inferior to enoxaparin, although not superior. Major bleeding rates in the three study arms ranged from 1.3% to 1.5%, demonstrating no significant difference between the two drugs ($P=1.0$ for dabigatran 150 mg and $P=.82$ for 220 mg). Clinically relevant bleeding rates ranged from 5.3% to 6.9%, and minor bleeding occurred in 8.4% to 9.9%. Not all $P$ values are provided, but the authors specify that no difference in any bleeding outcome between dabigatran and enoxaparin achieved statistical significance.  

Patients in the RE-MODEL study had liver enzymes measured on four occasions between enrollment and a three-month follow-up visit. Rates of significant enzyme elevation (3 X ULN) appear balanced between the dabigatran 150 mg, 220 mg and enoxaparin groups (3.7%, 2.8% and 4.0%, respectively). Blinded analysts screened for adverse cardiac events among all participants, and found seven occurrences in the dabigatran 150 mg arm (1.0%), three in the 220 mg arm (0.4%) and four in the enoxaparin arm (0.6%). Three additional cardiac events occurred during follow-up, one in the dabigatran 150 mg group and two in the enoxaparin group.  

The RE-NOVATE study, the third dabigatran trial reviewed, was organized by the same primary investigators as the BISTRO II and RE-MODEL trials, and received a validity score of six. Conducted in Europe, Australia and South Africa, this study
followed 3463 patients undergoing total hip replacement. Among these participants, 56.9% were female and 2.9% had a history of DVT or PE. The average age was 64.5 years, while weight and creatinine clearance were 79.3 kg and 90.1 mL/min. Hip replacement surgery, lasting a mean of 86.4 minutes, employed solely general anesthesia in 26.6%, solely neuraxial anesthesia in 66.5% and a combination of both in 8.6%. Dabigatran was given as 150 mg or 220 mg once daily, and was initiated as a half-dose one to four hours after surgery (mean 3.4 hours). The control therapy was 40 mg daily subcutaneous enoxaparin, starting either the evening prior to surgery or post-operatively, based on local standards. In their design, the investigators chose to extend therapy to one month (28-35 days), citing several studies and meta-analyses demonstrating the benefit in longer anticoagulation, most prominently the 2004 American College of Chest Physician (ACCP) guidelines.

The primary efficacy outcome in the RE-NOVATE study was defined as total VTE events plus all-cause mortality during the treatment period. Efficacy data was analyzed using a pre-defined non-inferiority margin of 7.7%. Among these patients, the primary outcome occurred in 8.6% treated with 150 mg dabigatran, 6.0% of those treated with 220 mg, and in 6.7% of the enoxaparin group. Based on the 95% confidence intervals for these rates, there was no significant difference in efficacy among all groups, and the authors state that the criteria for non-inferiority was met.

Major bleeding occurred in the 1.6% of the enoxaparin group, compared to 1.3% of the dabigatran 150 mg group ($P=.6$) and 2.0% of the dabigatran 220 mg group ($P=.44$), demonstrating no significant difference between the therapies. Clinically relevant and minor bleeding rates were distributed similarly among the three groups; the former
occurred in 3.5% to 4.7% of patients and the latter occurred in 6.1% to 6.4% of patients. P values or confidence intervals are not given for these results, but the authors specify that no bleeding outcomes differed between groups with statistical significance.36

Among RE-NOVATE patients, similar numbers in each group experienced adverse events and similar numbers discontinued treatment as a result.36 Seventy-seven percent of each group experienced some adverse event. Among these, 8% were deemed serious in both dabigatran groups, while 7% were deemed serious among enoxaparin users, and discontinuation resulted in 8%, 6% and 6% of the dabigatran 150 mg, 220 mg and enoxaparin groups, respectively. The most frequent adverse event was nausea, which occurred in 22% of dabigatran 150 mg users, 21% of dabigatran 220 mg users and 25% of enoxaparin users (P values not provided). Notable ALT elevation (> 3 X ULN) occurred at a significantly higher rate in the enoxaparin group (5% versus 3% in both dabigatran groups, P< .01 for both). Acute coronary events were distributed equally among the groups, occurring in eight members of the dabigatran 150 mg arm (0.69%), five members of the dabigatran 220 mg arm (0.44%) and nine members of the enoxaparin arm (0.78%). The enoxaparin group was noted to have three additional cardiac events in follow-up.36

The RE-MOBILIZE study,37 published two years after RE-MODEL35 and RE-NOVATE,36 was designed to address the discrepancies in enoxaparin dosing among the European trials. Following 2596 patients undergoing total knee replacement (TKR), this study was conducted primarily in North America, and used the North American approved enoxaparin regimen of 30 mg subcutaneously every 12 hours, starting 12-24 hours post-operatively.37 Other aspects of the study design remained the same as prior trials, and
earned a modified-validity score of six. Among RE-MOBILIZE patients, 57.7% of whom were female, the average participant was 66.1 years old, weighed 88 kg, and had a creatinine clearance of 82.9 mL/min. Surgery lasted a mean of 90.6 minutes, and general anesthesia was used in 52.9%. Spinal anesthesia was used in 46.5% of operations, while “other” anesthesia was used in 0.6%. Dabigatran was initiated 6-12 hours after surgery, starting with a half dose, and continuing at 150 or 220 mg once daily. Anticoagulation continued for 12-15 days (mean of 13 days), citing a 2003 analysis reporting improved efficacy of enoxaparin with extended therapy.\textsuperscript{12} The primary efficacy outcome was defined as the total incidence of VTE and death during the treatment period.\textsuperscript{37}

In RE-MOBILIZE patients, dabigatran could not demonstrate non-inferiority to enoxaparin.\textsuperscript{37} The primary outcome rate in the enoxaparin group was 25.3%. Among dabigatran patients, this rate was 33.7% in the 150 mg group and 31.7% in the 220 mg group. This data establishes absolute risk reductions of 8.4% ($P=.009$) and 5.8% ($P=.0234$) when using enoxaparin, compared to the tested doses of dabigatran, with a number needed to harm of 12 and 18, respectively. Major bleeding occurred in 0.6% of both dabigatran groups, and 1.4% of enoxaparin patients. Clinically relevant bleeding occurred in 2.5%, 2.7% and 2.4% of dabigatran 150 mg, 220 mg and enoxaparin patients, respectively. Liver enzymes were measured at four points over the course of the study, and significant ALT elevations ($\geq 3 \times$ ULN) were rare and distributed evenly among the groups (1.0% of dabigatran 150 mg patients, 0.7% of dabigatran 220 mg patients and 0.9% of enoxaparin patients). The same can be said for serious cardiac events (occurred in 0.11%, 0.10% and 0.11%, respectively) during the blinded treatment period. Adverse events during follow-up are not specifically delineated.\textsuperscript{37}
While the prior four studies looked at dabigatran as VTE prophylaxis, the RE-COVER study\textsuperscript{32} looked at the use of dabigatran in a new context: outpatient therapy following the diagnosis of acute venous thromboembolism. The trial was conducted in 29 countries across the globe, and earned a modified validity score of seven. All of the 2539 participants had a new, objectively verified DVT or PE, for which six months of anticoagulation was deemed appropriate therapy based on risk factors. Among these subjects, 41.6\% were female and 94.8\% were identified as white. The mean age was 54.7 years, with a weight of 84.9 kg and creatinine clearance of 105.1 mL/min. Nearly five percent of the subjects had active cancer and approximately one-quarter had a history of prior VTE. Aspirin therapy under 100 mg per day was allowed, but patients requiring other anti-platelet therapy were excluded from randomization. Included patients received either 150 mg daily dabigatran or adjusted-dose warfarin, following an initial period of parenteral anticoagulation with UFH (12.1\%), LMWH (90.0\%) or fondaparinux (3.4\%). Double-blinding was maintained through the use of placebo pills in both groups and a specially programmed coagulometer that would report true INR values for warfarin patients and sham INR values in the dabigatran group. During the monthly follow-up visits, warfarin patients were found to be within the correct range 60\% of the time, a rate noted by the authors to be consistent with good-quality anticoagulation management in a 2008 community cohort study.\textsuperscript{9} Therapy continued for six months, barring a serious adverse event, with follow-up one month after completion.\textsuperscript{32}

To qualify the therapeutic outcomes, baseline imaging of both legs and pulmonary arteries was obtained within 72 hours of randomization.\textsuperscript{32} Later imaging was done based on symptomatic indications, and then compared to baseline. The primary endpoint was
defined as symptomatic VTE or death associated with VTE, and efficacy was measured as the time from randomization to the occurrence of either event. Analysis was carried out to demonstrate non-inferiority, with a predetermined margin of 3.6% risk difference.

Bleeding events were described as major, clinically relevant or nuisance bleeding. Major bleeding had to be clinically overt and correlated to a hemoglobin drop of 20 g L$^{-1}$ or greater, a need for transfusion of at least two units red cells, bleeding in a “critical site” or fatal bleeding. Clinically relevant bleeding met one or more of the following criteria: gingival or nasal bleeding lasting over five minutes, spontaneous rectal bleeding described as more than spotting, gross hematuria that was either spontaneous or lasted over 24 hours, skin hematomas over 25 cm$^2$, bleeding necessitating hospitalization, surgical treatment, or a transfusion of under two units blood products or other bleeding deemed relevant by the investigator.

Upon completion of the treatment period, recurrent VTE or VTE-related death was suspected in 134 members of the dabigatran group and 130 members of the warfarin group. However, a blinded analysis of these cases confirmed the events in only 30 (2.4%) and 27 (2.1%) patients from each group, respectively. Based on this data, the absolute risk reduction was 0.4% in favor of warfarin (95% CI, -0.8 to 1.5). This corresponds to a hazard ratio of 1.10 (95% CI, 0.65 to 1.84), which met the study’s criteria for non-inferiority in the prevention of recurrent or fatal VTE. When examining the study period and the 30-day follow-up together, the primary event rates were 2.7% with dabigatran and 2.5% with warfarin, yielding a hazard ratio of 1.05 (95% CI, 0.65 to 1.70).
Looking at major bleeding events, rates were comparable between the two therapies\(^{32}\) (1.6% with dabigatran versus 1.9% with warfarin), yielding a hazard ratio of 0.82 (95% CI, 0.45 to 1.48). However, the authors do note a substantial difference in risk when clinically relevant bleeding events are added in, resulting in composite bleeding rates of 5.6% with dabigatran and 8.8% with warfarin (hazard ratio of 0.63; 95% CI, 0.47 to 0.84; \(P=.002\)). Adding in minor bleeding events, the data gives similar results (16.1% of dabigatran patients compared to 21.9% of warfarin patients; hazard ratio of 0.71; 95% CI, 0.59 to 0.85). The gastrointestinal tract was the one site where bleeding events occurred more frequently with dabigatran use (4.2% versus 2.8% with warfarin).\(^ {32}\)

The trial lists all adverse reactions reported by at least 3% of subjects,\(^ {32}\) and the only side effect demonstrating disparity among groups was dyspepsia, which was reported in 3.1% of dabigatran patients and only 0.7% of warfarin patients (\(P < .001\)). Nonetheless, discontinuation rates were significantly higher in the dabigatran group (9.0% versus 6.8%; \(P = .05\)). Liver-function tests were performed at unspecified intervals, and significant ALT elevations (> 3 X ULN) were uncommon and evenly distributed between the groups (3.4% versus 3.8% with warfarin; \(P = .68\)). Acute coronary syndrome occurred in five members of the dabigatran arm (0.4%) and three members of the warfarin arm (0.2%), suggesting no increased risk between therapies (\(P = .73\)).\(^ {32}\)

The PETRO study\(^ {28}\) represents the first trial investigating dabigatran’s efficacy in atrial fibrillation and earns a modified-JADAD score of four. PETRO looked at 502 patients with non-valvular atrial fibrillation and one or more additional risk factors for stroke (age over 75 years, prior transient ischemic attack (TIA) or stroke, documented coronary artery disease, hypertension requiring medical therapy, diabetes mellitus,
symptomatic heart failure or ejection fraction <40%). Among the enrolled patients, 18% were female, with a mean age of 70 years and median of three stroke risk factors. Duration of atrial fibrillation ranged from 0.05 to 30 years, with a median length of 4 years. At the start of the study, all patients had been on VKA therapy at least eight weeks, and had an INR of 2.0-3.0. Weight and creatinine clearance are not specified. An additional factor introduced by this study was the concomitant use of aspirin. Subjects were randomized into a 3 X 3 factorial distribution to receive either a combination of dabigatran (50 mg, 150 mg or 300 mg bid) and aspirin (0, 81 mg or 325 mg daily) or to receive adjusted-dose warfarin alone. While the dose of dabigatran was blinded, both warfarin and aspirin were open-label. Therapy lasted for 12 weeks, and analysis focused on bleeding rates, safety, laboratory changes and any occurrence of cardiovascular or peripheral embolic events. Bleeding was categorized as major, clinically relevant or nuisance bleeding, with major events defined as: either fatal or life-threatening, or occurring in an intracranial, intraocular, intraspinal or retroperitoneal location, or associated with a drop in hemoglobin of 2 g L⁻¹ or greater, the need for surgery or transfusion of two or more units blood products. Clinically relevant bleeding events described: epistaxis or gingival bleeding over five minutes duration, spontaneous rectal bleeding, gross hematuria, skin hematoma greater than 25 cm² size, bleeding resulting in hospitalization or the transfusion of under two units blood products, or any other event deemed relevant by the investigator. All bleeding events were adjudicated by blinded personnel, but the method of evaluation for other outcomes is unspecified.

Within the PETRO treatment period, it became evident that patients taking 600 mg total daily dabigatran along with aspirin were suffering from major hemorrhage with
much greater frequency. These patients were consolidated into a single group and proceeded to take 300 mg twice daily without aspirin. Five patients receiving lower dabigatran doses also discontinued aspirin during the trial. Further changes in dosing occurred within the treatment period; investigators decreased dabigatran dosing to once daily in 12 patients, based on measurements of creatinine clearance and trough activated partial thromboplastin time (aPTT), and these patients were evaluated in their original dosing groups. Among patients in the warfarin group, INR was within range 57.2% of the time.

Overall there were only two thromboembolic events during the study, both of which occurred in patients taking dabigatran 50 mg twice daily (1.96%), one with the use of 81 mg of aspirin and one with no aspirin. On the other hand, major bleeding events only occurred in patients taking 300 mg dabigatran along with aspirin; three events took place in patients taking 325 mg of aspirin and one event took place in a patient taking 81 mg aspirin. With an overall major bleeding rate of 6.3% in the dabigatran 300 mg plus aspirin patients, compared to 0% in all other treatment groups, this frequency was statistically significant even next to 300 mg dabigatran alone (P <.02). This significance persisted when clinically relevant and nuisance bleeding were added in (39.1% for 300 mg with aspirin compared to 13.3% without aspirin, P=.0003). The other disparity determined to have statistical significance was the low rate of total bleeding among the 50 mg dabigatran patients (regardless of aspirin use) compared to both the warfarin-using patients (6.5% versus 17.1%, P=.044) and the higher doses of dabigatran (17.8% for 150 mg and 21.9% for 300 mg; P of .01 and .0002, respectively). Looking at clinically
relevant bleeding events, rates were 1.9% among those taking dabigatran 50 mg, 7.7% among both the 150 and 300 mg groups, and 5.7% among those taking warfarin.\textsuperscript{28}

ALT elevations over three times the upper limit of normal occurred in four dabigatran patients (0.9%) and no warfarin patients.\textsuperscript{28} Acute coronary syndrome was observed in two patients, one taking dabigatran 50 mg twice daily and in one taking dabigatran 300 mg twice daily, both with 81 mg of aspirin. Additionally, four patients in the trial developed congestive heart failure, but the authors found no statistical significant underlying either outcome. Overall, 38 patients discontinued treatment, 29 due to adverse events. Of the latter group, all were dabigatran users; 4.7% of the 50 mg group, 5.3% of the 150 mg group and 8.9% of the 300 mg group stopped treatment because of adverse outcomes. The primary ADR was gastrointestinal upset, leading to discontinuation in 1.9-4.7% of the patients taking dabigatran and none of the warfarin users.\textsuperscript{28}

The Yamaguchi trial\textsuperscript{40} was conducted shortly after PETRO,\textsuperscript{28} but was never published. As a small, open-label study, this trial earned a validity score of three out of seven points. The study involved 166 Japanese patients with non-valvular atrial fibrillation and at least one additional risk factor for thromboembolism (age 75 years or older, prior stroke or TIA, hypertension, diabetes mellitus, left-sided heart failure or coronary artery disease).\textsuperscript{40} The actual distribution of ages, comorbidities or other medication use among the participants is not given. Comparing 110 mg or 150 mg of dabigatran twice daily to adjusted-dose warfarin, the trial looked at outcomes over 12 weeks of therapy. Patients were randomized but not blinded to which therapy they received. Efficacy endpoints included stroke or systemic embolism, TIA, adverse cardiac events or death. Safety endpoints included major and minor bleeding events (criteria not
given), adverse events and discontinuations. In addition, investigators monitored the pharmacokinetics of dabigatran, along with several laboratory values related to anticoagulation activity.40

During the Yamaguchi trial, no thromboembolic events occurred in the dabigatran groups, and one ischemic stroke occurred in the warfarin group.40 In the post-treatment period (length unspecified) one ischemic stroke occurred in the dabigatran 150 mg group. Major bleeding occurred in 0% and 1.7% of the dabigatran 110 and 150 mg groups, respectively, and in 3.2% of the warfarin group. When major and clinically significant bleeding were combined, the investigator noted a dose-dependent increase in bleeding among dabigatran users, which still remained lower than the warfarin group for both doses (4.3% in the dabigatran 110 mg group, 8.6% in the 150 mg group and 11.3% in the warfarin group). Looking at total bleeding rates, dabigatran 110 mg and warfarin appeared similar (21.7% and 24.2%, while dabigatran 150 mg demonstrated a higher incidence (34.5%). The author also reports an increase in major and clinically significant bleeding events among patients taking aspirin (rates not given). No risk ratios, confidence intervals or $P$ values are provided for Yamaguchi’s results.40

In regards to other adverse events in the trial, no patient in any group was found to have a liver function test (LFT) elevated over twice the upper limit of normal.40 The study reports “no serious adverse events related to the investigational drug,” although the criteria for this assessment are not specified.40 No information concerning non-serious adverse events or discontinuation rates is provided.40

The final study examined was the RE-LY study (Randomized Evaluation of Long-Term Anticoagulation TherapY),33 which compared two doses of dabigatran to
warfarin therapy for SPAF over a period of 39 months, and earned a validity score of six points. Of the 18,113 individuals enrolled, each had documented atrial fibrillation and one or more separate risk factor for stroke (aged 75 years or older, prior TIA or stroke, hypertension, diabetes mellitus, coronary artery disease, ejection fraction less than 40% or heart failure in the last six months meeting the New York Heart Association class II or higher criteria). Patients were recruited from 44 different countries, and enrollment was directed to include a balanced proportion of patients who were VKA naïve (total lifetime use <61 days). Among these enrollees 46.4% were female, with an average age of 71 years and weight of 82.7 kg. Twenty percent of these patients had history of TIA or stroke, while 79.9% reported hypertension and 16.6% had experienced a prior MI. Daily aspirin use under 100 mg was permitted, and occurred in approximately 20% of each test arm. \( P \) values are not given, but the authors specify that all three treatment arms were balanced in their baseline characteristics. Patients were randomized to receive either a blinded dose of dabigatran (110 or 150 mg twice daily) or open-label warfarin, which was dose-adjusted at least monthly. Patients were followed for a median period of two years. On conclusion of the study, the average time warfarin patients spent within therapeutic range was 64\%.33

The primary efficacy outcome in RE-LY was defined as stroke or systemic embolism during the treatment period.33 Non-inferiority analysis was done to satisfy a predetermined relative risk of less than 1.46, when compared to warfarin treatment. Other outcomes measured included MI, PE, TIA, hospitalization and death. Bleeding events were categorized as major or minor, with a subcategory for life-threatening bleeding.33,42 Life-threatening bleeding was defined by: symptomatic intracranial bleeding, a decrease
in hemoglobin greater than 50 g L\(^{-1}\), a requirement for surgery, transfusion of four or more units of blood products or any inotropic agents, or bleeding that was fatal. Bleeding that occurred in a critical area or organ, lead to a drop in hemoglobin of at least 20 g L\(^{-1}\) or a transfusion of at least two units of blood product constituted major bleeding. All other bleeding events were labeled as minor bleeding.\(^{33,42}\)

Based on the RE-LY results, dabigatran 110 mg twice daily was equivalent to warfarin for thromboembolic prophylaxis.\(^{33}\) With an event rate of 1.53% per year in this group, versus 1.69% per year in the warfarin group, the relative risk with 110 mg dabigatran therapy was 0.91 (95% CI, 0.74 to 1.11; \(P=0.34\)), thus meeting the pre-specified non-inferiority criteria. Among patients taking 150 mg of dabigatran, the prophylactic effect surpassed non-inferiority, and demonstrated superiority to warfarin; the primary outcome rate was 1.11% per year, yielding a relative risk of 0.66 with this therapy (95% CI, 0.53 to 0.82; \(P < .001\)). Bleeding rates also appeared to favor dabigatran therapy; major bleeding occurred in 2.71% of the dabigatran 110 mg group per year, in 3.11% of the dabigatran 150 mg group per year, and in 3.36% per year among warfarin users. This establishes a relative bleeding risk with dabigatran that is comparable to warfarin at the 150 mg dose (0.93; 95% CI, 0.81 to 1.07; \(P=.31\)) and superior to warfarin at 110 mg dose (0.80; 95% CI, 0.69 to 0.93; \(P =.003\)). For minor bleeding, dabigatran 110 mg established a relative risk of 0.79 versus warfarin (95% CI, 0.74 to 0.84; \(P<.001\)) and dabigatran 150 mg established a relative risk of 0.91 (95% CI, 0.85 to 0.97; \(P=.005\)). For total bleeding events, when compared to warfarin, dabigatran 110 mg demonstrates a relative risk of 0.78 (95% CI, 0.74 to 0.83; \(P<.001\)) and while dabigatran 150 shows a relative risk of 0.91 (95% CI, 0.86 to 0.97; \(P=.002\)). The
strongest risk reduction is seen in the category of life-threatening bleeding; here
dabigatran 110 mg yields a relative risk of 0.68 (95% CI, 0.55 to 0.83; \( P < .001 \)) and
dabigatran 150 mg a relative risk of 0.81 (95% CI, 0.66 to 0.99; \( P = .04 \)). Within the
bleeding results, two clinically important sites of bleeding are sub-categorized:
intracranial and gastrointestinal. Both dabigatran groups experienced significantly less
intracranial bleeding (relative risk of 0.31 and 0.40; \( P < .001 \) for both comparisons).
However, patients receiving dabigatran experienced more gastrointestinal bleeding
(1.12% and 1.51% per year) compared to warfarin (1.02% per year) and this disparity
reached statistical significance for the higher dabigatran dose (relative risk 1.50; \( P
< .001 \)).

RE-LY investigators also looked at hospitalization rates, death rates from vascular
causes and death rates from any cause. In this study, hospitalization rates were lowest in
the dabigatran 110 mg group (19.4% per year; relative risk of 0.92 compared to warfarin;
\( P = .003 \)) while deaths from vascular causes were lowest in the dabigatran 150 mg group
(relative risk 0.85 versus warfarin; \( P = .04 \)). Interestingly, the authors describe an
unexpected finding in the distribution of myocardial infarctions. The rate was low
overall (0.53-0.74%), but occurred more frequently in patients taking dabigatran than
warfarin. This difference reached statistical significance for the dabigatran 150 mg group
(relative risk 1.38; 95% CI, 1.00 to 1.91; \( P = .048 \)). To summarize all these therapeutic
factors, the investigators designed a “net clinical benefit” value which combined major
vascular events, major bleeding and death. By this measurement, the lower dose of
dabigatran was equivalent to warfarin anticoagulation, while higher dose dabigatran was
slightly superior (relative risk of 0.91; \( P = .04 \)).
Liver function testing was initially conducted on a monthly basis, then every three to four months during the later portion of the study. Enzyme levels greater than three times the upper limit of normal were seen with an equally low frequency among all participants (1.9-2.2%). Dyspepsia was the most commonly reported adverse event, and the only side effect that occurred more frequently among dabigatran users (11.8% in the dabigatran 110 mg group and 11.3% in the 150 mg group versus 5.8% of the warfarin group; \( P < .001 \) for both comparisons). Discontinuation rates were significantly higher in dabigatran users, both at one year of treatment (15% versus 10% with warfarin) and two years of treatment (21% versus 17%; \( P < .001 \) for both comparisons). Approximately 11% of these discontinuations were attributed to gastrointestinal symptoms, while the most frequent reason cited was “patient’s decision” (approximately 40% of dabigatran discontinuations).  

**DISCUSSION**

The eight trials reviewed outline the exciting potential for dabigatran use in three separate indications. Four examined the use of this novel anticoagulant for short-term anticoagulation following joint replacement surgery. The other four appraised dabigatran for indications requiring long-term treatment (six months to lifetime), although only two of these actually continued therapy beyond three months. While further studies are needed to flesh out the efficacy of dabigatran in each specific population, looking at these early studies together, offers a broad estimate of this new drug’s safety and therapeutic value.

**Dabigatran in Orthopedic Surgery**
A total of four RCT trials have compared dabigatran to enoxaparin for VTE prophylaxis following total joint replacement. Two of these trials found the agents to have equal efficacy (RE-MODEL and RE-NOVATE). One trial found dabigatran to demonstrate a superior efficacy (BISTRO II), but it was given in higher doses than other trials. The fourth study, RE-MOBILIZE, found enoxaparin to have superior efficacy, but it was given as delayed, higher-intensity therapy. In terms of bleeding events, rates were generally comparable, with the exception of the BISTRO II study, where major bleeding rates reached 3.8% to 4.7% with higher dabigatran doses (the authors still did not deem this statistically significant compared to enoxaparin therapy). All four studies were designed quite similarly, and share nearly identical strengths and limitations. Thus, the discrepancy among these conclusions is best explained by variations in the administration of both drugs, combined with possible differences in patient population and hospital practice.

**Patient population.** All four studies benefited from a large patient population, and test groups that were fairly well-balanced in characteristics such as age, weight and gender. The average age ranged from 64 to 68 years, with standard deviations near nine years. All trials enrolled more female subjects, with a range from 56% to 69% of participants. Average weight was 78-83 kg among the European groups, and 88 kg in the North American study. Surgical duration and anesthesia type appear balanced within each trial, however, it is interesting to note that North American patients (the population of the RE-MOBILIZE trial) underwent general anesthesia at approximately twice the rate of patients in the other studies (53% versus 24%), while neuraxial anesthesia was used in only 46.5% of cases, versus 73-78% in the European trials. The
resulting disparity among medication use, recovery times and risk of hematoma formation could contribute the discrepancy in event rates between the RE-MOBILIZE trial and the other three, both for thrombotic and hemorrhagic events.

Unfortunately, aside from basic demographics, there is little information given about the baseline health of the patients involved in these short-term trials. The RE-MOBILIZE\textsuperscript{37} and RE-NOVATE\textsuperscript{36} authors estimate an average creatinine clearance of 83 and 89 mL/min respectively, but baseline renal function is not given in the BISTRO II\textsuperscript{34} and RE-MODEL\textsuperscript{35} trials. Two to three percent of RE-NOVATE patients had a history of DVT or PE,\textsuperscript{36} but this very relevant risk factor is not specified in other trials. In the initial selection of participants, all four studies employed similar exclusion criteria, which does provide the groups with some homogeneity. Excluded from all four studies were patients with: bleeding diatheses, acute intracranial disease, active malignancy, major surgery, trauma, myocardial infarction, uncontrolled hypertension or gastrointestinal bleeding in the last three to six months, known liver disease or significant renal insufficiency.\textsuperscript{34-37} However, among the medical conditions which were acceptable, including but not limited to: heart failure, lung disease, musculoskeletal disease and tobacco dependence, there is no way of discerning the distribution within the trial groups. Similarly, all studies allowed low-dose aspirin and COX-2 inhibitors,\textsuperscript{34-37} and one study also allowed the use of short-acting non-steroidal anti-inflammatory (NSAID) drugs\textsuperscript{34}, all three of which have known cardiovascular interactions, but there is no information regarding the prevalence and allotment among participants. Overall, these studies drew from a fairly healthy population, as naturally occurs when recruiting patients undergoing elective surgery.\textsuperscript{31} This lack of diversity at baseline must be addressed in studies with broader inclusion
criteria and better accounting of medical comorbidities before dabigatran is utilized in the general hospital population.

**Statistical analysis.** All four studies suffer from a loss of efficacy data due to incomplete or inconclusive venography.\(^{34-37}\) Among treated patients, 21% to 29.5% were excluded from primary outcome analysis for this reason. This is apparently a widespread problem with venography interpretation, as all authors had taken a predicted 25% loss of data into account when sizing their studies. Because of this planning, all data still retained 90-95% power, as each study had intended.\(^{34-37}\) Nonetheless, the resulting analyses cannot truly be labeled as intention-to-treat, and it is possible that some bias is introduced.

**Frequency and perioperative timing of administration.** Overall, there is a remarkable difference in both primary event rates and bleeding rates between the TKR patients in the RE-MOBILIZE trial\(^ {37}\) and the TKR patients in the European trials.\(^ {34,35}\) Among the latter trials, VTE occurred in 37.7% to 44.6% of patients taking enoxaparin, and in 23.7% to 40.5% of patients taking various doses of dabigatran.\(^ {34,35}\) Under the RE-MOBILIZE protocol, a composite outcome of VTE or death occurred in only 25.3% of patients on enoxaparin, and in 31.1% to 33.7% of patients taking dabigatran.\(^ {37}\) Thus, the RE-MOBILIZE data demonstrate a slight decrease in events in the dabigatran arm, and a considerable decrease in events in the enoxaparin arm. Looking at bleeding rates, the RE-MOBILIZE patients also fared better: major bleeding occurred in 0.6% of dabigatran patients,\(^ {37}\) compared to 1.5% on the same dose in the RE-MODEL study.\(^ {35}\) In addition to the anesthesia differences described earlier, the differences in medication dose, frequency and treatment length between these trials may underlie the disparity in outcomes.
The BISTRO II trial employed 12-hour dosing of dabigatran and 24-hour dosing of enoxaparin, and concluded that dabigatran had a superior efficacy with a similar to slightly higher bleeding risk. The RE-MODEL and RE-NOVATE trials compared 24-hour dosing of dabigatran to 24-hour dosing of enoxaparin, and found both the efficacy and the bleeding outcomes to be similar. The RE-MOBILIZE trial compared 24-hour dosing of dabigatran to 12-hour dosing of enoxaparin, and found enoxaparin to have better efficacy with similar bleeding outcomes. This information, in addition to the pharmacokinetic studies described earlier, suggests that dabigatran may be more effective when administered twice daily. Likewise, enoxaparin may also be more effective when given every 12 hours, as described in the North American protocol.

An additional confounding factor is the varied time frames surrounding the first dose of each drug, both within and among the four trials. For dabigatran therapy, the European trials administered the first dose 1-4 hours post-operatively (average 2.6-3.6 hours). A post hoc analysis performed by the BISTRO II authors showed that VTE occurrence was significantly lower when this dose was given within two hours following surgery (14.1% versus 22.4%, \(P=.0005\)). On the other hand, patients in RE-MOBILIZE received a first dose of dabigatran 6-12 hours post-operatively (average 9.6 hours), which may have decreased its efficacy. The authors of RE-MOBILIZE minimize this potential for difference based on dabigatran’s pharmacokinetic profile, but the true effect is unclear.

Enoxaparin administration also varied between protocols. Among the BISTRO II, RE-MODEL and RE-NOVATE studies, sites were instructed to begin enoxaparin injections the evening prior to surgery, as is common among European guidelines.
However, differences in regional practice led to an array of administration schedules, with an average initiation at 14 hours prior to surgery in one trial. In the RE-MOBILIZE study, run by North American investigators, the first dose of enoxaparin was always given post-operatively, with an average initiation time of 20 hours following surgery. The subject of pre- versus post-operative use LMWH has been controversial, with varied theories and evidence concerning the ideal balance between efficacy and bleeding safety. However, a 2002 meta-analysis concluded that there was no significant change in VTE or bleeding rate among patients given LMWH 12 hours pre-operatively or 12-24 hours post-operatively and the ACCP guidelines are neutral on the subject. Thus, it is uncertain if the initial timing of enoxaparin administration represents a substantial confounding factor.

Further complicating the picture with regard to medication administration is the length of prophylactic therapy; patients in the RE-MOBILIZE study received anticoagulation therapy for an average of 14 days, compared to 7-8 days in BISTRO II and RE-MODEL. Current ACCP Guidelines recommend thromboprophylaxis following TKR last a minimum of ten days, so a trial comparing any new anticoagulant to conventional methods would ideally employ this evidence-based standard. However, when estimating the therapeutic benefit of dabigatran, it is also important to consider how anticoagulation is actually carried out by prescribers and patients. While RE-MOBILIZE’s intensive, extended therapy meets the current evidence-based guidelines, it is far from commonplace in practice, as evidenced by recent analyses. As the authors of RE-NOVATE point out, the average hospital stay is becoming increasingly shorter, and many patients do not continue anticoagulation after discharge, so very few patients even
reach ten days of therapy.\textsuperscript{7,10,36} If the option of a fixed-dose, oral anticoagulant existed, the chances of achieving post-discharge prophylaxis would undoubtedly increase in general practice, and this should be factored into the predictions of dabigatran’s overall efficacy.

Thus, while the four orthopedic surgery trials give conflicting analyses, there are clearly multiple areas of disparity, both in methods and overall results. This set of studies raises important questions regarding the ideal administration of anticoagulation therapy, and further exploration into the dosing of both enoxaparin and dabigatran is warranted. A broad conclusion cannot be drawn placing one set of data above another, but local practice should be taken into consideration when estimating the efficacy of a new therapy.

**Dabigatran in Acute Venous Thromboembolism**

The fifth study discussed, RE-COVER, compared once-daily dosing of dabigatran to warfarin therapy, and demonstrated dabigatran to have equivalent efficacy and lower total bleeding rates.\textsuperscript{32} This was based on data from a large, blinded study population. The average patient in this study\textsuperscript{32} was roughly ten years younger than in the joint replacement studies,\textsuperscript{34-37} but new health variables are introduced such as active cancer status.\textsuperscript{32} The baseline characteristics of participants are better delineated than in the orthopedic trials, and each appears balanced between the two groups. Unfortunately, exclusion criteria are vague in some areas, namely in precluding subjects with “recent unstable cardiovascular disease,” a broad characterization which includes a large number of patients potentially requiring anticoagulation therapy.\textsuperscript{32}
In terms of analysis, the trial is quite thorough, with 99% of the randomized patients included in the final outcomes assessment. The authors note that their figures represent a modified intention-to-treat approach, as they excluded a group of 25 patients who never received a dose of either drug following randomization. From that point forward however, all patients were analyzed in their appropriate groups, with the endpoints being either completion of six months therapy or 6 days from the final dose of a discontinued drug.

One limitation of the study, in comparison to the orthopedic trials, is a low overall rate of measurable events, although the study was still sized for statistical significance. This is a product of both the lower risk of VTE outside of the surgical setting and the study’s method of screening only symptomatic patients. At the point of efficacy analysis, there may have been asymptomatic thromboses, placing the patient at risk for adverse outcomes in the future. Repeating the vascular imaging in every patient on completion of therapy in the RE-COVER study would have allowed a more complete picture of therapeutic effect.

As in the orthopedic trials, it should be noted that a drug’s efficacy may differ between a clinical study and real-life practice, particularly for warfarin, as it requires such close monitoring and frequent follow-up. However, even with the structured regimen of the RE-COVER trial, INRs were only within range 60% of the time. This is consistent with a 2008 community-based cohort study, which found that the average time warfarin users spent within therapeutic INR range was 66.5%. Thus, for the typical warfarin user, the data from RE-COVER are quite applicable. However, one-third of patients in this community analysis were within range less than 60% of the time.
these patients with poor control on warfarin therapy, dabigatran would offer a greater reduction in both thrombotic and hemorrhagic events than indicated by these results.

**Dabigatran in Atrial Fibrillation**

Among the three studies investigating dabigatran’s value for stroke prevention in atrial fibrillation, only one offers statistical evidence of efficacy. The other two, because of their small size and short duration of therapy, cannot provide meaningful data for embolic events. However, all three trials offer varied degrees of insight regarding the safety and tolerability of dabigatran.

**Patient population.** All patients in these studies had documented non-valvular atrial fibrillation, plus one or more separate risk factor for stroke. This criteria parallels the definition of patients for whom VKA therapy is recommended, per evidence-based guidelines. The average patient in the PETRO and RE-LY studies was 70 and 71 years old, respectively, while the Yamaguchi trial did not report any baseline characteristics. Among the former trials, hypertension was seen in the majority of patients (67%-74% in PETRO and 79% in RE-LY). In both, diabetes mellitus was present in about one-fourth of participants and heart failure in one-third. Patients in the PETRO study had a median of three risk factors for stroke, while the RE-LY study reported a mean CHADS2 score of 2.1. When compared to the baseline characteristics provided by the orthopedic and acute VTE trials, both PETRO and RE-LY appear to utilize an older population with more cardiac risk factors. This is fitting.

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* CHADS2 score reflects a composite risk of stroke, based on factors of congestive heart failure, hypertension, age ≥ 75 years, and diabetes mellitus (all one point) and history of prior stroke or TIA (two points)
considering the therapeutic group it aims to address, and it is something that should be considered when viewing the disparity in adverse cardiac events.

**Yamaguchi trial.** Due to a combination of size and design limitation, this study offers the least reliable data concerning dabigatran. Drug administration was open-label, with no specified protocol to avoid bias in the process of reporting and evaluating endpoints. No information was given describing the randomization process or the baseline characteristics between groups, leaving out critical details such as history of prior stroke or exposure to warfarin. The short duration of therapy, small population size and low frequency of primary outcomes provide little insight into the efficacy of long-term treatment with dabigatran. However, the study does provide limited evidence that dabigatran appears safe in the Japanese population (patients of Asian descent have compromised only a small portion of dabigatran studies to date) with a bleeding profile similar to adjusted-dose warfarin.

**PETRO.** Like the Yamaguchi trial, PETRO suffers from a small size, short duration and several design flaws. With a few exceptions, no events in the PETRO study occurred with enough frequency to establish statistical import. Moreover, the stratification into so many dose groups with the additional variable of aspirin use makes these trends even harder to interpret. The safety of aspirin is certainly an important question for the population of patients with atrial fibrillation, but would have been better addressed in a later stage trial, when the optimum doses of dabigatran had been established. When interpreting the PETRO results, it should be noted that patients were taking anywhere from one-third to two times the total daily dabigatran dose that was used in later trials of long term use (50 – 600 mg daily in PETRO versus 150 - 300 mg daily
Another confounding factor was the use of warfarin prior to the trial period; all randomized patients had been on warfarin therapy for eight weeks or longer at the start of therapy, and had already achieved a therapeutic INR. This creates what has been termed a “survivor bias,” as only patients with a longer-established atrial fibrillation, who tolerated warfarin therapy in the past are included.

Given these factors of size and bias, the PETRO study does not provide reliable data concerning the efficacy of dabigatran for stroke prevention and offers only minimal insight regarding the safety and bleeding profile. From this trial, 361 dabigatran patients were rolled over into a long-term extension trial (PETRO-Ex) with an average of 29 months follow-up. However, as this study was neither randomized nor controlled, it could not be included for review.

RE-LY. With its large population, extended therapeutic exposure, and well-organized structure, the results of RE-LY offer the best evidence thus far concerning the efficacy and safety of dabigatran as an anticoagulant. Among the 18 113 participants, half were warfarin naïve- thus eliminating the potential of survivor bias. At baseline, groups were balanced and well-described in terms of age, gender, comorbidities and medication use. Follow-up was complete in 99.9% of patients and intention-to-treat analysis was used. One potential weakness in the RE-LY design is the non-blinded administration of the control drug, warfarin. However, the susceptibility to bias seems small since the primary outcomes of interest were measured clinical events, all of which were adjudicated by blinded panels. Nonetheless, bias could have factored into the more subjective phenomenon of ADRs for this new drug. Additionally, a reporting bias among patients or staff could have influenced the outcome measurements. Towards this end, the
authors argue that the balance of adverse outcomes reported in the study for both drugs (bleeding, myocardial infarction and discontinuation) diminishes the likelihood of a bias in either direction.\textsuperscript{33} When looking at bleeding rates in the RE-LY data\textsuperscript{33}, it should be noted that the category of “minor bleeding” in this trial encompasses a range of events that were differentiated as “clinically significant” and “minor” or “nuisance bleeding” in other trials.\textsuperscript{28,32,34-37} However, the criteria for major bleeding were the same as in other non-surgical trials.\textsuperscript{28,32} Overall, the RE-LY\textsuperscript{33} study provides valuable evidence for the therapeutic value of dabigatran in patients with atrial fibrillation. It is the largest and most comprehensive of all eight trials reviewed. However, given the monumental change it suggests in moving away from a 60 year old therapy, additional trials are needed to verify RE-LY’s results.

**Safety and Adverse Drug Reactions**

Valuable safety and tolerability information can be gleaned, to varying extents, from all the included trials. With six studies examining dabigatran therapy for up to 12 weeks, trials thus far have demonstrated the short-term safety of this drug in a fairly diverse population. Unfortunately, only two studies have investigated longer-term therapy, and safety in this setting remains a concern.

**Hepatotoxicity.** Liver damage was a major concern for direct thrombin inhibitors, following on the heels of ximelagatran’s FDA rejection. However, every study reviewed here demonstrates no hepatotoxicity attributable to dabigatran.\textsuperscript{28,32,33-37,40}

**Tolerability.** Several studies demonstrated a higher discontinuation rate among patients assigned to dabigatran.\textsuperscript{32,33,36,37} Part of this can be attributed to the survivor bias among patients with prior exposure to warfarin or enoxaparin, however, part of the
discontinuation was certainly related to gastrointestinal upset, which was a well-demonstrated side effect in many trials.28,32,33,36

**Bleeding.** Among the trials comparing dabigatran to enoxaparin, the rates of total bleeding were equivalent.34-37 On the other hand, in trials with warfarin as control therapy, dabigatran appeared to have a superior bleeding profile,32,33,40 with the exception of PETRO patients taking high dose dabigatran and concomitant aspirin.28 The increased risk of gastrointestinal bleeding with long-term dabigatran therapy, as demonstrated in both the RE-COVER and RE-LY studies,32,33 is certainly concerning. However, dabigatran also demonstrated one-third the rate intracranial bleeding seen in warfarin users,33 which should also be factored into any risk-benefit analysis.

**Acute Coronary Events.** Myocardial infarction (MI) is an obvious concern among patients at thromboembolic risk. Thus, the findings of increased MI occurrence among dabigatran users in the RE-LY study33 demands further investigation. Among the other seven trials, each reported occurrences of acute coronary syndrome, and no apparent trend emerged. However, RE-LY patients had a much longer exposure to dabigatran than any other study. One theory proposed by the authors is that warfarin has a proven cardioprotective effect which dabigatran may lack.33 Slightly increased rates of non-fatal MI were also noted among ximelagatran users, in pooled data from trials investigating its use with knee replacement.47 On the other hand, ximelagatran was specifically investigated as a potential cardioprotective post-MI therapy in combination with aspirin, and was found to have a beneficial cardiac effect in this trial.27,47 When considering the bigger picture of risks and benefits, it should be noted that even with the higher rate of MI in the RE-LY trial, dabigatran patients still had an overall rate of death
from vascular causes that was equal to warfarin patients in the 110 mg dose group and lower than warfarin patients in the 150 mg dose group. Clearly, further studies and sub-group analyses are needed to parcel out the factors underlying this adverse event.

**Limitations of Study**

The trials reviewed encompass a wide variety of health care settings and a spectrum of anticoagulation intensity. This was done in order to gather the most data available regarding dabigatran’s general safety, while considering several potential indications for its use. While there are physiologic similarities to thrombus formation in all settings, as described earlier, the baseline characteristics of these patients vary greatly, and one study result cannot be simply generalized for dabigatran use in another setting.

Furthermore, as a new pharmaceutical product, current studies of dabigatran are limited by a lack of experience and exposure. Three of the included trials were designed more for the purposes of dose-finding than efficacy analysis, and therefore lack the appropriate size or length of exposure to establish a true therapeutic comparison to warfarin use. Additionally, a limited number of investigators have conducted these trials, all of which were financially supported by the drug manufacturer Boehringer Ingelheim. Several of the primary investigators in every published study disclose a financial relationship to this company, either as an employee or a consultant. Although the variety of both beneficial and adverse outcomes disclosed in these clinical trials suggests a certain degree of fairness in reporting, this potential bias cannot be completely ignored.

Publication bias was minimized by reviewing the NIH clinical trials registry and the Boehringer Ingelheim clinical trial records for unpublished studies. However, the
information posted on such sites is not as complete or well-reviewed as published articles, and thus the one study this yielded\textsuperscript{40} is not as reliable. In addition, there was a fourth Phase III trial listed as completed on the NIH website, but no records were available on the pharmaceutical website (National Clinical Trial ID 00657150). Whether the results of this trial would contradict the efficacy suggested by other trials cannot be known.

**Future Research and Development**

For dabigatran’s application to surgical patients, further studies are needed comparing dabigatran to varying intensities of enoxaparin therapy as well to fondaparinux, a parenteral anticoagulant with emerging value over enoxaparin.\textsuperscript{20} Such evidence would help streamline the confusing array of local perioperative protocols, and would more clearly establish where dabigatran may fit into this spectrum of guidelines. Even if higher intensity parenteral therapy proves more efficacious, dabigatran could still improve post-operative outcomes by offering a fixed-dose, oral medication for outpatient use. This would allow patients to easily continue anticoagulation therapy for a month after orthopedic surgery, and thus achieve the fullest possible VTE prophylaxis.

When considering acute VTE, dabigatran stands as a potential therapy for both immediate therapy and secondary prophylaxis. One study has already demonstrated efficacy in the former context, when combined with an initial period of parenteral anticoagulation.\textsuperscript{33} A long-term study examining secondary prevention of VTE, REMEDY, has been underway since 2008,\textsuperscript{20} and will offer valuable data regarding both the efficacy of dabigatran in this setting, and its safety for long-term use.
One exciting potential that was not addressed by any study is the use of dabigatran as monotherapy for acute VTE. Based on its known mechanism of direct thrombin inhibition, it is postulated that dabigatran may be able to inhibit fibrin production by both free and clot-bound thrombin, a characteristic that distinguishes it from members of heparin family. This increased anticoagulation activity, combined with a short time to therapeutic onset, could eliminate the need for initial parenteral anticoagulation, which is a routine addition to warfarin therapy that adds to inpatient time, cost and inconvenience.

Stroke prevention in atrial fibrillation is perhaps the most promising venue for this new drug, as these patients usually require indefinite anticoagulation, and have no alternative to warfarin for oral therapy. However, only one statistically robust study currently supports dabigatran use in this setting. Further studies are indicated to better understand the safety of this drug in long-term use, exploring how it interacts with various cardiovascular risk factors and concomitant medications.

One factor not addressed by these studies, but important to every patient and clinician, is cost of therapy. Wolowacz et al performed a cost-effectiveness analysis comparing dabigatran and enoxaparin, based on the data from Phase III trials in knee replacement patients, and concluded that dabigatran was cost-saving, primarily through lower administration costs. However, the price difference between dabigatran and warfarin is much greater; one author estimated a month of dabigatran to cost ten times what warfarin therapy would, including monitoring. Dabigatran will likely not be an option for all patients initially because of these monetary issues, nonetheless, if oral thrombin inhibitors promote better compliance with anticoagulation guidelines, both by
patients and providers, they have the potential to greatly reduce thromboembolic morbidity and mortality, and thus lower healthcare costs over time.

CONCLUSION

Decisions surrounding anticoagulation are difficult for patients and clinicians alike. Overall compliance with evidence-based guidelines is poor, in both hospital and community settings. 6-10 This is likely due to the risks and inconveniences associated with conventional therapy. As the first new oral anticoagulant in over 50 years, dabigatran etexilate stands to provide substantial improvements in both the ease and safety of outpatient anticoagulation. Further data regarding the cardiovascular safety of dabigatran will likely emerge in the next few years, and it may not prove to be the optimal therapy for all patients. However, millions of patients at thromboembolic risk stand to benefit from this long awaited alternative to warfarin, and every clinician should be tuned into its progress as the Phase III trials come to an end.
REFERENCES


34. Eriksson BI, Dahl OE, Buller HR, et al. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic


40. Yamaguchi T, MD. Open label, randomised exploratory dose response study in pharmacodynamics and safety of BIBR 1048 (110 mg b.i.d. and 150 mg b.i.d. for 12
weeks in patients with non-valvular atrial fibrillation in comparison to warfarin.


<table>
<thead>
<tr>
<th>STUDY/ AUTHOR YEAR PUBLISHED</th>
<th>STUDY TYPE/ LOCATION</th>
<th>PATIENT NO./ POPULATION</th>
<th>INTERVENTION</th>
<th>COMPARISON</th>
<th>OUTCOMES</th>
<th>VALIDITY SCORE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BISTRO II&lt;sup&gt;34&lt;/sup&gt;/ Eriksson et al/ 2005</td>
<td>Double-blinded RCT/ multi-center dose-finding study in Europe and South Africa</td>
<td>1949/ Pts undergoing total hip or knee replacement</td>
<td>Dabigatran 50, 150 or 225 mg bid, or 300 mg qd, starting 1-4 hours post-op, continuing 6-10 days</td>
<td>Enoxaparin 40 mg daily, starting night before surgery and continuing for 6-10 days</td>
<td>VTE, bleeding events, adverse events, pharmacokinetic parameters</td>
<td>6/7</td>
<td>Loss of 24%-25% of treated patients in efficacy analysis</td>
</tr>
<tr>
<td>RE-MODEL&lt;sup&gt;35&lt;/sup&gt;/ Eriksson et al/ 2007</td>
<td>Double-blinded RCT/ multi-center in Europe, Australia and South Africa</td>
<td>2076/ Pts undergoing total knee replacement</td>
<td>Dabigatran 150 or 220 mg qd, starting with ½ dose 1-4 hours post-op, continuing 6-10 days</td>
<td>Enoxaparin 40 mg qd starting evening prior to surgery, continuing 6-10 days</td>
<td>VTE + all-cause mortality, bleeding events, liver function, adverse events</td>
<td>6/7</td>
<td>Loss of 25%-26% of treated patients in efficacy analysis</td>
</tr>
<tr>
<td>RE-NOVATE&lt;sup&gt;36&lt;/sup&gt;/ Eriksson et al/ 2007</td>
<td>Double-blinded RCT/ multi-center in Europe, Australia and South Africa</td>
<td>3463/ Pts undergoing total hip replacement</td>
<td>Dabigatran 150 or 220 mg qd, starting with ½ dose 1-4 hours post-op, cont. 28-35 days</td>
<td>Enoxaparin 40 mg qd starting evening before surgery, continuing 28-35 days</td>
<td>VTE + all-cause mortality, bleeding events, liver function, adverse events</td>
<td>6/7</td>
<td>Loss of 22-25% of treated patients in efficacy analysis</td>
</tr>
<tr>
<td>RE-MOBILIZE&lt;sup&gt;37&lt;/sup&gt;/ Ginsberg et al/ 2009</td>
<td>Double-blinded RCT/ multi-center in North America</td>
<td>2596/ Pts undergoing total knee replacement</td>
<td>Dabigatran 150 or 220 mg qd, starting with ½ dose 6-12 hours post-op, cont. 12-15 days</td>
<td>Enoxaparin 30 mg bid, starting 12-24 hours post-op, cont. 12-15 days</td>
<td>VTE + all-cause mortality, bleeding events, liver function, adverse events</td>
<td>6/7</td>
<td>Loss of 26%-30% of treated patients in efficacy analysis</td>
</tr>
<tr>
<td>RE-COVER&lt;sup&gt;32&lt;/sup&gt;/ Schulman et al/ 2009</td>
<td>Double-blinded RCT, multi-center, 29 countries</td>
<td>2539/ Pts with acute, symptomatic VTE</td>
<td>Dabigatran 150 mg bid for 6 months, following initial parenteral anticoagulation</td>
<td>Warfarin adjusted towards an INR of 2.0-3.0 for 6 months, following initial parenteral anticoagulation</td>
<td>Time to symptomatic VTE or death, bleeding events, liver function, adverse events</td>
<td>7/7</td>
<td>All patients had a mean of 10 days initial parenteral anticoagulation with UFH, LMWH or fondaparinux</td>
</tr>
</tbody>
</table>
**Table 1 (continued). Characteristics of Included Studies**

<table>
<thead>
<tr>
<th>STUDY/AUTHOR/YEAR PUBLISHED</th>
<th>STUDY TYPE/LOCATION</th>
<th>PATIENT NO.¶/POPULATION</th>
<th>INTERVENTION</th>
<th>COMPARISON</th>
<th>OUTCOMES</th>
<th>VALIDITY SCORE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PETRO²⁸/ Ezekowitz et al/ 2007</td>
<td>Partially blinded RCT, multi-center, dose-finding study in Europe and United States</td>
<td>502/ Pts with AF and 1 or more additional stroke risk factor</td>
<td>Dabigatran 50, 150 or 300 mg bid plus 0, 81 or 325 mg aspirin for 12 weeks</td>
<td>Warfarin alone, adjusted towards INR of 2.0-3.0 for 12 weeks</td>
<td>Cardiovascular or peripheral embolic events, bleeding events, adverse events, laboratory changes</td>
<td>4/7</td>
<td>Small size; incomplete blinding; unclear method of adjudication for non-bleeding events</td>
</tr>
<tr>
<td>Yamaguchi⁴⁰/ 2007 (unpublished)</td>
<td>Open-label RCT, multi-center, dose-finding study in Japan</td>
<td>166/Pts with AF and 1 or more additional stroke risk factor</td>
<td>Dabigatran 110 or 150 mg bid for 12 weeks</td>
<td>Warfarin adjusted towards an INR of 2.0-3.0 (1.6-2.6 in patients aged 70+) for 12 weeks</td>
<td>Stroke, TIA, systemic embolism, MI, adverse events, bleeding events, laboratory changes</td>
<td>3/7</td>
<td>Small size; randomization or baseline characteristics not described; open-label therapy; unclear method of adjudication</td>
</tr>
<tr>
<td>RE-LY²³/ Connolly et al/ 2009</td>
<td>Partially blinded RCT, multi-center, 44 countries</td>
<td>18 113/ Pts with AF and 1 or more additional stroke risk factor</td>
<td>Dabigatran 110 or 150 mg bid, continuing for a median of 2.0 years</td>
<td>Warfarin adjusted towards an INR of 2.0-3.0, continuing for a median of 2.0 years.</td>
<td>Stroke or systemic embolic event, bleeding events, all-cause mortality, hospitalization, myocardial infarction, liver function, adverse events</td>
<td>6/7</td>
<td>Incomplete blinding</td>
</tr>
</tbody>
</table>

AF=atrial fibrillation; bid=twice daily; qd=once daily
¶ Indicates the number of patients receiving one or more dose of study drug
Table 2. Components of Modified-JADAD Scoring

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>POINTS AWARDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study size &gt; 1000 patients?</td>
<td>Yes............1 No/cannot tell......0</td>
</tr>
<tr>
<td>Was the study described as random?</td>
<td>Yes............1 No/cannot tell......0</td>
</tr>
<tr>
<td>Was the randomization scheme described and appropriate?</td>
<td>Yes............1 No/cannot tell......0</td>
</tr>
<tr>
<td>Was the study described as double-blind?</td>
<td>Yes............1 No/cannot tell......0</td>
</tr>
<tr>
<td>Were all the outcome evaluators blinded to treatment group?</td>
<td>Yes............1 No/cannot tell......0</td>
</tr>
<tr>
<td>Was there a description of dropouts and withdrawals?</td>
<td>Yes............1 No/cannot tell......0</td>
</tr>
<tr>
<td>Was intention-to-treat analysis used?</td>
<td>Yes............1 No/cannot tell......0</td>
</tr>
</tbody>
</table>

Table 3. Perioperative Bleeding Event Definitions$^{34,39}$

<table>
<thead>
<tr>
<th>MAJOR BLEEDING</th>
<th>CLINICALLY SIGNIFICANT BLEEDING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroperitoneal bleeding</td>
<td>Gingival bleeding or epistaxis &gt; 5 minutes duration</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>Spontaneous rectal bleeding</td>
</tr>
<tr>
<td>Intraocular bleeding</td>
<td>Spontaneous gross hematuria</td>
</tr>
<tr>
<td>Intraspinal bleeding</td>
<td>Intervention-related hematuria lasting &gt;24 hours</td>
</tr>
<tr>
<td>Clinically overt bleeding leading to:</td>
<td>Spontaneous skin hematoma ≥ 25 cm$^2$</td>
</tr>
<tr>
<td>≥ 20 g L$^{-1}$ decrease in hemoglobin level</td>
<td>Wound hematoma ≥ 100 cm$^2$</td>
</tr>
<tr>
<td>Transfusion of ≥ 2 units of blood product</td>
<td>Other bleeding deemed significant by the investigators</td>
</tr>
<tr>
<td>Treatment cessation</td>
<td></td>
</tr>
<tr>
<td>Re-operation</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>

Criteria used in orthopedic surgery trials$^{34,37}$
All bleeding events not meeting one of the above qualifications were described as minor bleeding
<table>
<thead>
<tr>
<th>STUDY/SETTING</th>
<th>DABIGATRAN OUTCOMES</th>
<th>WARFARIN OUTCOMES</th>
<th>ADVERSE EVENTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BISTRO II</strong>&lt;sup&gt;34&lt;/sup&gt;/ VTE prophylaxis following TKR or THR</td>
<td></td>
<td></td>
<td></td>
<td>~Therapy length 6-10 days ~Enoxaparin started pre-operatively in most patients, while dabigatran was started post-operatively</td>
</tr>
<tr>
<td></td>
<td>VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 mg bid</td>
<td>28.5 (23.5-33.9)</td>
<td></td>
<td>24 serious adverse events deemed attributable to medication. Definitions and distribution not provided</td>
</tr>
<tr>
<td></td>
<td>150 mg bid</td>
<td>17.4 (13.1-22.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>300 mg qd</td>
<td>16.6 (12.5-21.5)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>225 mg bid</td>
<td>13.1 (9.5-17.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 mg bid</td>
<td>0.3 (0.0-1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>150 mg bid</td>
<td>4.1 (2.4-6.6)</td>
<td></td>
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<tr>
<td></td>
<td>300 mg qd</td>
<td>4.7 (2.8-7.3)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>225 mg bid</td>
<td>3.8 (2.2-6.2)</td>
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<tr>
<td></td>
<td>VTE</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>50 mg bid</td>
<td>28.5 (23.5-33.9)</td>
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<tr>
<td></td>
<td>150 mg bid</td>
<td>17.4 (13.1-22.3)</td>
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<tr>
<td></td>
<td>300 mg qd</td>
<td>16.6 (12.5-21.5)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>225 mg bid</td>
<td>13.1 (9.5-17.5)</td>
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<tr>
<td></td>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 mg bid</td>
<td>0.3 (0.0-1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>150 mg bid</td>
<td>4.1 (2.4-6.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>300 mg qd</td>
<td>4.7 (2.8-7.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>225 mg bid</td>
<td>3.8 (2.2-6.2)</td>
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</tr>
<tr>
<td><strong>RE-MODEL</strong>&lt;sup&gt;35&lt;/sup&gt;/ VTE prophylaxis following TKR</td>
<td>VTE + all-cause mortality</td>
<td>VTE + all-cause mortality</td>
<td>Discontinuation</td>
<td>~Therapy length 6-10 days ~Enoxaparin started pre-operatively in most patients, while dabigatran was started post-operatively</td>
</tr>
<tr>
<td></td>
<td>150 mg qd</td>
<td>40.5 (36.3-44.7)</td>
<td>40 mg qd</td>
<td>37.7 (33.5-41.9)</td>
</tr>
<tr>
<td></td>
<td>220 mg qd</td>
<td>36.4 (32.2-40.6)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td></td>
<td>Major bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>150 mg qd</td>
<td>1.3 (0.6-2.4)</td>
<td>40 mg qd</td>
<td>1.3 (0.6-2.4)</td>
</tr>
<tr>
<td></td>
<td>220 mg qd</td>
<td>1.5 (0.7-2.7)</td>
<td></td>
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</tr>
<tr>
<td><strong>RE-NOVATE</strong>&lt;sup&gt;36&lt;/sup&gt;/ VTE prophylaxis following THR</td>
<td>VTE + all-cause mortality</td>
<td>VTE + all-cause mortality</td>
<td>Serious adverse events</td>
<td>~Therapy length 28-35 days ~Enoxaparin started pre-operatively in most patients, while dabigatran was started post-operatively</td>
</tr>
<tr>
<td></td>
<td>150 mg qd</td>
<td>8.6 (6.7-10.4)</td>
<td>40 mg qd</td>
<td>6.7 (5.1-8.3)</td>
</tr>
<tr>
<td></td>
<td>220 mg qd</td>
<td>6.0 (4.5-7.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td></td>
<td>Major bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>150 mg qd</td>
<td>1.3 (0.7-2.1)</td>
<td>40 mg qd</td>
<td>1.6 (0.9-2.5)</td>
</tr>
<tr>
<td></td>
<td>220 mg qd</td>
<td>2.0 (1.3-3.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RE-MOBILIZE</strong>&lt;sup&gt;37&lt;/sup&gt;/ VTE prophylaxis following TKR</td>
<td>VTE + all-cause mortality</td>
<td>VTE + all-cause mortality</td>
<td>Serious adverse events</td>
<td>~Therapy length 12-15 days ~Enoxaparin or dabigatran started post-operatively in all patients ~Confidence intervals not given for clinical outcomes</td>
</tr>
<tr>
<td></td>
<td>150 mg qd</td>
<td>33.7</td>
<td>30 mg bid</td>
<td>25.3</td>
</tr>
<tr>
<td></td>
<td>220 mg qd</td>
<td>31.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td></td>
<td>Major bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>150 mg qd</td>
<td>0.6</td>
<td>30 mg bid</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>220 mg qd</td>
<td>0.6</td>
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Table 4. Summary of Outcomes
<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Treatment</th>
<th>Recurrent VTE or VTE-death</th>
<th>Recurrent VTE or VTE-death</th>
<th>Serious adverse event</th>
<th>Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Acute VTE therapy</td>
<td>150 mg bid, therapy</td>
<td>2.4%</td>
<td>Therapy + 30 days</td>
<td>2.7%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Major + clinically relevant bleeding</td>
<td>5.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150 mg bid</td>
<td>8.8%; HR 0.63 (0.47-0.84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Major + clinically relevant bleeding</td>
<td>2.4%; HR 1.10 (0.65-1.84)</td>
</tr>
<tr>
<td>PETRO&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Stroke prevention in atrial fibrillation</td>
<td>Thromboembolic events</td>
<td>0 of 70 (0%)</td>
<td>Thromboembolic events</td>
<td>0 of 70 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg bid</td>
<td>2 of 107 (1.9%)</td>
<td>Discontinuation</td>
<td>Dabigatran 150 mg bid 5.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg bid</td>
<td>0 of 169</td>
<td>Dabigatran 300 mg bid 8.9%</td>
<td>Warfarin 0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 mg bid</td>
<td>0 of 169</td>
<td>Acute coronary syndrome:</td>
<td>Dabigatran 50 mg 0.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Major + clinically relevant bleeding</td>
<td>Dabigatran 300 mg 0.6%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50 mg bid</td>
<td>4 of 107 (5.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150 mg bid</td>
<td>13 of 169 (7.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>300 mg bid</td>
<td>17 of 169 (10.1%)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Major + clinically relevant bleeding</td>
<td>5.6%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>110 mg bid</td>
<td>2 of 46 (4.3%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>150 mg bid</td>
<td>5 of 58 (8.6%)</td>
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<td></td>
<td></td>
<td>Major + clinically relevant bleeding</td>
<td>2.7%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>110 mg bid</td>
<td>2.71%/year</td>
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<td>150 mg bid</td>
<td>3.11%/year</td>
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<td>110 mg bid</td>
<td>3.36%/year; RR 0.80 (0.69-0.93)</td>
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<tr>
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<td></td>
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<td></td>
<td>150 mg bid</td>
<td>0.72%/year</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>3.11%/year</td>
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<td></td>
<td></td>
<td></td>
<td>0.93 (0.81-1.07)</td>
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</tbody>
</table>

~Dabigatran patients had significantly lower total bleeding rates, but higher rate of GI bleeding.

~Compared dabigatran ± ASA to warfarin alone. All major bleeding occurred in patients taking 300 mg dabigatran + ASA.

~All participants on adjusted-dose warfarin prior to starting study.

~Unpublished study with minimal analysis provided.