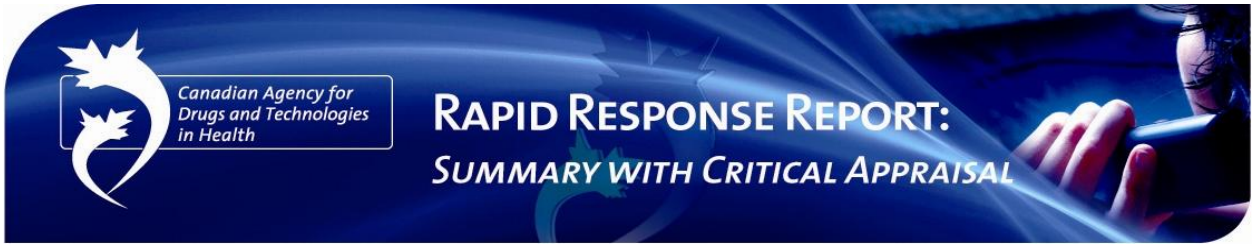

TITLE: Dabigatran for Stroke Prevention in Atrial Fibrillation: A Review of the Evidence on Safety

DATE: 06 March 2012

CONTEXT AND POLICY ISSUES

Atrial fibrillation (AF) is a type of cardiac dysrhythmia that is estimated to affect between 200,000 and 250,000 Canadians.[1] Stroke is an important cause of disability and death from AF, where approximately 15% of strokes are caused by AF.[2]

Since demonstrating its efficacy in stroke prevention in AF in the early 1990s, warfarin, a vitamin K antagonist (VKA), has been the drug of choice for this indication.[3] Evidence from several randomized controlled trials (RCTs) has shown that long-term anticoagulation therapy with warfarin reduces the risk for ischemic stroke by 68% in patients with nonvalvular AF (NVAF).[4]

More recently, a new class of oral anticoagulants, the direct thrombin inhibitors, has been developed. Dabigatran etexilate (Pradax) is the first of a new class of oral anticoagulants to reach the market.[5] With a more targeted mechanism of anticoagulation, dabigatran offers several potential clinical advantages over warfarin therapy, including obviating the need for routine monitoring; a faster onset and offset of action; no required dietary restrictions for patients; and few drug interactions.[6] Anticoagulation agents are associated with a risk of bleeding complications. Bleeding in patients treated with warfarin can be managed with the administration of vitamin K[7] but for the new anticoagulants there is no established specific antidote for reversal of the anticoagulation effect.[8] On October 26, 2010, Health Canada approved dabigatran for the prevention of stroke and systemic embolism in patients with AF.[9] On June 22, 2011, CADTH released the CEDAC recommendation on dabigatran for the prevention of stroke and systemic embolism in patients with AF (Table 1).[10]

Table 1: CEDAC recommendation[10]

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that dabigatran be listed for the prevention of stroke and systemic embolism in patients with atrial fibrillation meeting one of the following criteria: • Patients in whom warfarin is indicated but who fail to achieve adequate international normalized ratio (INR) control, despite monitored warfarin treatment, such as with: regular INR testing, dosage adjustment according to a validated nomogram, and patient

education. Patients who fail to achieve adequate INR control should be referred to an anticoagulation management service, if available.
or

- Patients who have a history of a serious hypersensitivity reaction to warfarin.

In order to inform upcoming listing decisions and considering that the new class of anticoagulants will be used on a long-term basis in some patients, Canadian publicly-funded drug plans require additional information on the adverse events associated with the use of thee drugs. The purpose of this supplemental report is to summarize information retrieved from the literature, regarding adverse events associated with dabigatran, the first of this drug class to be marketed in Canada.

RESEARCH QUESTION

What are the adverse events associated with the use of dabigatran?

KEY MESSAGE

Bleeding is typically the main safety issue of concern with all anticoagulants, including dabigatran. In RE-LY, the major randomized controlled trial (RCT) comparing dabigatran with warfarin, the risk of severe bleeding was reduced with the lower 110-mg dose of dabigatran compared with adjusted-dose warfarin, but there was no such reduction with the higher, 150-mg dose. However, there was evidence that in elderly patients there was no reduction in severe bleeding risk at either dose versus warfarin, and in the post-marketing period there was some evidence from case reports that elderly patients and/or those with severe renal impairment are at risk for serious bleeding events.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed In Process, Ovid MEDLINE, Ovid EMBASE, AdisOnline Reactions Weekly database, The Cochrane Library (2011, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies containing safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and May 20, 2011. The search was rerun on January 18, 2012 to capture any articles published since the original search date. The search of major health technology agencies was also updated to include documents published since May 2011.

Selection Criteria and Methods

Two reviewers were involved in screening titles and abstracts from the list of identified citations. Potentially relevant articles were retrieved and reviewed for final selection. Articles reporting on adverse events with dabigatran were selected for inclusion, according to the criteria listed in Table 2. A narrative approach was taken to summarize the relevant information.

Table 2: Selection Criteria

Population	Patients with atrial fibrillation requiring anticoagulant therapy for the prevention of stroke
Intervention	Dabigatran
Comparator	Warfarin or other vitamin K antagonists Non-comparative studies
Outcomes	Major or minor bleeding, transfusions, other adverse events
Study Designs	Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials, non-randomized trials, case series, case reports

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria or were duplicate publications of the same study.

SUMMARY OF EVIDENCE

Quantity of Research Available

There were a total of 10 relevant reports identified from the literature search results. One report came from a systematic review and network meta-analysis,[11] while the remaining nine[12-20] came from the RE-LY trial.

Of the nine reports from the RE-LY trial, one was the trial's original RCT publication,[12] one was an addendum of previously unreported events from the original RCT,[13] and the remaining seven[14-20] reports were post-hoc subgroup analyses.

Six published case reports were identified from the literature.[21-26] Regulatory updates were retrieved from the grey literature.[27-39] Post-marketing safety information was obtained from the Health Canada Vigilance Database.[40]

The information from the various reports is summarized below and details are provided in Appendices 1 to 3.

Summary of Findings

Systematic reviews and meta-analyses

Roskell et al.[11] performed a systematic review and network meta-analysis to examine the direct and indirect evidence for efficacy and safety of treatments (i.e., various anticoagulant and antiplatelet agents) used for stroke prevention in AF; dabigatran served as the intervention against which direct and indirect comparisons were made with alternate treatment options. The study design was limited to RCTs. For the outcomes of all-cause mortality, intracranial hemorrhage, and extracranial hemorrhage, 17, 11, and nine trials, respectively, of adjusted-dose VKA were included compared with only one trial of dabigatran for these same outcomes. Since the lone data providing direct evidence for dabigatran came from the RE-LY trial (covered

below), only results from the indirect comparisons analysis between dabigatran and adjusted-dose VKA were reviewed.(see Appendices 1 and 2)

For the indirect comparisons of dabigatran 110 mg versus adjusted-dose VKA, there was no difference in relative risk (RR) between treatments on the outcome of all-cause mortality [RR: 0.92; 95% confidence interval (CI): 0.79, 1.06]; a lower risk in favour of dabigatran for intracranial hemorrhage (RR: 0.33; 95% CI: 0.15, 0.72); and no difference between treatments for extracranial hemorrhage (RR: 0.96; 95% CI: 0.75, 1.22).

For the indirect comparisons of dabigatran 150 mg vs. adjusted-dose VKA, there was no difference between treatments on the outcome of all-cause mortality (RR: 0.89; 95% CI: 0.77, 1.03); no difference between treatments for intracranial hemorrhage (RR: 0.53; 95% CI: 0.27, 1.03); and no difference between treatments for extracranial hemorrhage (RR: 1.09; 95% CI: 0.86, 1.37). The absence of a statistically significant benefit from the 150- mg dose versus warfarin on intracranial hemorrhage from the indirect comparisons evidence is in contrast to the benefit observed from the direct evidence. This disparity may stem from the imprecision in the point estimate from the indirect evidence as noted by the wider confidence intervals.

Randomized controlled trials

In the RE-LY trial, Connolly et al.[12] compared two doses (blinded) of dabigatran (110 mg, 150 mg) against adjusted-dose warfarin (unblinded) in a prospective, multinational RCT of 18,113 patients with NVAF, who had at least one additional risk factor for stroke. The primary safety outcome was major hemorrhage. All-cause mortality was a secondary outcome. Findings are summarized in Table 1, and provided in detail in Appendix 2. The main safety conclusion from RE-LY was that, in comparison with warfarin, dabigatran 110 mg was associated with a lower rate of major bleeding while dabigatran 150 mg was associated with a similar rate of major bleeding. Both doses of dabigatran lowered the risk for intracranial bleeding and minor bleeding compared with warfarin. The risk for major gastrointestinal bleeding was similar between the 110- mg dose and warfarin, but was higher for the 150- mg dose. No transfusion data were reported; however, a subsequent publication by Eikelboom et al[18] do report on these data (See below).

In the subsequent addendum report by Connolly et al.,[13] 69 previously unreported major hemorrhages are described. These new events were identified following a thorough audit that was initiated after discovering some unreported events during routine site closure visits. The resulting slight numerical changes that occurred to some outcome data did not change the interpretation of the findings in the original publication with regard to the statistical comparison between groups (Table 3). For completeness, these revised data are presented in Appendix 2.

Table 3: Summary of selected RE-LY trial safety outcomes[12,13]

Outcome	D110 vs warfarin	D150 vs warfarin
All-cause mortality	↔	↔
Major bleeding	↓	↔
Intracranial hemorrhage	↓	↓
Major gastrointestinal bleeding	↔	↑
Minor bleeding	↓	↓
Transfusions[18]	↔	↔

D110=dabigatran 110 mg; **D150**=dabigatran 150 mg; ↔= no difference in risk; ↓=lower risk; ↑=higher risk
Numerical data can be found in Appendix 2

Non-randomized studies

Post-hoc subgroup analyses from the RE-LY trial

Eikelboom et al.[18] present safety data for various types of previously unreported major bleeding events, including several pre-specified subgroup analyses. Appendix 3 presents the definitions of major and minor bleeding events. Subgroups were defined by age (<65, 65-74, ≥75 years), sex, body weight (<50, 50-99, ≥100 kg), creatinine clearance (<50, 50-79, ≥80 mL/min), and ASA use (baseline use versus no baseline use).

For the full trial, no difference was found in the risk of red cell transfusions with either dabigatran 110 mg or 150 mg compared with warfarin. A threshold interaction p-value (p_i) of <0.001 was established by the authors to adjust for multiple testing. Subgroup analyses found no significant interactions with treatment by sex, body weight, creatinine clearance, or baseline ASA use. However, an interaction between age and treatment was noted in major bleeding, where in patients 75 years or older, there was no difference in the risk for major bleeding with either dabigatran 110 mg or 150 mg and warfarin. In patients less than 75 years old, there was a lower risk of major bleeding with both the 110 mg and 150 mg doses compared with warfarin. Although a higher risk of gastrointestinal bleeding was observed with both the 110 mg and 150 mg doses compared with warfarin in patients 75 years or older, the age by treatment interaction (p_i=0.02 and 0.06, respectively) did not reach statistical significance according to the threshold set.

Nagarakanti et al.[14] conducted a post-hoc sub-analysis of patients who underwent cardioversion during the course of the RE-LY trial. A total of 1,983 cardioversions were performed in 1,270 patients. Major bleeding occurring less than 30 days post-procedure was the only safety outcome of interest reported and did not differ compared with warfarin in either the dabigatran 110- mg or 150- mg group.

Diener et al.[16] compared the consistency of the main trial's results in a pre-specified subgroup analysis of RE-LY patients with previous transient ischemia attack (TIA) or stroke (20.0% of original study population) against those who did not have a previous TIA or stroke. No significant treatment by previous stroke or TIA history interactions were noted, such that the results of this subgroup analysis were consistent with those of the main trial for all-cause mortality, major bleeding, intracranial bleeding, and gastrointestinal major bleeding; minor bleeding and transfusions were not reported.

Ezekowitz et al.[15] performed a pre-specified subgroup analysis of warfarin patients in the RE-LY trial to compare the consistency of the results from the full trial in patients who were considered 'VKA-naïve' against those who were 'VKA-experienced'. In the RE-LY trial the pre-specified definition of 'VKA-naive' was a total of up to 62 days of lifetime exposure to VKA therapy. In RE-LY, 50.4% of patients were considered VKA-naïve. Results from the subgroup analysis yielded similar results to the main trial for the outcomes of intracranial bleeding and gastrointestinal bleeding. Although major bleeding did not differ between dabigatran 110 mg and warfarin in VKA-naïve patients, dabigatran 110 mg was associated with less major bleeding compared with warfarin in the full trial; this treatment by VKA status interaction, however, did not reach significance (p_i=0.25). No subgroup data were reported for all-cause mortality, minor bleeding, or transfusions.

Wallentin et al.[17] performed a pre-specified subgroup analysis to compare the consistency of the main trial's results in patients randomized to warfarin who achieved different levels of INR control during the RE-LY trial. The time spent in the therapeutic INR range, or TTR, was described as a mean TTR achieved by each study centre (cTTR); this served as a proxy for individual patient TTR, where the higher the TTR, the better the INR control. The following interquartile limits were identified post hoc for the subgroup analysis by cTTR: <57.1%, 57.1-65.5%, 65.5-72.6%, and >72.6%.

To explore whether there was variation in the risk of bleeds within the different ranges of cTTR, the authors conducted statistical analyses which incorporated relevant interaction terms in the model to address this issue. There was a statistically significant interaction noted between cTTR and assigned treatment for the analyses pertaining to both the occurrence of major bleeds and major gastrointestinal bleeds with the 150 mg dabigatran dose; this suggests that, at centres with poorer INR control, patients taking the 150 mg dose tended to have a lower risk of major bleeding. The investigators attributed the lower risk of major bleeding to possible underdosing of warfarin, or poor patient compliance at centers with poorer INR control, or to meticulous reporting of bleeding events at centres with better INR control. There was no interaction with all-cause mortality or intracranial bleeding; minor bleeding and transfusions were not reported.

Oldgren et al.[19] compared the consistency of the main trial's results in a post-hoc, exploratory subgroup analysis of RE-LY patients according to their baseline $CHADS_2$ risk score. For this analysis, patients were arranged into one of three $CHADS_2$ risk score categories: 0 to 1 (n=5775), 2 (n=6455), or 3 to 6 (n=5882). No significant interactions were noted between $CHADS_2$ score and treatment. The results were consistent with the main trial for total mortality, major and intracranial bleeding; gastrointestinal major bleeding, minor bleeding, and transfusions were not reported.

Hohnloser et al.[20] performed a post-hoc exploratory sub-analysis to specifically compare the effects of dabigatran with warfarin on myocardial ischemic events – especially myocardial infarction (MI) – in RE-LY trial patients. A separate sub-analysis further explored the effect of treatment on myocardial ischemic events by prior coronary artery disease or MI. 'Total MI', consisting of clinical and silent MI, were examined along with 'other myocardial events' consisting of unstable angina, cardiac death, or cardiac arrest.

A greater number of total MI events, driven by clinical MIs, occurred in patients taking either dose of dabigatran compared with warfarin-treated patients, but this difference was not statistically significant [HR: 1.29 (95% CI: 0.96, 1.75), p=0.09 for D110 vs warfarin; HR: 1.27 (95% CI: 0.94, 1.71), p=0.12 for D150 vs warfarin). Of note, about 1/3 of all clinical MIs occurred while off study drug. There were no statistically significant treatment differences in other myocardial events, and no emergent pattern in the direction of effect suggestive of an excess risk in dabigatran-treated patients. In addition, there was no treatment by prior CAD/MI interaction on these outcomes.

Case reports

In July 2011, Legrand et al reported on two cases of serious bleeding in elderly patients, including one death.[21] Both patients were being treated for AF, one taking dabigatran 75 mg BID and the other dabigatran 110 mg BID. In their commentary, the authors highlighted the fact that dabigatran is eliminated renally, and thus elderly patients are prone to accumulation of and subsequent toxicity from the drug. They noted that the area under the curve (AUC) of

dabigatran, a measure of the drug elimination from the body, increases 2.7 fold in healthy volunteers with moderate renal impairment and 6 fold in patients with severe renal impairment. Both of the cases were females with low body weight (40kg and 45kg) and the authors noted that, despite an elderly population in RE-LY (mean age 71.5 years), the mean weight was 83kg, thus underweight elderly patients were underrepresented.

One specific serious bleeding complication that was described in more than one case report was intra-alveolar hemorrhage. In one case, a 73 year-old male developed acute post-operative respiratory distress and intra-alveolar hemorrhage following surgery. The patient had a 20 year history of thrombocytopenia.[23]

There were few other case reports aside from bleeding. Rash was reported, as well as hematoma and hypersensitivity. In one patient, the rash occurred after two weeks of dabigatran 150 mg BID, and resolved after discontinuing dabigatran and subsequent treatment with oral corticosteroids. The patient was a 20 year-old male, thus age does not appear to be an issue in this case. The authors noted that, although hypersensitivity reactions did not appear to be a frequent issue with dabigatran in clinical trials, monitoring for hypersensitivity should be considered.[22]

Moore et al.,[25] report on a case of spontaneous splenic hemorrhage in a 78 year-old woman with significant cardiovascular history following initiation of dabigatran for atrial fibrillation. The patient had been switched from warfarin to dabigatran one week prior to her emergency department presentation. Patient received 2 units of fresh frozen plasma and 2 units of packed red blood cells before undergoing radiological intervention to embolize and coil the splenic artery. No information was provided on the clinical outcome of this case.

Kulik et al.[24] describe the case of a frail 74 year-old woman with mild renal insufficiency and a history of atrial fibrillation (AF), who underwent coronary artery bypass graft surgery (CABG). Prior to admission, patient had not been receiving anticoagulation therapy for stroke prevention in AF because of her refusal to take warfarin. Patient subsequently accepted treatment initiation with dabigatran (75 mg BID) post-CABG. A chest x-ray taken before her transfer to a rehabilitation facility revealed a small left pleural effusion. Patient was readmitted to hospital two days after her transfer due to a massive left hemothorax and gastrointestinal bleeding. Patient was intubated and underwent a thoracostomy. A severe coagulopathy was also noted with INR of 21.5 and a partial thromboplastin time of 161.2. Emergency dialysis was instituted, resolving the coagulopathy and bleeding after two treatments. Patient recovered and was discharged back to the rehabilitation facility two weeks later without anticoagulation therapy.

Casado Naranjo et al[26] report on a case of fatal hemorrhage following administration of recombinant tissue plasminogen activator (rt-PA) for acute stroke in a 62 year-old diabetic man, who was recovering from electric cardioversion for non-valvular AF. Patient had been prescribed dabigatran (110 mg BID) post-op after previously refusing a vitamin K antagonist (i.e., acenocoumarol). Prior to cardioversion, patient was pretreated for one month on enoxaparin. Three hours after the third dose of dabigatran, the patient experienced sudden onset aphasia and hemiplegia. A perfusion CT revealed a deficit of more than 2/3 in the area of the left middle cerebral artery. Coagulation parameters were within normal limits. Following informed consent, thrombolysis was initiated 190 minutes after symptom onset. Neurological status did not change initially, but deteriorated 12 hours later when the patient lapsed into a coma. A CT scan detected a lobar hemorrhage with mass effect accompanied by normal coagulation parameters. The patient was subsequently intubated and transferred to the

intensive care unit, but died two days later. The authors comment that, unlike [conventional] anticoagulants (e.g., VKAs), there is uncertainty about the inherent risks of bleeding associated with the administration of rt-PA in the setting of dabigatran-treated patients. They indicate that this case report will serve as a cautionary tale.

Post-marketing information

A review of the data from the Health Canada Vigilance Database[40] from June 1, 2011 to September 30, 2011 for spontaneous adverse drug reaction (ADR) reporting related to dabigatran treatment revealed 508 ADR reports, of which 500 (89%) were considered serious. Of the serious ADR reports, 62 were associated with death and 14 with disability; 54 were considered life-threatening, and 297 occurred in association with hospitalizations.

Of the 508 ADR reports filed, 192 were associated with the 150- mg dosing and 179 with the 110- mg dosing. Reported exposures ranged from 2 to 186 days. Mean reported age was 74.8 years (median= 78.0 years). More reports detailed ADRs in men (n=296) than in women (n=175). According to MedDRA System Organ Class, 129 (25%) ADR reports were classified as Gastrointestinal Disorders, which were the most common type of spontaneous ADR reported.(Tables 4 and 5) Gastrointestinal hemorrhage (25.6%) was the most common type of ADR reported within the Gastrointestinal Disorders class, while any hemorrhage accounted for just under half (48.8%) of all ADRs reported within the class.

Table 4: Adverse drug reactions (ADR) by MedDRA SOC reported in association with dabigatran

ADR by MedDRA SOC	Number
Total	508
Nervous system disorders	73
General disorders and administration site conditions	33
Investigations	77
Cardiac disorders	30
Gastrointestinal disorders	129
Respiratory, thoracic and mediastinal disorders	21
Musculoskeletal and connective tissue disorders	4
Blood and lymphatic system disorders	16
Injury, poisoning and procedural complcations	23
Skin and subcutaneous tissue disorders	14
Vascular disorders	33
Renal and urinary disorders	14
Infections and infestations	10
Ear and labyrinth disorders	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5
Social circumstances	1
Psychiatric disorders	3

ADR by MedDRA SOC	Number
Eye disorders	4
Hepatobiliary disorders	3
Metabolism and nutrition disorders	5
Surgical and medical procedures	6
Immune system disorders	1

Table 5: Gastrointestinal adverse drug reactions (ADR) reported in association with dabigatran

Type of Gastrointestinal ADR	Number
Total	129
Any hemorrhage:	63 (48.8%)
Gastrointestinal	33
Rectal	14
Lower gastrointestinal	9
Other	7
Diarrhea	10 (7.8%)
Hematochezia	5 (3.9%)
Nausea	4 (3.1%)
Upper abdominal pain	4 (3.1%)
Other	43 (33.3%)

Regulatory updates

Bleeding-related alerts

Japan's health agency issued a safety advisory after five deaths where dabigatran could not be ruled out as the cause. One of the patients had kidney failure, while the other four patients were over 80 years of age. At the time of the advisory, approximately 64,000 patients had received dabigatran in Japan. Therefore, the incidence of death that led to this advisory was 0.008%. Physicians have been advised to monitor for signs of bleeding and anemia, as well to assess renal function before and during treatment. The manufacturer noted that special caution is warranted in elderly patients and patients with risk factors for bleeding. Risk factors such as advanced age, renal impairment, low body weight, and concomitant medications were believed to have contributed to the Japanese deaths.[29]

A safety advisory was also issued in New Zealand regarding acute hemorrhage with dabigatran, causing hospital admission. The two featured cases were both elderly males (82 and 92 years old) whose bleeding events occurred in July 2011. In each case, the patient had been switched from warfarin to dabigatran; one patient switched to the dabigatran 150 mg BID dose and the other to dabigatran 110 mg BID. In each case, the renal function was reduced, with patients' creatinine clearance below 30 mL/min. Both patients appear to have survived, but each was treated with pro-coagulants such as vitamin K, fresh frozen plasma, prothrominex, red blood cells and tranexamic acid. In their background narrative in the alert, the authors note that since July 1, 2011 when dabigatran became fully funded, there have been reports of hospital admissions with bleeding (mainly gastrointestinal) related to dabigatran treatment.[27] A subsequent news release in September 2011 noted that regulators in New Zealand were being criticized because there were two reported deaths and 36 cases of serious bleeding with

dabigatran since being listed for AF. The report also noted that between 6,000 and 10,000 patients had used dabigatran up to this point, although it did not specify if all were for AF.[28]

In the US, the Institute for Safe Medication Practices (ISMP) reported that a high number of adverse event reports (n = 307) had been received by the FDA within weeks of the approval of dabigatran for stroke prevention in patients with atrial fibrillation. The predominant adverse events reported were equally divided between thromboembolic events and bleeding. ISMP expressed the opinion that such a large number of reports generated early following the launch of a new drug product may be a signal that safety issues may grow as use of dabigatran increases and additional alternatives to warfarin are approved.[30]

On November 2, 2011 the manufacturer of dabigatran released information on the number of deaths related to the use of its new oral anticoagulant.[31,32] In total, dabigatran has been linked to 50 deaths from bleeding complications worldwide. The manufacturer also confirmed that among these, as of August 2011, 14 patients who used dabigatran in Japan had died from internal bleeding because of decreased excretion of the drug.[32] Japanese regulators requested in August that the manufacturer issues a strong warning to physicians about the potential for fatal bleeding associated with the use of dabigatran.[31]

On November 3rd, 2011, the Australian Therapeutic Goods Administration (TGA) posted a summary[33] of a review it had completed of dabigatran-associated bleeding events reported to the TGA over a 4-month period. Analysis of these data showed that 1) some bleeding events occurred when transitioning from warfarin to dabigatran, 2) many adverse events were occurring on the lower dosage [110-mg] regimen, and 3) the gastrointestinal tract was the most common bleeding site for dabigatran while intracranial bleeding was more common for warfarin. Following a review of international reports of bleeding events associated with dabigatran, the TGA issued a safety advisory[35] for assessing renal function. This renal evaluation would be performed prior to initiating dabigatran and as indicated over the course of treatment using calculated creatinine clearance as a guide. A summary of these recommendations is provided in Table 6.

Table 6: Summary of TGA renal function assessment recommendations[35]

Recommendations
Kidney function should be assessed in all patients prior to beginning Pradaxa* therapy.
Patients with severe kidney impairment (i.e. CrCL<30 mL/min) should not take Pradaxa*.
While on treatment, kidney function should be assessed in clinical situations where a decline in kidney function is suspected. Such situations include low blood volume, dehydration and when certain medications are taken at the same time.
In elderly patients (> 75 years) or in patients with moderate kidney impairment, kidney function should be assessed at least once a year.

*Australian trade name for dabigatran

In a press release[38] dated November 18th, 2011, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) describes new recommendations for inclusion into the product information for dabigatran. Specifically, a recommendation to assess renal function has been added for all patients prior to starting dabigatran therapy, with repeated renal function testing at least annually in patients over 75 years old or in any patient when a decline in renal function is suspected. The UK Medicines and Healthcare products and Regulatory Agency (MHRA) issued similar recommendations for renal function assessment in dabigatran-treated patients in December 2011.[39]

On December 7, 2011, the FDA announced through its website that it was investigating post-marketing reports of serious bleeding events associated with dabigatran. No changes in labeling have been recommended at this time.[34]

Other safety-related alerts

The FDA had issued a safety alert[36] in March of 2011, relating to the proper storage and handling of dabigatran capsules. Dabigatran capsules were to be stored in their original packaging (e.g., vial, blister) prior to dose administration in order to prevent loss of potency from product breakdown – and by extension, risk for stroke and systemic embolism. The FDA is currently investigating whether, once opened, product stability and potency can be assured beyond the 30-day manufacturer's recommendation.

On November 3rd, 2011, Health Canada issued a safety alert[37] related to the risk of potential harm secondary to medication errors from brand name confusion between Pradax and the antiplatelet, Plavix. Five Canadian cases of drug name confusion were reported to the manufacturer and Health Canada since January 2011, one of which resulted in a non-serious bleeding event following a medical procedure.

Discussion and Limitations

Although we were able to identify one systematic review and network meta-analysis,[11] the comparative data on dabigatran versus warfarin were limited. However, the indirect evidence presented appears to support the direct evidence from the head-to-head RE-LY trial,[12,13] albeit with less precision in the estimates of effect.

Reports in the post-marketing period have focused on safety concerns associated with the use of dabigatran in the elderly and/or patients with renal impairment. Reduced renal function is expected in the elderly, and given the renal elimination of dabigatran, it is reasonable to be concerned about drug accumulation in this population. The Health Canada monograph recommends the 110 mg BID dose for elderly patients. Dabigatran is contraindicated in patients with severe renal impairment in Canada. In other jurisdictions, such as the US, a lower dose (dabigatran 75 mg BID) may be used in these patients.

The RE-LY trial[12,13] represents the only source of direct evidence of dabigatran versus warfarin in patients with NVAF for major safety outcomes. Of note, the long-term (up to 28 months) observational, safety extension trial, RELY-ABLE is targeted for completion in April 2013.[41] The results from the seven reports of subgroup analyses from RE-LY must be interpreted with caution because of the limitations associated with post-hoc (non-randomized) analyses, namely that the possibility of bias from an imbalance in unmeasured confounders cannot be ruled out. The use of centres' mean TTR (cTTR) as a proxy for INR control should be interpreted with caution as it is associated with several limitations. Importantly, cTTR does not reflect the INR control of individual patients, and as a post-randomization variable, it may simply be reflecting the effect of other variables on outcomes, such as differences in overall clinical care between centres.

There are important limitations to relying on case reports in assessing safety. The lack of control group limits the ability to place events into context. For example, it is difficult if not impossible to determine whether five fatalities in Japan represent a safety issue or simply deaths that would have occurred regardless of whether the patients were on dabigatran. These reports are also

voluntary, and are unlikely to represent all occurrences of serious events with dabigatran. Thus, although the number of events involving dabigatran is likely underreported, the available evidence to directly attribute these reported events to dabigatran is also limited. A further limitation in analyzing case reports from the literature and from regulatory bodies is the potential for double-counting. Cases that are reviewed as part of a national or international safety advisory might also be published in the literature, and it can be very difficult, if not impossible, to determine whether these cases are indeed identical and are being counted twice. These limitations also apply to the Canada Vigilance data, as these are self-reported by health professionals and members of the public. Although they represent observation or suspicion of adverse reactions, uncertainty around the total number of reactions and patients using dabigatran prevents estimating actual risks of adverse reactions with such data. In addition, it is not clear how the incidence of adverse events possibly due to dabigatran relates to the incidence of adverse event in patients who are taking warfarin or other oral anticoagulants.

CONCLUSIONS

Several regulatory authorities have issued safety warnings on the use of new oral anticoagulants, some of which include additional guidance around renal function screening and monitoring. A review of published and grey literature updated since the original CDR review of dabigatran yielded limited additional information regarding the drug's safety. It indicates that, compared with adjusted-dose warfarin, the risk of major bleeding is lower with dabigatran 110 mg but not with dabigatran 150 mg. Both doses of dabigatran lowered the risk for intracranial bleeding and minor bleeding compared with warfarin. The risk for major gastrointestinal bleeding was similar between the 110 mg dose and warfarin, but was higher for the 150 mg dose. The finding in the original RE-LY publication for a possibly increased risk of myocardial infarction (MI) in dabigatran-treated patients compared with warfarin remains to be clarified; a post-hoc subgroup analysis could not rule out an association, though the magnitude of such a risk is likely to be small. An emerging area of focus is the use of new oral anticoagulants in elderly patients and/or patients with renal impairment, and the potential for increased risk of severe bleeding in this population. Although this report focuses on dabigatran, the first marketed drug in this class, more high-quality evidence is required to determine the risks associated with all agents in this new class of oral anticoagulants.

ADDITIONAL INFORMATION

The Canadian Agency for Drugs and Technologies in Health is preparing a therapeutic review of novel oral anticoagulants:

Safety and Effectiveness of New Oral Anti-coagulants Compared to Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients with Atrial Fibrillation.
http://www.cadth.ca/en/products/therapeutic-reviews/anticoagulants

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Heart and Stroke Foundation of Canada [Internet]. Ottawa: Heart and Stroke Foundation of Canada; 2011. Statistics; 2011 [cited 2011 Jun 13]. Available from: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3483991/k.34A8/Statistics.htm

2. Bereznicki LRE, Peterson GM. New antithrombotics for atrial fibrillation. Cardiovasc Ther. 2010 Oct;28(5):278-86.

3. Schwartz NE, Albers GW. Dabigatran challenges warfarin's superiority for stroke prevention in atrial fibrillation. Stroke. 2010 Jun;41(6):1307-9.

4. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? Arch Intern Med. 2000 Jan 10;160(1):41-6.

5. Boehringer Ingelheim [Internet]. Ingelheim am Rhein (GR): Boehringer Ingelheim; 2011. Pradax™ (dabigatran etexilate) gains approval in Canada for stroke prevention in atrial fibrillation; 2010 Oct 27 [cited 2011 Jun 16]. Available from: http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2010/27_october_2010_dabigatran.html

6. Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. Circulation. 2011 Apr 5;123(13):1436-50.

7. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest. 2008 Jun;133(6 Suppl):160S-98S.

8. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, et al. Dabigatran etexilate--a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost. 2010 Jun;103(6):1116-27.

9. Health Canada. Notice of compliance (NOC) database [Internet]. Ottawa: Health Canada. Dabigatran; 2011 [cited 2011 Sep 16]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/noc-acc/index-eng.php

10. Common Drug Review. Dabigatran etexilate (Pradax - Boehringer Ingelheim (Canada) Ltd.). New indication: prevention of stroke and systemic embolism in patients with atrial fibrillation [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2011 Jun 22. [cited 2012 Feb 23]. (CEDAC final recommendation). Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_Pradax_June-27-11.pdf

11. Roskell NS, Lip GY, Noack H, Clemens A, Plumb JM. Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparisons versus dabigatran etexilate. Thromb Haemost. 2010 Dec;104(6):1106-15.

12. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51.

13. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L. Newly identified events in the RE-LY trial. N Engl J Med. 2010 Nov 4;363(19):1875-6.

14. Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation [Internet]. 2011 Jan 18 [cited 2011 Jun 13];123(2):131-6. Available from: http://circ.ahajournals.org/cgi/reprint/123/2/131

15. Ezekowitz MD, Wallentin L, Connolly SJ, Parekh A, Chernick MR, Pogue J, et al. Dabigatran and warfarin in vitamin K antagonist-naive and -experienced cohorts with atrial fibrillation. Circulation. 2010 Nov 30;122(22):2246-53.

16. Diener HC, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. Lancet Neurol. 2010 Dec;9(12):1157-63.

17. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet. 2010 Sep 18;376(9745):975-83.

18. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial. Circulation [Internet]. 2011 May 16 [cited 2011 Jun 20];123:2363-72. Available from: http://circ.ahajournals.org/cgi/reprint/123/21/2363

19. Oldgren J, Alings M, Darius H, Diener HC, Eikelboom J, Ezekowitz MD, et al. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the CHADS2 score: a subgroup analysis of the RE-LY trial. Ann Intern Med. 2011 Nov 15;155(10):660-7.

20. Hohnloser SH, Oldgren J, Yang S, Wallentin L, Ezekowitz M, Reilly P, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial. Circulation. 2012 Feb 7;125(5):669-76.

21. Legrand M, Mateo J, Aribaud A, Ginisty S, Eftekhari P, Huy PT, et al. The use of dabigatran in elderly patients. Arch Intern Med. 2011 Jul 25;171(14):1285-6.

22. Whitehead H, Boyd JM, Blais DM, Hummel J. Drug-induced exanthem following dabigatran. Ann Pharmacother. 2011 Oct;45(10):e53.

23. Hanf W, Duntze J, Hida H, Blanc Q, Reynaud C. [The implication of a direct antithrombine in the appearance of (serious) postoperative acute respiratory distress]. Ann Fr Anesth Reanim. 2009 Oct;28(10):885-8. French.

24. Kulik A, Saltzman MB, Morris JJ. Dabigatran after cardiac surgery: caution advised. J Thorac Cardiovasc Surg. 2011 Nov;142(5):1288.

25. Moore CH, Snashall J, Boniface K, Scott J. Spontaneous splenic hemorrhage after initiation of dabigatran (Pradaxa) for atrial fibrillation. Am J Emerg Med. 2011 Dec 23. Epub ahead of print.

26. Casado Naranjo I, Portilla-Cuenca JC, Jimenez Caballero PE, Calle Escobar ML, Romero Sevilla RM. Fatal intracerebral hemorrhage associated with administration of recombinant tissue plasminogen activator in a stroke patient on treatment with dabigatran. Cerebrovasc Dis [Internet]. 2011 [cited 2012 Jan 23];32(6):614-5. Available from: http://content.karger.com/produktedb/produkte.asp?DOI=000334578&typ=pdf

27. Safe and Quality Use of Medicines Group. Urgent: acute haemorrhage associated with dabigatran initiation causing hospital admissions [Internet]. [Auckland (NZ)]: District Health Boards NZ (DHBNZ) Safety and Quality Use of Medicines Group; 2011 Jul. [cited 2011 Sep 12]. (Alert 11). Available from: http://www.safeuseofmedicines.co.nz/LinkClick.aspx?fileticket=PhlCGQY2RAQ%3D&tabid=118&mid=460&language=en-NZ

28. Staton T. NZ officials under fire over Pradaxa side effects [Internet]. Washington (DC): FierceMarkets; 2011 Sep 12. [cited 2011 Sep 13]. Available from: http://www.fiercepharma.com/story/nz-officials-under-fire-over-pradaxa-side-effects/2011-09-12#ixzz1XrCODujl

29. Wood S. Deaths prompt dabigatran safety advisory in Japan. Montreal (QC): WebMD; 2011 Aug 17. [cited 2011 Sep 19]. Available from: http://www.theheart.org/article/1264365.do Free subscription required.

30. QuarterWatch™ 2010 (quarter 4 and annual summary): signals for two newly approved drugs: dabigatran and dalfampridine. ISMP Medication Safety Alert! Acute Care. 2011 Oct 6;16(20):1-3.

31. Boehringer says about 50 deaths related to Pradaxa [Internet]. New York: Thomson Reuters; 2011 Nov 2. [cited 2011 Nov 8]. Available from: http://www.reuters.com/article/2011/11/02/boehringer-pradaxa-idUSL5E7M21TB20111102

32. Cullen A. Boehringer confirms Pradaxa-related deaths, Die Zeit reports [Internet]. New York: Bloomberg; 2011 Nov 2. [cited 2011 Nov 8]. Available from: http://www.bloomberg.com/news/2011-11-02/boehringer-confirms-pradaxa-related-deaths-die-zeit-reports.html

33. Dabigatran (Pradaxa) and the risk of bleeding. Aust Prescr [Internet]. 2011 [cited 2012 Jan 23];34(6):191. Available from: http://www.australianprescriber.com/upload/pdf/articles/1240.pdf

34. U.S. Food and Drug Administration. MedWatch: the FDA safety information and adverse event reporting program [Internet]. Silver Spring (MD): FDA; 2012. Pradaxa (dabigatran etexilate mesylate):drug safety communication - safety review of post-market reports of serious bleeding events; 2011 Dec 7 [cited 2012 Feb 8]. Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm282820.htm

35. Therapeutic Goods Administration [Internet]. Woden (Australia): Australian Government Department of Health and Ageing, Therapeutic Goods Administration; 2012. Dabigatran (Pradaxa) & the risk of bleeding: new recommendations for monitoring kidney function. Safety advisory; 2011 Nov 3 [cited 2012 Feb 8]. Available from: http://www.tga.gov.au/safety/alerts-medicine-dabigatran-111103.htm

36. U.S. Food and Drug Administration. MedWatch: the FDA safety information and adverse event reporting program [Internet]. Silver Spring (MD): FDA; 2012. Pradaxa (dabigatran etexilate mesylate) capsules: special storage and handling requirements; 2011 Mar 30 [cited 2012 Feb 8]. Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm249005.htm

37. Health Canada. MedEffect Canada: advisories, warnings and recalls for health professionals [Internet]. Ottawa: Health Canada. Pradax (dabigatran etexilate) and Plavix (clopidogrel bisulfate): risk of potential patient harm associated with brand name confusion; 2011 Nov 3 [cited 2012 Feb 8]. Available from: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2011/plavix_2_hpc-cps-eng.php

38. European Medicines Agency. European Medicines Agency updates on safety of Pradaxa [Internet]. London (UK): EMA; 2011 Nov 18. [cited 2012 Feb 8]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/11/news_detail_001390.jsp&mid=WC0b01ac058004d5c1&jsenabled=true

39. Medicines and Healthcare products Regulatory Agency (MHRA). Dabigatran (Pradaxa): risk of serious haemorrhage-need for renal function testing. Drug Saf Update [Internet]. 2011 Dec [cited 2012 Feb 8];5(5):A2. Available from: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON137771

40. Health Canada. Canada vigilance adverse reaction online database [Internet]. Ottawa: Health Canada; 1965 Jan 1 - 2011 Sep 30 [cited 2012 Jan 18]. Available from: http://webprod3.hc-sc.gc.ca/arquery-rechercheei/index-eng.jsp

41. ClinicalTrials.gov [Internet]. Bethseda (MD): National Library of Medicine; 2000 -. Identifier NCT00808067, RELY-ABLE long term multi-center extension of dabigatran treatment in patients with atrial fibrillation who completed RE-LY trial; 2011 Jun 1 [cited 2011 Jun 13]. Available from: http://clinicaltrials.gov/ct2/show/NCT00808067

42. Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J. 2009 May;157(5):805-10.

43. Therapeutics Initiative. Dabigatran for atrial fibrillation: why we can not rely on RE-LY. Ther Lett [Internet]. 2011 Mar [cited 2011 Jun 13];80. Available from: http://www.ti.ubc.ca/sites/ti.ubc.ca/files/80.pdf

Appendix 1: Study Characteristics of Relevant Reports

Author and Publication Year	Design	Population	Intervention	Comparator(s)	Clinical Outcomes
Systematic review/Meta-analysis					
Roskell et al., 2010[11]	Systematic review (RCTs only) and network meta-analysis	Patients with AF receiving treatment for stroke prevention	dabigatran etexilate 150 mg or 110 mg (D110, D150)	adjusted-dose VKA; fixed low-dose warfarin +/- ASA; ASA monotherapy; ASA + clopidogrel; Indobuphen; Idraparinux; Triflunisal; Ximelagatran; placebo	(all) stroke; ischemic stroke; systemic embolism; all-cause mortality; intracranial hemorrhage (excluding hemorrhagic stroke); extracranial hemorrhage (major bleeds); acute myocardial infarction
Randomized controlled trials					
Connolly et al., 2009[12,42] RE-LY trial	Prospective, randomized (1:1:1), multicentre, multinational non-inferiority trial Median follow-up : 2 years	Adults (n=18,113) with non-valvular atrial fibrillation With previous stroke or TIA, LV ejection fraction < 40%, heart failure (NYHA class II or higher), or age > 75 years; OR age $\geq$ 65 y + either diabetes, hypertension, or coronary artery disease	Dabigatran (blinded) : 150 mg or 110 mg D150 : n=6,076 D110 : n=6,015	Adjusted dose warfarin (unblinded) targeting an INR of 2-3 Warfarin: n=6,022	1° efficacy: stroke or systemic embolism 1° safety : major hemorrhage 1° net clinical benefit : composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major hemorrhage 2° : stroke, systemic embolism, death; myocardial infarction, pulmonary embolism, transient ischemic attack,

Author and Publication Year	Design	Population	Intervention	Comparator(s)	Clinical Outcomes
Connolly et al., 2010[13] Addendum to RE-LY trial					hospitalization
Non-randomized studies					
Eikelboom et al., 2011[18]	Pre-specified sub-analysis from RE-LY trial	Patient subgroups by age, gender, creatinine clearance, baseline use of ASA	As per Connolly et al.[12]	As per Connolly et al.[12]	Safety focus: various types of major bleeding in key subgroups
Nagarakanti et al., 2011[14]	Post-hoc sub-analysis from RE-LY trial	Patients who underwent cardioversion during the RE-LY trial *Notes: Study protocol recommended continuing assigned treatment during cardioversion; most cardioversions were electric (~84%); normal sinus rhythm usually achieved at discharge (~89%).*			Stroke and systemic embolism, major bleeding < 30 days after cardioversion
Diener et al., 2010[16]	Pre-specified sub-analysis from RE-LY trial	Patients with previous TIA or stroke			As per Connolly et al.[12]
Ezekowitz et al., 2010[15]	Pre-specified sub-analysis from RE-LY trial	Patients experienced vs naive with VKAs			

Author and Publication Year	Design	Population	Intervention	Comparator(s)	Clinical Outcomes
Wallentin et al., 2010[17]	Pre-specified sub-analysis from RE-LY trial	Patients taking warfarin by level of INR control achieved			
Oldgren et al., 2011[19]	Post-hoc, exploratory sub-analysis from RE-LY trial	Patient subgroup by $CHADS_2$ risk score			
Hohnloser et al.,[20]	Post-hoc, exploratory sub-analysis from RE-LY trial	As per Connolly et al.;[12] patient subgroup by prior history of MI/CAD			MI and other myocardial ischemic events

D110=dabigatran 110 mg; D150= dabigatran 150 mg; n=sample size; VKAs= vitamin K antagonists; MI=myocardial infarction; CAD=coronary artery disease

Appendix 2: Study Findings, Conclusions and Limitations

Author and Publication Year	Study Findings	Limitations
HTA/Systematic review/Meta-analysis:		
Roskell et al., 2010[11] Systematic review and network meta-analysis	***All-cause mortality:*** **D110:** No difference vs adjusted-dose VKA (RR: 0.92; 95% CI: 0.79, 1.06) **D150:** No difference vs adjusted-dose VKA (RR: 0.89; 95% CI: 0.77, 1.03) ***Extracranial hemorrhage (=major bleeding):*** **D110:** No difference vs adjusted-dose VKA (RR: 0.96; 95% CI: 0.75, 1.22) **D150:** No difference vs adjusted-dose VKA (RR:1.09; 95% CI: 0.86, 1.37) ***Intracranial hemorrhage (excluding hemorrhagic stroke)*:** **D110:** Lower risk vs adjusted-dose VKA (RR:0.33; 95% CI: 0.15, 0.72) **D150:** No difference vs adjusted-dose VKA (RR:0.53; 95% CI: 0.27, 1.03) ***Major gastrointestinal bleeding:*** Not reported ***Minor bleeding:*** Not reported ***Transfusions:*** Not reported	Definition of ICH may have varied across trials. No adjustments for multiple comparisons. Potential for historical bias from older trials when clinical management of stroke risk factors was suboptimal Potentially more restrictive enrolment criteria in older included trials (Of note: Lead author was a paid consultant to dabigatran manufacturer for this project; manufacturer's internal staff contributed to design, analyses, interpretation of paper.)
Author's Conclusions: No formal concluding statements about the study outcomes were made with regard to the performance of dabigatran etexilate versus the specific comparator, VKA therapy.		
Randomized controlled trials:		
Connolly et al., 2009[12] RE-LY trial	***All-cause mortality:*** **D110:** No difference vs warfarin (RR:0.91; 95% CI: 0.80, 1.03; p=0.13) **D150:** No difference vs warfarin (RR:0.88; 95% CI: 0.77, 1.00; p=0.051) ***Major bleeding:*** **D110:** Lower vs warfarin (RR:0.80; 95% CI: 0.69, 0.93; p=0.003) **D150:** No difference vs warfarin (RR:0.93; 95% CI: 0.81, 1.07; p=0.31) ***Intracranial bleeding*** *(=hemorrhagic stroke and subdural or subarachnoid hemorrhage)*: **D110:** Lower vs warfarin (RR:0.31; 95% CI: 0.20, 0.47; p<0.001) **D150:** Lower vs warfarin (RR:0.40; 95% CI: 0.27, 0.60; p<0.001) ***Major bleeding – gastrointestinal:***	Concomitant use of ASA was permitted. (baseline use ~40%) Long-term VKA therapy at baseline was ~50% Unblinded comparison between warfarin and dabigatran Higher annual incidence of ICH in warfarin group compared with previous trials[43] Relatively short follow-up (median of 2 years)

Author and Publication Year	Study Findings	Limitations
	D110: No difference vs warfarin (RR:1.10; 95% CI: 0.86, 1.41; p=0.43) **D150:** Higher vs warfarin (RR:1.50; 95% CI: 1.19, 1.89; p<0.001) ***Minor bleeding:*** **D110:** Lower vs warfarin (RR:0.79; 95% CI: 0.74, 0.84; p<0.001) **D150:** Lower vs warfarin (RR:0.91; 95% CI: 0.85, 0.97; p=0.005) ***Transfusions:*** Not reported in this publication. Refer to Eikelboom et al.[18]	
Author's Conclusions: "As compared with warfarin, the 110- mg dose of dabigatran was associated with...lower rates of major hemorrhage; the 150- mg dose of dabigatran was associated with... a similar rate of major hemorrhage." p.1148-9		
Connolly et al., 2010[13] Addendum to RE-LY trial	Several previously unreported efficacy and safety events were identified following the primary publication;[12] subsequent to a thorough audit, 81 new events were identified in 80 patients, including 69 major hemorrhages. However, these small numerical changes in the data did not change the interpretation of the original findings: **Revised – *All-cause mortality:*** **D110:** as per Connolly et al[12] **D150:** as per Connolly et al[12] **Revised – *Major bleeding:*** **D110:** Lower vs warfarin (RR:0.80; 95% CI: 0.70, 0.93; p=0.003) **D150:** No difference vs warfarin (RR:0.93; 95% CI: 0.81, 1.07; p=0.32) **Revised – *Intracranial bleeding:*** **D110:** Lower vs warfarin (RR:0.30; 95% CI: 0.19, 0.45; p<0.001) **D150:** Lower vs warfarin (RR:0.41; 95% CI: 0.28, 0.60; p<0.001) **Revised – *Major bleeding – gastrointestinal:*** **D110:** No difference vs warfarin (RR:1.08; 95% CI: 0.85, 1.38; p=0.52) **D150:** Higher vs warfarin (RR:1.48; 95% CI: 1.18, 1.85; p=0.001) **Revised – *Minor bleeding:*** **D110:** as per Connolly et al[12] **D150:** Lower vs warfarin (RR:0.91; 95% CI: 0.86, 0.97; p=0.005)	
Author's Conclusions: "Inclusion of the newly identified events did not materially change the study results...The study conclusions remain unchanged." p.1876		

Author and Publication Year	Study Findings	Limitations
Non-randomized studies:		
Eikelboom et al., 2011[18] Pre-specified sub-analysis from RE-LY trial: • Patient subgroups by age, gender, creatinine clearance, baseline use of ASA	*Pre-specified subgroups:* *Age (y): <65, 65-74, ≥ 75* *Sex: male, female* *Body weight (kg): <50, 50-99, ≥ 100* *Creatinine clearance (mL/min): <50, 50-79, ≥80* *ASA : Baseline vs no baseline use* ***There were no significant interactions between treatment and any of the following variables: sex, body weight, creatinine clearance, or concomitant ASA.*** ***All-cause mortality:*** Not reported ***Major bleeding:*** **Age:** Increasing age was associated with higher risk in both D110 (p_i=0.0003) and D150 (p_i= 0.0001) groups vs warfarin. **Age < 75 y:** Lower risk with both D110 (RR: 0.62; 95% CI: 0.50, 0.77) and D150 (RR: 0.70; 95% CI: 0.57, 0.86) vs warfarin. **Age ≥ 75 y:** No difference in risk with either D110 (RR: 1.01; 95% CI: 0.83, 1.23) or D150 (RR: 1.18; 95% CI: 0.98, 1.42) vs warfarin. ***Intracranial bleeding*:** **Age:** Both D110 (p_i=0.28) and D150 (p_i=0.91) were associated with lower risk vs warfarin, independent of age. **Age < 75 y:** Lower risk with both D110 (RR: 0.22; 95% CI: 0.11, 0.45) and D150 (RR: 0.43; 95% CI: 0.25, 0.74) vs warfarin. **Age ≥ 75 y:** Lower risk with both D110 (RR: 0.37; 95% CI: 0.21, 0.64) and D150 (RR:0.42; 95% CI: 0.25, 0.70) vs warfarin. ***Gastrointestinal bleeding:*** **Age:** No significant interaction* with age (<75 y vs ≥ 75 y) in either D110 (p_i=0.02) or D150 (p_i=0.06) vs warfarin. **Age < 75 y:** No difference in risk with either D110 (0.82; 95% CI: 0.58, 1.15) or D150 (RR:1.19; 95% CI: 0.87, 1.63) vs warfarin. **Age ≥ 75 y:** Higher risk with both D110 (RR:1.39; 95% CI: 1.03, 1.98) and D150 (RR:1.79; 95% CI: 1.35, 2.37) vs warfarin. ***Minor bleeding†:*** Overall: As per Connolly et al[13] ***Red cell transfusions†:*** Overall: There was no difference with either D110	Adjustments were made for multiple testing, but the designated threshold interaction p (p_i) of <0.001 may have been overly conservative.

Author and Publication Year	Study Findings	Limitations
	(RR: 0.90; 95% CI: 0.75, 1.09; p=0.29) or D150 (RR:1.10; 95% CI: 0.92, 1.31; p=0.30) vs warfarin *According to threshold p_i<0.0001 set by authors. †*Outcome data presented according to randomized treatment allocation.*	
Author's Conclusions: "At ages < 75 years, the higher dabigatran dose seems preferable because of the lower risk of stroke without any increased risk of bleeding, whereas at higher ages, the lower dabigatran dose might be considered a means to reduce the risk of bleeding in selected patients who are at high risk of bleeding." p. 2370-1		
Nagarakanti et al., 2011[14] Post-hoc sub-analysis from RE-LY trial: • Patients who underwent cardioversion during the RE-LY trial	***Total mortality:*** Not reported. ***Major bleeding*** *(<30 days post-procedure):* No difference wth either D110 (RR: 2.82; 95% CI: 0.90, 8.82; p_i=0.0617) or D150 (RR: 0.99; 95% CI: 0.25, 3.93; p_i=0.9865) vs warfarin ***Intracranial bleeding*:** Not reported. ***Major gastrointestinal bleeding:*** Not reported. ***Minor bleeding:*** Not reported. ***Transfusions:*** Not reported.	Retrospective analysis Small number of events No data on left atrial size, presence and severity of mitral regurgitation, and thrombus size and mobility
Author's Conclusions: "...major bleeding rates after cardioversion were low in both the dabigatran- and warfarin-assigned groups... with a slightly higher rate in the D110 arm compared with warfarin. However, the use of nonstudy anticoagulant and antiplatelet therapies before cardioversion was higher in both the D110 and D150 arms compared with warfarin, and the use of these therapies after cardioversion was greater only in the D110 arm. These rates suggest that investigators were not as comfortable using dabigatran alone as warfarin alone in the pericardioversion period." p.134-5		
Diener et al., 2010[16] Pre-specified sub-analysis from RE-LY trial: • Patients with previous TIA or stroke	*Previous stroke or TIA: 20.0% of RE-LY patients* ***No significant interaction of previous stroke or TIA with treatment for all-cause mortality or major, intracranial, life-threatening, non-life-threatening, gastrointestinal, or extracranial bleeding.*** ***All-cause mortality:*** **Previous stroke or TIA:** Lower[a] risk with D110 (RR:0.70; 95% CI: 0.53, 0.94) vs warfarin; no difference between D150 (RR:0.95; 95% CI: 0.73, 1.24) vs warfarin **No previous stroke or TIA:** No difference between D110 (RR:0.96; 95% CI: 0.83, 1.11) vs warfarin; lower[b] risk on D150 (RR:0.86; 95% CI: 0.74, 0.99) vs warfarin	No adjustments made for multiple testing

Author and Publication Year	Study Findings	Limitations
	[a] *Interaction P=0.062* [b] *Interaction P=0.49* ***Major bleeding:*** **Previous stroke or TIA:** Lower with D110 (RR:0.66; 95% CI: 0.48, 0.90) vs warfarin; no difference with D150 (RR:1.01; 95% CI: 0.77, 1.34) vs warfarin **No previous stroke or TIA:** Lower with D110 (RR:0.85; 95% CI: 0.72, 0.99) vs warfarin; no difference with D150 (RR:0.91; 95% CI: 0.77, 1.06) vs warfarin ***Intracranial bleeding:*** **Previous stroke or TIA:** Lower risk with both D110 (RR:0.20; 95% CI: 0.08, 0.47) and D150 (RR:0.41; 95% CI: 0.21, 0.79) vs warfarin **No previous stroke or TIA:** Lower risk with both D110 (RR:0.35; 95% CI: 0.21, 0.57) and D150 (RR:0.43; 95% CI: 0.27, 0.68) vs warfarin ***Gastrointestinal major bleed:*** **Previous stroke or TIA:** No difference with D110 (RR:0.99; 95% CI: 0.61, 1.60) vs warfarin; higher risk with D150 (RR:1.67; 95% CI: 1.09, 2.56) vs warfarin **No previous stroke or TIA:** No difference with D110 (RR:1.11; 95% CI: 0.86, 1.43) vs warfarin; higher risk with D150 (RR:1.43; 95% CI: 1.12, 1.81) vs warfarin ***Minor bleeding:*** Not reported ***Transfusions:*** Not reported.	
Author's Conclusions: "The two doses of dabigatran might have had differential effects in this analysis of secondary stroke prevention in patients with previous stroke or transient ischemic attack." p.1162		
Ezekowitz et al., 2010[15] Pre-specified sub-analysis from RE-LY trial: • Patients experienced vs naive with VKAs	*VKA-naïve* : 50.4% of RE-LY patients* *TTR* : 64% overall; 62%-naive, 67%-experienced ***All-cause mortality:*** Not reported ***Major bleeding****: No treatment by VKA status interactions* **VKA-experienced:** Lower with D110 vs warfarin (RR:0.74; 95% CI, 0.60 to 0.90; p=0.003); no difference with D150 (RR: 0.92; 95% CI: 0.76, 1.12; p=0.41) vs warfarin **VKA-naive:** No difference with D110 (RR: 0.87; 95% CI: 0.72, 1.07; p=0.19) or D150 (RR: 0.94; 95% CI: 0.77, 1.15; p=0.55) vs warfarin	Unclear whether adjustments were made for multiple testing Definitions for 'VKA naïve/experienced' would be expected to vary across trials since no standard definitions exist.

Author and Publication Year	Study Findings	Limitations
	Intracranial bleeding**:** *No treatment by VKA status interactions* **VKA-experienced:** Lower with both D110 (RR:0.32; 95% CI: 0.18, 0.56; p<0.001) and D150 (RR:0.40; 95% CI: 0.24, 0.67; p<0.001) vs warfarin **VKA-naive:** Lower with both D110 (RR:0.27; 95% CI: 0.14, 0.52; p<0.001) and D150 (RR:0.46; 95% CI: 0.27, 0.78; p=0.005) vs warfarin ***Gastrointestinal bleeding:*** *No treatment by VKA status interactions* **VKA-experienced:** No difference with D110 (RR: 0.96; 95% CI: 0.70, 1.32; p=0.80) vs warfarin; higher with D150 (RR:1.42; 95% CI: 1.06, 1.89; p=0.02) vs warfarin **VKA-naive:** No difference with D110 (RR: 1.23; 95% CI: 0.89, 1.68; p=0.20) vs warfarin; higher with D150 (RR:1.56; 95% CI: 1.15, 2.10; p=0.004) vs warfarin ***Minor bleeding:*** Not reported ***Transfusions:*** Not reported. * RE-LY trial's pre-specified definition of VKA-naive: total of up to 62 days of lifetime exposure to VKA therapy.	
Author's Conclusions: " …there was no significant interaction between treatment and prior VKA use on major outcomes. The only exception was for the combined secondary outcome measure of life-threatening bleeding, disabling stroke, and death in the D150 group compared with warfarin and only for the [alternative] *not-on-a-VKA-at-randomization* definition (P=0.04). The alternative definitions were not part of the pre-specified analysis, and the importance of this interaction remains unclear." p.2250		
Wallentin et al., 2010[17] Pre-specified sub-analysis from RE-LY trial: • Patients taking warfarin by level of INR control achieved	*cTTR quartiles: <57.1%, 57.1-65.5%, 65.5-72.6%, or >72.6%* ***Total mortality:*** There was no interaction between cTTR and treatment in either D110 (p_i=0.066) and D150 (p_i=0.052) groups vs warfarin. ***Major bleeding:*** Lower cTTR was associated with a more favourable HR for D150 vs warfarin (lowest quartile HR=0.71 vs highest quartile HR=1.16,p_i=0.03). ***Intracranial bleeding*****:** There was no interaction of cTTR in either D110 (p_i=0.71) or D150 (p_i=0.89) vs warfarin. ***Major gastrointestinal bleeding:*** Higher cTTR was associated with a less	Secondary outcomes were not pre-specified cTTR was used as a proxy for individual TTR cTTR was a post-randomization variable No adjustments made for multiple testing

Author and Publication Year	Study Findings	Limitations
	favourable HR in D150 vs warfarin (lowest quartile HR=1.08 vs highest quartile HR= 2.00, p_i=0.019). ***Minor bleeding:*** Not reported ***Transfusions:*** Not reported.	
Author's Conclusions: "We noted lower rates of total bleeding at sites with a lower cTTR in all three groups of the trial. These rates might be low because of underdosing or poor compliance at sites with lower cTTR or more thorough recording of bleedings at sites with better cTTR. In the warfarin group, but not in the dabigatran groups, there was a lower risk of both total major and gastrointestinal major bleeding at sites with better INR control, which is in accordance with other studies." "The absence of a significant interaction between cTTR and hemorrhagic stroke rates suggests that the effect of INR control on overall event rates is mainly driven by interactions between INR and non-hemorrhagic events, which is consistent with previous findings with warfarin." p. 981-2		
Oldgren et al., 2011[19] Post-hoc, exploratory sub-analysis from RE-LY trial: • Patient subgroup by $CHADS_2$ risk score	$CHADS_2$ score tertiles: 0-1, 2, and 3-6 ***Total mortality:*** *No treatment by $CHADS_2$ score interactions* Only the lowest tertile of $CHADS_2$ score was associated with a more favourable ARR for D150 (ARR: 0.71; 95% CI: 0.03, 1.39) compared with warfarin; there were no differences in the outcome between treatments with higher $CHADS_2$ scores. ***Major bleeding:*** *No treatment by $CHADS_2$ score interactions* Only the lowest tertile of $CHADS_2$ score was associated with a more favourable ARR for both D110 (ARR: 0.98; 95% CI: 0.29, 1.66) and D150 (ARR: 0.73; 95% CI: 0.02, 1.43) compared with warfarin; there were no differences in the outcome between treatments with higher $CHADS_2$ scores. ***Intracranial bleeding*****:** *No treatment by $CHADS_2$ score interactions* Both D110 and D150 were associated with an increasingly favourable ARR (0.34, 0.47, 0.81 and 0.34, 0.43, 0.55, respectively) compared with warfarin as the $CHADS_2$ score increased. ***Major gastrointestinal bleeding:*** Not reported ***Minor bleeding:*** Not reported ***Transfusions:*** Not reported.	Subanalysis not pre-specified No adjustments made for multiple testing
Author's Conclusions: "Increased $CHADS_2$ scores were associated with increased risks for… major and intracranial bleeding, and death in patients with atrial fibrillation treated with the oral vitamin K antagonist		

Author and Publication Year	Study Findings	Limitations
warfarin or with 1 of 2 doses of… dabigatran, 110 or 150 mg twice daily… rates of intracranial bleeding were lower with both dabigatran doses than with warfarin treatment, without significant heterogeneity in subgroups defined by $CHADS_2$ scores."		
Hohnloser et al., 2012[20] Post-hoc, exploratory sub-analysis from RE-LY trial:	*Specific sub-analysis to explore possible excess treatment-related myocardial infarction (MI) or other myocardial ischemic events* ***Total MI:*** clinical + silent There was a non-statistically significantly greater rate of MIs, driven by clinical MIs, in patients taking either dose of dabigatran compared with warfarin. About 1/3 of all clinical MIs occurred while off study drug. **D110 vs warfarin**: HR: 1.29; 95% CI: 0.96, 1.75; p=0.09 **D150 vs warfarin**: HR: 1.27; 95% CI: 0.94, 1.71; p=0.12 **D(110 or 150) vs warfarin**: HR: 1.28; 95% CI: 0.98, 1.67; p=0.07 There was no statistically significant difference in MI event rates between patients with prior CAD/MI compared with patients without prior CAD/MI. No pattern suggestive of an excess in other myocardial ischemic events (notably unstable angina, cardiac death, or cardiac arrest) in dabigatran-treated patients emerged.	Sub-analysis not pre-specified No adjustments made for multiple testing
Author's Conclusions: "A non-significant higher number of MI was observed with dabigatran compared to warfarin in RE-LY, but there was no excess of other myocardial ischemic events."		

CI=confidence interval; D110=dabigatran 110 mg; D150=dabigatran 150 mg; HR=hazard ratio; ICH=intracranial hemorrhage; p_i= probability of interaction; RR=relative risk; VKAs=vitamin K antagonists; ARR=absolute risk reduction; CAD=coronary artery disease

Appendix 3: Definition of Major and Minor Bleeding Events in the RE-LY Trial

Major Bleeding: *(≥ 1 of the following)*	**Minor Bleeding**
• Reduction in Hgb ≥ 20 g/L	Clinical bleeds that do not fulfill criteria for major bleeds
• Transfusion of ≥ 2 units of blood or packed cells	
• Symptomatic bleeding in critical area or organ o Intraocular o Intracranial o Intraspinal o Intramuscular with compartment syndrome o Retroperitoneal o Intra-articular o pericardial	
Life-threatening: *(≥ 1 of the following)*	
• Fatal, symptomatic	
• Reduction in Hgb ≥ 50 g/L	
• Transfusion ≥ 4 units blood or packed cells	
• With hypotension, requiring i.v. inotropic agents	
• Requiring surgical intervention	

Hgb=hemoglobin; i.v.=intravenous