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Month/Year of Review: January 2011
Generic Name: Dabigatran

End date of literature search: December 2011
Brand Name (Manufacturer): Pradaxa (Boehringer Ingelheim)
Dossier received: Yes
Comparator Therapies: Enoxaparin and warfarin

PDL Class: No current PDL class
Preferred Anticoagulants: enoxaparin and dalteparin
Non-preferred Anticoagulants: fondiparinux, tinzaparin, rivaroxaban (pending) and dabigatran (pending)
No PDL-status/no restrictions: warfarin

FDA Approved Indications: To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF).

Summary:

- Dabigatran is a direct thrombin inhibitor used for oral stroke prophylaxis in patients with AF, as an alternative to vitamin K antagonists (VKA) such as warfarin. Dabigatran has few drug/food interactions and is not a substrate, inhibitor or inducer of CYP450 enzymes.[1]
- The recommended dabigatran dose is 150mg twice daily for AF. Dose adjustment to 75mg twice daily if CrCl 15-30 mL/min. No adjustments required with moderate hepatic dysfunction.

Efficacy and Safety Summary for FDA Approved Indications

Atrial Fribrillation

- Dabigatran approval was based on a large, prospective, non-blinded, randomized trial, the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY).[2] RE-LY was a multi-center, multi-national, parallel group, non-inferiority trial comparing two blinded doses of dabigatran (110mg twice daily or 150 mg twice daily) with open-label warfarin with a target international normalized ratio (INR) range of 2-3. Mean time in therapeutic range (TTR) was 64%.[2]
- A high degree of bias is associated with an open-label study design. The FDA cited this concern in their review but felt that because there were significant differences shown in the double-blind comparison between the dabigatran doses, this helped to substantiate the results.[3] The rates of intracranial bleeds was the primary factor contributing to the composite outcomes.
- Two doses were studied in RE-LY, a 110 mg dose and a 150 mg dose. The 110mg dose was not approved and did not demonstrate superiority over warfarin. There was moderate-strength of evidence that dabigatran 150mg was superior to warfarin for the primary composite endpoint of stroke or systemic embolism (RR 0.65; 95% CI, 0.52 to 0.81; p<0.001, NNT 167). There was low-strength of evidence

that dabigatran 150mg had similar rates of all-cause mortality compared to warfarin. FDA analysis of RE-LY states that in patients whom INRs are well controlled, warfarin and dabigatran 150 mg twice daily carry the same risk of stroke or fatal events.[3]

- There was low-strength of evidence of similar rates of major bleeding with dabigatran 150mg, compared to warfarin, which was influenced by the TTR. There were significantly more gastrointestinal bleeds in the dabigatran 150mg group compared to warfarin. Dabigatran was associated with less intracranial bleeding, which was statistically significant and independent of TTR.[4]

Other Considerations:

- Dabigatran is associated with dyspepsia, which is the most commonly cited reason for drug discontinuation. In the dabigatran 150mg group annual discontinuation rates were 2% compared to 0.6% of warfarin patients.[2]
- An increased rate of myocardial infarctions (MI) were seen with both doses of dabigatran but neither were statistically significant after newly identified events were included in the revised data.[5]
- There is no antidote to reverse bleeding in a bleeding emergency. Unlike warfarin, vitamin K administration will not reduce the anticoagulant effects of dabigatran in the event of a major bleed.[1]
- The FDA has recently announced that they will be conducting a safety review of post-marketing reports of serious bleeding associated with dabigatran. At this time the FDA believes the benefits of dabigatran still exceed the risk.

Efficacy and Safety Summary on off-label Uses

Surgery Prophylaxis

- Three studies evaluated the use of dabigatran for prevention of VTE after TKR and THR. In TKR, the evidence found that dabigatran was noninferior to enoxaparin (European dosing regimen of 40mg daily was used compared to North American regimen of 30 mg twice daily) however, it was deemed inferior to enoxaparin when the North American dosing regimen was used. One fair quality study in THR showed dabigatran to be non-inferior to enoxaparin. All surgery prophylaxis studies included asymptomatic and symptomatic DVTs, in which the clinical utility of asymptomatic DVTs is unknown. Overall, the use of dabigatran for prophylaxis of DVT in patients undergoing THR and TKR has low level evidence to support its use.

Acute DVT Treatment

- There is one fair quality study of dabigatran use in the acute treatment of VTE (RECOVER), which demonstrated that dabigatran was noninferior to warfarin with similar rates of bleeding.

Cost Considerations:

Costs will be discussed in the executive session.

PDL Placement Recommendation:
There is low-moderate level of evidence to support the use of dabigatran in AF. The relative efficacy of dabiagatran compared to warfarin is still uncertain due to potential bias toward dabigatran as a result of an open-label study design. Sub-optimal INR control in the warfarin group in RE-LY suggests patients with well controlled INRs may not benefit from dabigatran treatment. It is recommended dabigatran be added to the PDL as a second line agent requiring prior authorization.

Data on using dabigatran for acute VTE is limited, however, due to limited oral anticoagulant options, dabigatran should be added to the PDL with a PA restriction for this indication as a second line option.

BACKGROUND/CURRENT LANDSCAPE
The vitamin K antagonist (VKA), warfarin, has served as the gold standard for oral anticoagulation and is a covered therapy for Oregon Health Plan (OHP) patients. Approximately 350 patients utilized long term anticoagulation (>45 days), representing over 2,000 prescription claims within the last six months within the OHP population. A meta-analysis for stroke prevention in patients with non-valvular AF found warfarin therapy to reduce stroke by 60%, which was 40% more efficacious than anti-platelet therapy.[12] The Cochrane Database for Systematic Reviews estimates that approximately 25 strokes and 12 disabling or fatal strokes would be prevented per year, for every 1000 primary prevention patients with AF treated with warfarin.[13] However, there is a significant clinical need for an alternative to warfarin for treatment and prophylaxis of numerous conditions that require anticoagulation. Warfarin has a narrow therapeutic index, drug and dietary interactions, variable pharmacokinetics, and unpredictable pharmacodynamic responses, resulting in reduced protection against thromboembolic events and potentially causing serious bleeds.[14] Consequently, warfarin is often underutilized, with only 64% of eligible patients taking warfarin therapy.[15] Even with optimal management, some patients do not achieve adequate INR control.

Patients with AF are at a four to five-fold increased risk of stroke and systemic embolism compared to those without AF. Annual rates of stroke in patients with AF are estimated to be between 3-8%, depending on additional risk factors.[16] Anticoagulants are a key component to managing patients with AF that are at an increased risk of stroke from cardioembolic events. Stroke risk in AF patients is most commonly estimated using the $CHADS_2$ risk stratification scheme. This scheme estimates stroke risk based on: presence of heart failure, presence of hypertension, age ≥75 years, presence of diabetes mellitus, and a history of previous stroke or transient ischemic attack (Table 1).[17] The greater the number of risk factors present, the greater the risk of stroke. Current CHEST guidelines recommend anticoagulation for patients with AF and suggest aspirin therapy for patients with up to one risk factor and treatment with a VKA for patients with one or more risk factors or in secondary prevention patients.[18] The guidelines also recommend VKA therapy for patients with a $CHADS_2$ score of ≥2.

Table 1. $CHADS_2$ Classification Scheme for Stroke Risk[17]

	Risk Factor	Points
C	Congestive Heart Failure	1
H	Hypertension	1
A	Age ≥75 years	1
D	Diabetes	1
S_2	History of stroke or TIA	2

Observed rates of venous thromboembolism(VTE) after total hip and knee replacement surgery occurs in approximately 5% of patients without recommended prophylactic anticoagulation. A recent guideline by the American Academy of Orthopaedic Surgeons gives a moderate recommendation for the use of prophylactic pharmacological agents for VTE prevention in those patients that are not at elevated risk. Due to insufficient evidence they are unable to recommend any particular preventative strategy or treatment duration.[19] The CHEST guidelines recommend at least 10 days of therapy and up to 35 days with either warfarin, low molecular weight heparin (LMWH), or fondaparinux for knee and hip replacement.[18] OHP covers all LMWH products, fondaparinux (Arixtra®) and desirudin (Iprivask®). In the previous six months approximately 200 patients received short term anticoagulation (<45 days) accounting for almost 200 prescription claims.

VTE is a serious medical condition that can lead to pulmonary embolism and related risk of morbidity and mortality.[20] CHEST guidelines recommend initial treatment with LMWH, unfractionated heparin (UFH) or fondaparinux for at least 5 days and initiation of warfarin on the first treatment day.[18] Discontinuation of heparin preparations should occur when the INR reaches 2.0 or more for at least 24 hours. For patients with DVT or PE secondary to a reversible risk factor, the guidelines recommend treatment with warfarin for 3 months. Treatment recommendations for patients with unprovoked DVT or PE include warfarin for at least 3 months and up to a year or longer based on clinical judgment.

CLINICAL PHARMACOLOGY

Dabigatran is a competitive, direct thrombin inhibitor with active metabolites (acyl glucuronides). Dabigatran inhibits free and clot-bound thrombin, as well as thrombin-induced platelet aggregation. During the common pathway of the coagulation cascade, thrombin is required for the conversion of fibrinogen to fibrin which is then cross-linked to form a thrombus. Inhibition of this transformation prevents the development of thrombi.[1]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints

All Studies:	All-cause Mortality
	Major bleeding
DVT:	Symptomatic DVT
DVT Prophylaxis:	PE
	Symptomatic DVT
AF:	Stroke

Study Endpoints:

RE-LY: Stroke or Systemic Embolism
RECOVER: VTE and Related death
REMOBILIZE, REMODEL, RENOVATE: Total VTE and All-cause mortality

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR/ NNH[3]	Quality Rating[4]; Comments
RE-LY[2,5]									
Connolly SJ, et al Phase III, RCT, PG	1. Dabigatran 110mg bid 2. Dabigatran 150mg bid 3. Warfarin adjusted to INR of 2-3	Age: 71 yrs Male: 64% Prior stroke/TIA: 20% $CHADS_2$: 2 Avg. TTR (warfarin): 64%	1. 6015 2. 6076 3. 6022	Median F/U 24 months	<u>Stroke or Systemic Embolism:</u> D 110mg: 182 (1.54%) W: 199 (1.71%) RR 0.90 95% CI 0.74 to 1.10, p<0.001 for noninferiority P= 0.30 for superiority D 150mg: 134 (1.11%) W: 199 (1.71%) RR 0.65 95% CI 0.52-0.81, p<0.001 for superiority <u>Stroke:</u> D 110mg: 171 (1.44%) W: 185 (1.57%) RR .92 95% CI 0.74 to 1.13 P=0.41 D 150mg: 122 (1.01%)	NS ARR 0.60% NNT 167 NS ARR 0.56%	<u>Major Bleeds:</u> D 110mg: 2.87% RR 0.80 95% CI 0.70 to 0.93 p=0.003 D 150mg: 3.32% RR 0.93 95% CI 0.81 to 1.07 p=0.32 W: 3.57%	ARR 0.7% NNH 142 NS	• Fair • Open-label design may bias results in favor of dabigatran • TTR for warfarin patients was 64% suggesting suboptimal warfarin use. • Major bleeds were less in dabigatran groups only in centers where TTRs were worse than median. • INR testing protocol was not clearly outlined. TTR has a direct effect on safety and efficacy. • Use in a broader patient population is needed to define MI risk, GI bleeding and effect of no antidote.

					W: 185 (1.57%) RR 0.64 95% CI 0.51 to 0.81 P<0.001 <u>All Cause Mortality:</u> D 110mg: 446 (3.75%) W: 487 (4.13%) RR 0.91 95% CI 0.80 to 1.03 P=0.13 D 150mg: 438 (3.64%) W: 487 (4.13%) RR 0.88 95% CI 0.77 to 1.00 P=0.051	NNT 179 NS NS			
RE-COVER[11]									
Schulman S, et al Phase III, RCT, DB, PG	1. Dabigatran 150mg bid 2. Warfarin adjusted to INR of 2-3 .	Age: 54 yrs Male: 58% Avg. TTR (warfarin): 60% <u>Inclusion:</u> Patients 18 or older with acute, symptomatic, objectively verifie proximal DVT of the legs or pulmonary embolism whom 6 mo. of anti-coagulation was deemed appropriate. <u>Exclusion:</u> Symptoms >14 days, PE with	1. 1273 2. 1266	Median F/U 5.5 months tx with 1 month F/U	<u>VTE or Related death:</u> D 150mg: 30 (2.4%) W: 27 (2.1%) HR 1.10 95% CI -0.65 to 1.84 p<0.001 <u>Symptomatic DVT:</u> D 150mg: 16 (1.3%) W: 18 (1.4%) HR 0.87 95% CI 0.44 to 1.71 <u>All Cause Mortality:</u> D 150mg: 21 (1.6%) W: 21 (1.7%) HR 0.98 95% CI 0.53 to 1.79	ARR 0.4% NNT 250	<u>Major Bleeding:</u> D 150mg: 20 (1.6%) W: 24 (1.9%) HR 0.82 95% CI 0.45 to 1.48 p=0.38	NS	• Fair • No protocol was given for INR testing. TTR for warfarin patients could influence efficacy and safety results • TTR for warfarin patients wa 60%.

		hemodynamic instability or requiring thrombolytics, additional warfari indication, high risk of bleeding, unstable CV disease, and renal and liver abnormalities							
RE-MOBILIZE[6]									
Ginsberg JS, et al Phase III, RCT, DB, PG	1. Dabigatran 220mg QD 2. Dabigatran 150mg QD 3. Enoxaparin 30mg BID (North American suggested dosing)	Age: 66 yrs Male: 43% Time to first dose: 9.5 hrs First dose of dabigatran. was ½ assigned dose <u>Inclusion:</u> Patients 18 and over undergoing primary elective unilateral knee arthroplasty <u>Exclusion:</u> Bleeding disorder uncontrolled htn, surgery, condition or medication predisposing pt. to bleeding, abnormal liver fxn renal insufficiency	1. 604 2. 649 3. 643	Median tx duration : 14 days F/U: 3 mo	<u>Total VTE + all-cause mortality:</u> D 220mg: 188 (31.1%) E: 163 (25.3%) RR 1.2 95% CI 1.0 to 1.5 D 150mg: 219 (33.7%) E: 163 (25.3%) RR 1.33 95% CI 1.1 to 1.6 <u>Nonfatal PE:</u> D 220mg: 6 (1.0%) E: 5 (0.8%) RR 1.3 95% CI 0.40 to 4.2 D 150mg: 0 (0%) E: 5 (0.8%)	NA NA NA	<u>Major Bleeding:</u> D 220mg: 5 (0.6%) E: 12 (1.4%) RR 0.42 95% CI 0.15 to 1.2 D 150mg: 5 (0.6%) E: 12 (1.4%) RR 0.42 95% CI 0.15 to 1.2		• Fair • Dabigatran deemed inferior due to exceeding non-inferiority margin • High number of patients (26 30%) excluded from analysis • Primary outcome was a composite endpoint including symptomatic and asymptomatic (venography). The importance and clinical relevance of asymptomatic DVT is unknown • No protocol given for VTE diagnosis • Concomitant use of ASA and selective cox-2 inhibitors allowed • Compression stockings allowed • Bilateral venography
RE-MODEL [7]									
Eriksson BI, et al	1. Dabigatran 220mg QD	Age: 68 yrs Male: 45% Time to first	1. 503	Median Tx duration: 8 days	<u>Total VTE + all-cause mortality:</u> D 220mg: 183 (36.4%)		<u>Major Bleeding:</u> D 220mg: 9 (1.5%) E: 9 (1.3%)		• Fair • Primary endpoint including

Phase III, RCT, DB, PG	2. Dabigatran 150mg QD 3. Enoxaparin 40mg QD (European suggested dosing for TKR)	dose: 3.5 hrs First dose of dabigatran was ½ assigned dose Inclusion: Patients 18 and older undergoing unilateral TKR Exclusion: Same as above	2. 526 3. 512		E: 193 (37.7%) RR 0.97 95% CI 0.82 to 1.1 D 150mg: 213 (40.5%) E: 193 (37.7%) RR 1.1 95% CI -0.23 to 0.1 Nonfatal PE: D 220mg: 0 (0%) E: 1 (0.1%) D 150mg: 1 (0.1%) E: 1 (0.1%) RR 0.98 95% CI 0.06 to 15.7 Symptomatic DVT: D 220mg: 1 (0.1%) E: 8 (1.2%) RR 1.0 95% CI 0.06 to 16 D 150mg: 1 (0.1%) E: 8 (1.2%) RR 0.37 95% CI 0.1 to 1.4		RR 1.1 95% CI 0.46 to 2.8 D 150mg: 9 (1.3%) E: 9 (1.3%) RR 0.99 95% CI 0.40 to 2.5		symptomatic and asymptomatic (venography). The importance and clinical relevance of asymptomatic DVTs is unknown • Excluded 25% of patients in primary outcome analysis • No protocol given for VTE diagnosis • Unclear if central adjudicators were blinded • Dosing regimen for enoxaparin is common in Europe for joint replacement but not in North America.
RE-NOVATE [8]									
Eriksson BI, et al Phase III, RCT, DB, PG	1. Dabigatran 220mg QD 2. Dabigatran 150mg QD 3. Enoxaparin 40mg QD	Age: 64 yrs Male: 44% Inclusion: Patients 18 and older undergoing unilateral THR Exclusion: Same as above	1. 880 2. 874 3. 897	Median Tx duration: 33 days Median f/u: 94 days	Total VTE + all-cause mortality : D 220mg: 53 (6.0%) E: 60 (6.7%) RR 0.90 95% CI 0.63 to 1.3 D150mg: 75 (8.6%) E: 60 (6.7%) RR 1.3 95% CI 0.93 to 1.8	NA	Major Bleeding: D 220mg: 23 (2.0%) E: 18 (1.6%) RR 1.3 95% CI 0.74 to 2.4 D 150mg: 15 (1.3%) E: 18 (1.6%) RR 0.83 95% CI 0.42 to 1.6		• Fair • Primary endpoint including symptomatic and asymptomatic (venography). The importance and clinical relevance of asymptomatic DVTs is unknown • Excluded 23% of patients in primary outcome analysis (mITT) • No protocol given for VTE diagnosis

					PE: D 220mg: 5 (0.4%) E: 3 (0.3%) RR 1.7 95% CI 0.40 to 7.0 D 150mg: 1 (0.1%) E: 3 (0.3%) RR 0.33 95% CI 0.03 to 3.2 Symptomatic DVT: D 220mg: 6 (0.5%) E: 1 (0.1%) RR 6.0 95% CI 0.73 to 50 D 150mg: 9 (0.8%) E: 1 (0.1%) RR 8.90 95% CI 1.1 to 70				• Dosing regimen for enoxaparin is common in Europe for joint replacement

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: TTR= time in therapeutic range

Study Details –

FDA approval of dabigatran was based on a phase III trial in 18,113 patients with AF, the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY).[2,5] RE-LY was a multi-center, multi-national, prospective, randomized, parallel group, non-inferiority trial comparing two blinded doses of dabigatran (110mg twice daily or 150 mg twice daily) with open-label warfarin with a target INR range of 2-3. Patients had at least one $CHADS_2$ risk factor. Median follow-up was two years and the primary endpoint of the trial was time to first occurrence of stroke (ischemic or hemorrhagic) or systemic embolic event (SEE). The primary safety outcome measure was major bleeding. Patients had similar baseline characteristics, with a mean age of 71, an average $CHADS_2$ score of 2.1 and 64% were male. Over half of the enrolled patients had been on previous long-term VKA therapy and the other half were treatment naïve to VKA.

There was low-strength of evidence from the RELY trial that dabigatran 110mg was non-inferior to warfarin for the primary endpoint of stroke or systemic embolism. There was also low-strength of evidence for dabigatran 110mg that incidence of stroke and all-cause mortality rates were similar to warfarin (RR 0.91; 95% CI, 0.80 to 1.03; p=0.13) with low-strength of evidence of reduced rates of major bleeding. There was low-strength of evidence that dabigatran 150mg was superior to warfarin for the primary endpoint of stroke or systemic embolism (RR 0.65; 95% CI, 0.52 to 0.81; p<0.001) and for the component outcome of stroke, with a NNT of 167 and 179, respectively. There was low-strength of evidence that dabigatran 150mg had similar rates of all-cause mortality compared to warfarin and no difference in major bleeding rates.

RELY was subject to a high risk of bias based on open-label warfarin arm as a comparator. The FDA cited this concern in their review but felt that because there was significant differences shown in the double-blind comparison between the dabigatran doses that this helped to substantiate the results.[3]

FDA analysis of RE-LY states that in patients whom INRs are well controlled, warfarin and dabigatran 150 mg twice daily carry the same risk of stroke or fatal events.[3] Additionally, the FDA associated the benefits in all-cause mortality rates in favor of dabigatran was driven by centers where TTR was worse than the median. The incidence of major bleeds and gastrointestinal bleeding decreased in the warfarin groups as TTR improved and major bleeds were less in dabigatran groups only at centers in which TTR was worse than the median. However, rates of intracranial bleeds were not affected by TTR, with consistently lower incidences in both dabigatran groups.[4] Intracranial bleeds were also the major contributor of the primary composite outcome.

Off-label Indications

Acute VTE Treatment

In RECOVER a non-inferiority study of dabigatran compared to warfarin for the acute treatment of VTE was done in over 2500 patients. Participants were randomly assigned in a blinded manner to dabigatran 150mg twice daily or warfarin, dose-adjusted to an INR of 2.0-3.0, after

initial treatment with parenteral anticoagulation (median duration of 9 days).[11] The primary outcome measure was the 6-month incidence of recurrent symptomatic, objectively confirmed VTE and related deaths. Noninferiority was determined for the hazard ratio with the predefined margin of 2.75 and the difference in risk with the predefined margin of 3.6 percentage points.

RECOVER had moderate-strength of evidence that dabigatran is noninferior to warfarin for the primary endpoint of VTE or related death. Additionally, there was moderate-strength of evidence that major bleeding rates were similar for dabigatran and warfarin.

The RE-COVER study showed dabigatran to be as effective as warfarin over a six month time period for acute treatment of VTE. Warfarin treated patients were noted to be in the therapeutic range only 60% of the time, which could overestimate the effectiveness of dabigatran in comparison. A statistically significant number of patients discontinued treatment in the dabigatran group compared to warfarin, suggesting clinically relevant issues with tolerability with long term use.

VTE Prevention

Dabigatran was studied for prevention of VTE after TKR in 5,266 patients in the RE-MOBILIZE and REMODEL studies.[6,7] In the RE-MOBILIZE study patients received either dabigatran 220mg or dabigatran 150mg once daily or enoxaparin 30mg twice daily (North American dosing regimen) in a randomized, double blind fashion for a mean treatment duration of 14 days. In the REMODEL study patients received dabigatran 150mg, dabigatran 220mg once daily or enoxaparin 40mg subcutaneous once daily (European dosing regimen) in a randomized, double blind design for a median treatment of 8 days. The primary efficacy outcome was the composite of total VTE events (symptomatic or venographic) and all-cause mortality.

The two studies had conflicting primary endpoint results, with RE-MOBILIZE having low-strength of evidence that dabigatran 220mg and 150mg doses were inferior to enoxaparin in the prevention of VTE after TKR. In the REMODEL study there was low-strength of evidence that showed both doses of dabigatran were non-inferior to enoxaparin. In respect to component endpoints, there was low-strength of evidence that enoxaparin had less distal DVTs. Major bleeding rates were low in both studies, with slightly higher rates with enoxaparin in REMOBILIZE and equal or less major bleeding with enoxaparin than dabigatran in the REMODEL study.

RE-NOVATE evaluated the efficacy of dabigatran for the prevention of VTE in patients undergoing THR compared to enoxaparin.[8] Patients received dabigatran 150mg, dabigatran 220mg once daily or enoxaparin 40mg subcutaneous once daily in a randomized, double blind design for a median duration of 33 days. The primary efficacy outcomes was the composite of total venous thromboembolism (venographic or symptomatic) and mortality from all causes.

There was low-strength of evidence that dabigatran was noninferior to enoxaparin for the primary outcome measure in THR. There was also low-strength of evidence of reduced VTE related mortality with dabigatran 220mg compared to enoxaparin, although not statistically significant. Data for major bleeding rates demonstrated a moderate-strength of evidence that dabigatran 220mg was associated with more major bleeding than enoxaparin and dabigatran 150mg was associated with less major bleeding.

High numbers of patients were excluded because of the inability to adequately assess thromboembolism by contrast venography. The primary outcome was a composite measurement of symptomatic and venographic data, in which asymptomatic DVTs accounted for the majority of the events. The clinical importance of asymptomatic DVTs has yet to be determined and a bias in detecting events may have been present to do unilateral instead of bilateral venography. Canadian Agency for Drugs and Technologies in Health (CADTH) preformed a systematic review and found no statistically significant differences between dabigatran and enoxaparin in the safety and efficacy endpoints when used for TKR and THR prophylaxis.[9] The Cochrane Database for Systematic Reviews also evaluated direct thrombin inhibitors (DTI) for the prevention of VTE following TKR and THR. They concluded that no difference was found when only symptomatic VTE events were compared between groups. They caution, that the occurrence rate of symptomatic VTEs are so low, that none of the studies enrolled enough participants for them to be powered appropriately to make this determination.[10] A sensitivity analysis on the timing of anticoagulation initiation was also performed, based on evidence that this variable may impact the effectiveness of therapy as much as the actual treatment itself. The analysis found that direct thrombin inhibitor treatment started before surgery, resulted in less VTEs than treatment started after surgery, in comparison with LMWH. The Cochrane report concludes that DTIs are considered equally effective to LMWH in the prevention of VTEs in patients undergoing TKR and THR, but, overall there is insufficient evidence to support the use of dabigatran in preference to LMWH.[10] The American Academy of Orthopedic Surgeons Guideline on Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty analyzed data on pharmacologic agents, including dabigatran, for the prevention of VTE and found no difference between treatments in regards to efficacy or safety.[19]

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications):

Active pathological bleeding and history of serious hypersensitivity reaction are contraindications to dabigatran therapy.[1]

Bleeding: Like all anticoagulants, dabigatran increases the risk of bleeding and can cause significant or even fatal bleeding in certain patients. The risk for bleeding increases with dose and when other drugs that also increase the risk of bleeding are used concurrently. These include anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of non-steroidal anti-inflammatory medications.[1,2]

Overall, the rate of major bleeding was comparable to active controls in the studies except for a lower rate for dabigatran 110mg in RE-LY. In the RE-LY trial, there was a lower rate of life-threatening bleeds, especially intracranial bleeds with the dabigatran group compared to warfarin, while rates of GI bleeds were more common with dabigatran. When patient's INR is within range >65.5% of the time, rates of major bleeds are higher with dabigatran 150mg treatment.[2] Also, in patient's >80 years of age, dabigatran 150 mg was associated with significantly more major bleeding events compared to warfarin.[2]

Myocardial Infarction: A higher number of myocardial infarctions were seen in the dabigatran groups compared to warfarin in the RE-LY trial.[2] According to the FDA's review of the data, the reason for the excess events is unclear and cannot be adequately explained by baseline characteristics or concomitant treatments.[3] Rates were not dose-dependent and could be more significant in a broader population.

Tolerability (Drop-out rates, management strategies):

Gastrointestinal events were the most frequently cited adverse event resulting in treatment discontinuation. The risk of dyspepsia with dabigatran therapy was highest within the first few weeks of treatment. Annual treatment discontinuation rates due to dyspepsia were higher with dabigatran compared to warfarin, 2% vs. 0.6%, respectively.[2] Overall dropout rates due to adverse events were also higher with dabigatran 150mg (21%) compared to warfarin (16%).[2]

Pregnancy/Lactation rating:
Dabigatran is Pregnancy Category C and has been shown to decrease the number of implantations and increase the number of dead offspring when used in female rats.[1,3] It is not known if dabigatran is excreted in human milk.[1]

Unanswered safety questions:
Revised data showed a higher incidence of MI in both dabigatran groups compared to warfarin but they were not statistically significant.[5] Cardiovascular effects will need to be followed as dabigatran is used in the general population to ensure there is no increased risk. Unlike warfarin, vitamin K administration will not reduce the anticoagulant effects of dabigatran in the event of a major bleed. While there is no antidote to dabigatran, administration of fresh frozen plasma, red blood cells, or dialysis are unproven options to reduce hemorrhagic complications.[1] Other questions include the safety of using tissue plasminogen activator in patients taking dabigatran.

Dose Index (efficacy/toxic):
For patients with a creatinine clearance (CrCl) >30 mL/min, the recommended dose of dabigatran is 150 mg twice daily without regards to meals. For patients with CrCl between 15-30mL/min, the recommended dose of dabigatran in 75 mg orally twice daily.[1] Use of dabigatran in patients with a CrCl <15 mL/min or on dialysis is not recommended[1]. In patients with moderate renal impairment(CrCl 30-50 mL/min), concomitant use of the P-gp inhibitor dronedarone or systemic ketoconazole would produce dabigatran concentrations similar to those with severe renal impairment. The manufacturer recommends reducing the dose to dabigatran 75mg twice daily.[1] It is not recommended to use dabigatran and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30mL/min). Dabigatran concentrations increase with severity of renal impairment, based on pharmacokinetic modeling.[21] No dose adjustment is necessary for patients with mild hepatic dysfunction.
Capsules must be swallowed whole. Chewing, crushing, breaking, or emptying the contents of the capsule can result in up to a 75% increase in oral bioavailability[1]. Once opened, the product should be used within 4 months and kept in its original bottle.[21] If a dose is missed, it should be taken as soon as possible, unless it is within six hours of the next scheduled dose, then the dose should be skipped.[1]

Initially, liver function tests were performed monthly, due to hepatoxicity related to another direct thrombin inhibitor, ximelagatran. At six months the safety monitoring board deemed this frequency of testing to be unnecessary as dabigatran therapy resulted in similar liver function test elevations as warfarin, 1.9% vs. 2.2%, respectively.[2]

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	First DataBank	ISMP	Clinical Judgment
LA/SA for dabigatran (generic)	None	None	None	None	Dalteparin
LA/SA for Pradaxa (brand)	None	None	None	None	Plavix Paclitaxel

					Procardia XL Prenexa

Common Drug-Related Adverse Events *[2]			
Adverse Events (1) **(MedDRA System Organ Class and Preferred Term)**	**Dabigatran 110 mg bid** **n (%)**	**Dabigatran 150 mg bid** **n (%)**	**Warfarin** **n (%)**
Number of Patients	**n=6015**	**n= 6076**	**n=6022**
Cardiac Disorders			
Chest Pain	312 (5.2)	377 (6.2)	357 (5.9)
Atrial Fibrillation	303 (5.1)	313 (5.2)	327 (5.5)
Gastrointestinal Disorders			
Diarrhea	330 (5.5)	357 (5.9)	349 (5.8)
Dyspepsia	707 (11.8)	688 (11.3)	348 (5.8)
Respiratory Disorders			
Cough	344 (5.7)	348 (5.7)	364 (6.0)
Dyspnea	557 (9.3)	580 (9.5)	586 (9.7)
Musculoskeletal Disorders			
Arthralgia	270 (4.5)	335 (5.5)	346 (5.7)
Back Pain	316 (5.3)	314 (5.2)	337 (5.6)
Nervous System Disorders			
Headache	457 (7.6)	458 (7.6)	554 (9.2)
Dizziness	486 (8.1)	506 (8.3)	568 (9.4)
Vascular Disorders			
Peripheral Edema	473 (7.9)	478 (7.9)	468 (7.8)
Other			
Fatigue	399 (6.6)	401 (6.6)	372 (6.2)
Nasopharyngitis	337 (5.6)	330 (5.4)	336 (5.6)

* Adverse events occurring in more than 5% of patients in dabigatran treatment groups.

DOSE & AVAILABILITY[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Dabigatran 150 mg	Capsule	Oral	Twice daily	CrCl 15-30mg/mL use elderly dosing	No change seen in moderate hepatic dysfunction	N/A	75mg twice daily*	May be taken with or without food Dabigatran 110mg dosage form used in studies is not available

* The 75 mg twice daily dose has not been studied. Concerns over dabigatran accumulation in patients with normal renal function have been raised. Patients with renal impairment may have a higher risk of drug accumulation and subsequent bleeding.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	3-7%*
Protein Binding	35%
Elimination	7% urine, 86% feces
Half-Life	12-17 hours
Metabolism	Conjugation to acyl glucuronides

* Do not crush capsules, bioavailability increases 75%.

ALLERGIES/INTERACTIONS

Drug-Drug:

Concomitant use of dabigatran with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should be avoided.[1] P-gp inhibition and impaired renal function are the most important risk factors that may cause increases in dabigatran concentrations[1] In clinical studies exploring the impact of dabigatran on other drug therapies, dabigatran did not meaningfully impact the pharmacokinetics of amiodarone, atorvastatin, clarithromycin, diclofenac, clopidogrel, digoxin, pantoprazole, or ranitidine.[1] In patients with moderate renal impairment, concomitant use of the P-gp inhibitor dronedarone or systemic ketoconazole would produce dabigatran concentrations similar to those with severe renal impairment. The manufacturer recommends reducing the dose to dabigatran 75mg twice daily.[21]

Food-Drug:

No food-drug interactions have been reported.[1]

Allergy/Cross Reactive Substances:

In the RE-LY trial, drug hypersensitivity was reported in <0.1% of patients. No cross-sensitivities have been reported.[1]

APPENDIX:

Oral Direct Thrombin Inhibitors

Goal(s):

- Promote safe and effective therapies for oral direct thrombin inhibitors.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Does the patient have a diagnosis of nonvalvular atrial fibrillation?	**Yes:** Go to #2	**No:** Go to #4
2. Will the prescriber consider a change to warfarin?	**Yes:** Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #3
3. Is the patient unable to take preferred oral anticoagulant,warfarin, due to one of the following: - unstable INR - warfarin allergy - contraindications to warfarin therapy - drug-drug interactions - intolerable side effects	**Yes:** Approve for 1 yr.	**No:** Deny. Recommend warfarin trial.
4. Does the patient have a diagnosis requiring acute or recurrent DVT treatment?	**Yes**: Go to #5	**No:** Deny (Medical Appropriateness)
5. Will the prescriber consider a change to a preferred anticoagulant?	**Yes:** Additional information can be found at:	**No:** Go to #6

	http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	
6. Is the patient unable to tolerate preferred anticoagulants due to one of the following: - allergy - contraindications to therapy - drug-drug interactions - intolerable side effects	**Yes:** Approve up to 1 year	**No:** Deny. Recommend trial of preferred anticoagulants.

REFERENCES

1. Pradaxa® Prescribing Information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. November 2010.
2. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation (RE-LY). N Engl J Med. 2009;361:1139-51.
3. Dabigatran, FDA Center for Drug Evaluation and Research. Summary Review Document. October 19, 2010. Accessed 6/13/11. www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000SumR.pdf
4. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalized ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet. 2010;376:975-83.
5. Connolly S, Ezekowitz M, Yusuf S, et al. Newly Identified Events in the RE-LY Trial. N Engl J Med 2010;363;1875-1876.
6. RE-MOBILIZE Writing Committee, Ginsberg JS, Davidson BL, Comp PC et al. Oral thrombin inhibitor dabigatran etexilate vs. North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. J Arthroplasty. 2009;24(1):1-9.
7. Eriksson BI, Dahl OE, Rosencher N, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost. 2007;5:2178-85.
8. Eriksson BI, Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for the prevention of venous thromboembolism after total hip replacement: a randomized, double-blind, non-inferiority trial. Lancet. 2007;370:949-956. (RE-NOVATE)
9. Ndegwa S, Moulton K, Argáez C. Dabigatran and Rivaroxaban versus Other Anticoagulants for Thromboprophylaxis After Major Orthopedic Surgery: Systematic Review of Comparative Clinical-Effectiveness and Safety. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.
10. Salazar, Carlos A, Malaga, German, Malasquez. Giuliana. Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement. The Cochrane Database of Syst Rev. 2011(3): CD005981.
11. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24):2342-52.
12. Hart R, Pearce L, Aguilar M. Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. Ann Intern Med. 2007;146:857-867.
13. Aguilar, M, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. The Cochrane Database of Syst Rev. 2009 (1): CD001927.
14. Coumadin® Prescribing Information. Bristol-Myers Squibb, Inc. Princeton, NJ. January 2010.
15. Birman-Deych E, Radford M, Nilasena D, et al. Use and Effectiveness of Warfarin in Medicare Beneficiaries with Atrial Fibrillation. Stroke. 2006;37:1070-1074.

16. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation. CHEST. 2008;133(6): 546S-592S.
17. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke. Results from the National Registry of Atrial Fibrillation. JAMA. 2001;2864-70.
18. Hirsh J, Guyatt G, Albers G, et al. Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133;71S-109S.
19. American Academy of Orthopaedic Surgeons. Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty Evidence-Based Guideline and Evidence Report, 2011. (Accessed October 27, 2011, at http://www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdf.)
20. Vardi M, Zittan E, Bitterman H, et al. Subcutaneous unfractionated heparin for the initial treatment of venous thromboembolism. Cochrane Database of Systematic Reviews. 2009, Issue 4.
21. Food and Drug Administration. Supplemental New Drug Application for Pradaxa. 11/09/2011. Accessed 11/20/2011. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/022512s007ltr.pdf.