Evidence Review

Topic: New Oral Anticoagulants

Background

Elective total hip arthroplasty (THA) and total knee arthroplasty (TKA) are associated with a high risk of postoperative venous thromboembolism(VTE), a serious and potentially fatal condition when it presents as deep vein thrombosis (DVT) or pulmonary embolism (PE)[1]. The current care path recommends anticoagulation with low molecular weight heparin (LMWH) or warfarin following THA or TKA for thromboprophylaxis. A review of the new oral anticoagulants has been requested for consideration for addition to the care path.

It is estimated that 40-60% of patients undergoing orthopedic surgery who do not receive prophylaxis will develop venographic DVT. DVT is often asymptomatic, and goes undetected; however up to 30% of venographic DVT will present in the proximal veins and may embolise and result in pulmonary embolism[2]. The use of heparin (enoxaparin, dalteparin), vitamin K antagonists (warfarin) and mechanical methods to prevent venous thromboembolism after major orthopedic surgery is now standard practice[3].

In 2008, Health Canada approved two new orally administered anticoagulants, dabigatran etexilate (Pradax) and rivaroxaban (Xarelto). Dabigatran etexilate (Pradax) was issued a notice of decision on June 10, 2008. It states: "Pradax is indicated for the prevention of venous throboembolic events (VTE) in patients who have undergone elective total hip replacement of total knee replacement surgery.[4]" On September 15, 2008, similar approval was issued for Rivaroxaban (Xarelto). There are other oral anticoagulants, including apixaban, in development, however have not been approved for use by Health Canada to date

Search Strategy

A search of the Cochrane Database of Systematic Reviews was conducted with the following search strategy:

Search Term: (oral anticoagulant).mp AND (arthroplasty OR hip OR knee OR orthopaedic OR orthopedic).mp

No Cochrane systematic review was found on dabigatran etexilate or rivaroxaban use following elective THA or TKA.

Search for non-Cochrane reviews and RCTs.

A Search for RCTs was performed on MEDLINE, EMBASE and International Pharmaceutical Abstracts databases. The search was limited to English language studies published in 2005 or later. The following selection criteria were used:

Specific search strategies:

Search Term: ABJHI Arthroplasty Search (See Appendix 1) AND (Rivaroxaban OR Dabigatran OR apixaban OR oral anticoagulant)

Study Inclusion Criteria

The selection criteria for included studies were as follows:

- RCTs and reviews for approved oral anticoagulants
- Studies available electronically
- Studies with publication dates of 2005 or later
- Studies limited to English-language reporting

Study Exclusion Criteria

The selection criteria for excluded studies was as follows:

- Ex Vivo studies

Evidence Selected

Of the articles retrieved, five were RCTs related to dabigatran of which one was omitted for its focus on ex vivo results. Nine Rivaroxaban RCTs were obtained and are reviewed here. One trial related to apixaban was retrieved but those findings are not presented here as it is not approved for use at this time.

Ten review articles and two "expert opinion" letters were retrieved in the search but will not be presented here. These papers have been cited to recognize the contextual contribution of these works to the writer.

Results

Dabigatran

Eriksson et al. 2005[5] compared dabigatran 50, 150, 225 mg twice daily (BID) and 300mg once daily (QD) started 1-4 hours post surgery with the European enoxaparin dosing regimen, 40 mg daily, started 12 hours pre surgery in THA and TKA patients. The primary endpoint was VTE incidence detected by venography or symptomatic events.

A significant dose-dependent decrease in VTE frequency was identified with increasing dabigatran dose. There was no significant difference between the 150 mg BID and 300mg QD groups with respect to VTE. Compared to enoxaparin, three of the four dosing groups, 150, 225 BID and 300 mg QD, resulted in significantly fewer occurrences of venographic VTE. A post hoc analysis of administration time indicated significantly lower VTE when dabigatran was given within 2 hours following of surgery compared to when given outside of 2 hours. Major bleeding episodes for dabigatran doses of 150, 225 mg BID and 300 mg QD were significantly increased when compared to the 50 mg BID dabigatran dose. A non-significant trend toward increase bleeding was identified when these doses were compared to enoxaparin.
The authors conclude that this study demonstrated a dose relationship for both efficacy and safety with an optimal dabigatran dosing range of 100-300mg QD.

Eriksson et al (2007)[6] REMODEL, Ginsberg et al (2009)[7] RE-MOBILIZE and Eriksson (2007)[8] RE-NOVATE dabigatran studies are reviewed together in light of the methodological similarities on the following measures:

- Primary efficacy endpoint - composite of total VTE events (symptomatic or venographic DVT, symptomatic PE) and all cause mortality during treatment
- Secondary efficacy endpoint - composite of major VTE (includes proximal DVT, PE), and VTE-related mortality; proximal DVT; incidence of total VTE and all-cause mortality during follow-up; and the individual components of the primary efficacy outcome
- Primary safety outcome – incidence of bleeding events (major = fatal, clinically overt, requiring treatment cessation – did include surgical site bleeding)

These studies allowed for the simultaneous use of aspirin, selective cyclooxygenase 2 inhibitors and compression stockings. Intermittent compression devices were prohibited.

A common limitation was the inability to obtain and adjudicate venography for approximately 30% of patients who were not available.

In the REMODEL study[6], dabigatran 220 or 150 mg QD started 1-4 hours post op was compared to the European dosing regimen for enoxaparin 40 mg QD beginning pre surgery in TKA patients. Medication was continued for 6-10 days followed by venography. The primary endpoint occurred in 36.4% and 40.5% of Dabigatran 220 and 150 mg groups respectively, and in 37.7% of the enoxaparin group. The secondary endpoint occurred in 2.6% and 3.8% of dabigatran 220 and 150 mg group respectively and in 3.5% of the enoxaparin group. Both doses of dabigatran were found to be non inferior to enoxaparin.
Bleeding rates were not statistically different with 1.5% and 1.3% of the dabigatran 220 and 150mg groups respectively and in 1.3% of the enoxaparin group. There did not appear to be any significant safety concerns.

The RE-MOBILIZE study[7] also compared dabigatran to enoxaparin in TKA patients. Patients received either dabigatran 220 or 150mg QD beginning with a half dose 6-12 hours post-op, or enoxaparin 30mg BID started 12-24 hours post-op. Treatment continued for 12-15 days and venography was completed within 12 hours of the final dose. The treatment period was defined as the time from first dose to 3 days following the final dose. Patients were followed for three months.
In this study, dabigatran failed to show non-inferiority to enoxaparin. The primary endpoint was observed in 31.1% and 33.7% of the dabigatran 220 and 150 mg groups respectively and in 25.3% of the enoxaparin patients. The secondary endpoint occurred in 3.4% and 3.0% of the 220 and 150mg dabigatran groups respectively and 2.2% in the enoxaparin group. There was no significant difference found with respect to bleeding events with 0.6% for both dabigatran doses and 1.4% enoxaparin.
The authors suggest that the failure of dabigatran to demonstrate efficacy in this trial may be due to the delayed start time for administration of dabigatran from 1-4 hours in the REMODEL study to 6-12 hours in RE-MOBILIZE. The longer duration of medication, 6-10 days versus 12-15 days, may have had a greater positive impact on enoxaparin leading to the identification of dabigatran as inferior in the RE-MOBILIZE protocol.

The RE-NOVATE study[8] compared dabigatran 220 or 150 mg QD started 1-4 hours post op to the European dosing regimen of Enoxaparin, 40mg QD started pre surgery, in the THA patient population. Treatment duration was 28-35 days followed by venography. Treatment period defined as the first dose to three days after final dose.
Both doses of dabigatran showed non inferiority to enoxaparin with respect to reducing the risk of total venous thromboembolism and all cause mortality after hip replacement. There was no significant difference with respect to major venous VTE and VTE related mortality or major bleeding rates with 2.0% and 1.3% for the 220mg and 150mg dabigatran groups compared to 1.6% for the enoxaparin group. Six deaths occurred in the dabigatran group, compared to none in the enoxaparin group, although none were thought to be related to the treatment drug.
The authors noted that the frequency of VTE was reduced in comparison to prior dabigatran studies where medication administration was for shorter duration (5-11 days) and propose extended duration use be considered. The authors indicated that the lower bleeding rates in this study compared to REMODEL and REMOBILIZE may be due to the reduction in the first dose of dabigatran. The authors conclude that the given the absence of major bleeding post discharge, indicates "…safety of use in an outpatient setting".

One additional study was obtained related to dabigatran but it is excluded from this review as it focus on ex vivo outcomes[9].

Rivaroxaban

Of the Rivaroxaban studies reviewed methodological similarities were identified on the following measures::

- Primary efficacy endpoint was DVT, PE or all-cause mortality
- Secondary efficacy endpoint was defined as major VTE and symptomatic VTE
- Primary safety outcome was major bleeding (not including surgical site bleeding) **study did not include bleeding leading to treatment cessation, or surgical site bleeding unless these events led to reoperation or fatality**

Turpie et al. (2005)[10] compared BAY 59-7939 (rivaroxaban) 2.5, 5, 10, 20 and 30 mg BID started 6-8 hours and the North American Dosing Regimen of Enoxaparin, 30 mg BID started 12-24 hours after TKA .
There was no significant dose relationship for efficacy of BAY 59-7939 with the primary outcome observed in 31.75%, 40.4%, 23.3%, 35.1%, and 25.4% of the 2.5,5,10 20 and 30mg BID doses respectively. Enoxaparin obtained the primary endpoint in 44.3% of cases. The secondary endpoint occurred in 3.2%,5.3%,6.7%,3.5% and 0% of the 2.5,5,10 20 and 30mg BID BAY 59-7939 dosing groups respectively and in 4.3% of enoxaparin cases.
A significant dose relationship was evident for BAY 59-7939 with major bleeding occurring in 1.0, 0, 1.9, 3.1 and 7.5% of the 2.5,5,10 20 and 30mg BID BAY 59-7939 dosing groups respectively. Major bleeding occurred in 1.9% of the enoxaparin cases. Adverse events also increased as BAY 59-7939's dose increased.
This 2005 study was used to establish a potential optimal dose **range of 2.5-10mg.**

Eriksson et al. (2006)[11], a second dose escalation study, compared BAY 5979-39 (rivaroxaban) 2.5, 5, 10, 20, or 30 mg BID doses started 6-8 hours post surgery to enoxaparin 40mg QD started pre surgery in THA patients. Treatment continued until venography at 5-9 days post surgery. Patients were seen in follow up 30-60 days after the final dose. Based on a regulatory request, the BAY 5979-39 30mg BID group was suspended prior to study completion.
There was no statistical evidence to support a dose-response relationship between BAY 5979-39 and the primary efficacy endpoint. The primary endpoint occurred in 15.4%, 13.8, 11.9%, 18.2% and 6.9% of the 2.5, 5, 10, 20 and 30mg BID groups respectively. Enoxaparin achieved the primary endpoint in 17.0% of cases which was not significantly different than any of the BAY 5979-39 doses. The incidence of the secondary efficacy endpoint for BAY 59-7939 doses 2.5, 5, 10, 20 and 30mg BIG was 2.9%, 0.9%, 1.0%, 3.0%, and 3.4% which compared favorably to enoxaparin with 4.7%.
There was a significant dose trend toward increased major post operative bleeding with incidence of major bleeding observed in 0.8%, 2.2%, 2.3%, 4.5%, and 5.4% of the 2.5,5,10, 20 and 30mg BID BAY 5979-39 doses respectively. Major bleeding occurred in 1.5% of the enoxaparin group. The incidence of serious adverse events also increased with dosing of BAY 59-7939.
Although there was no significant dose trend toward increased efficacy, there was a significant trend toward increased bleeding. The authors concluded, "…the wide therapeutic window demonstrated for BAY 59-7939 suggests that it would have a potentially favorable risk-benefit ratio in clinical practice."

A third dose escalation study, Eriksson et al (2007)[12], compared Rivaroxaban 2.5, 5, 10, 20 and 30mg BID started 6-8 hours post surgery, rivaroxaban group 30mg QD started 6-8 hours post surgery and Enoxaparin 40mg QD started pre op in THA patients. Medication continued until venography at day 5-9 with patients returning within 30-60 days for follow-up.
The primary endpoint occurred in 22.2%, 23.8%, 20.0%, 10.2% and 17.4% of the rivaroxaban 2.5,5,10, 20and 30 mg BID dose groups respectively. In those who received rivaroxaban 30mg QD, the primary endpoint occurred in 15.1%. The enoxaparin group had 16.8% occurrence rate of the primary endpoint. There was no statistically significant dose relationship with respect to the primary end point.
The secondary efficacy endpoint did demonstrate a significant dose-relationship. Lower VTE rates were associated with rivaroxaban dosing of 10mg BID or greater.
Major bleeding increased as the rivaroxaban dosage increased. No other significant adverse events were noted.
The authors conclude that once daily dosing appears feasible and efficacious for VTE prevention. They recommend further study to establish dosing and delivery regime.

The final dosing escalation study reviewed, Eriksson et al. (2006)[13], compared rivaroxaban 5, 10, 20, 30, and 40 mg QD administered 6-8 hours post surgery to enoxaparin 40mg QD started pre op in THA patients. Drugs were continued pending venography results on day 5-9.
The primary endpoint occurred in 14.9%, 10.6%, 8.5%, 13.5% and 6.4% of patients receiving rivaroxaban 5, 10, 20, 30 and 40 mg respectively and 25.2% of enoxaparin patients. The trend towards increased efficacy did not reach statistical significance. The secondary efficacy endpoint did reach statistical significance with occurrence in 8.5%, 2.7%, 0.9%, 1.9% and 1.1% of the rivaroxaban 5, 10, 20, 30 and 40 mg groups respectively. The enoxaparin group experienced the secondary endpoint in 2.8% of patients.
There was also a significant dose trend for major post operative bleeding observed in 2.3%, 0.7%, 4.3%, 4.9% and 5.1% of patients receiving rivaroxaban 5, 10, 20, 30 or 40mg respectively. Enoxaparin 40mg demonstrated 1.9% major bleeding.
The authors compared this study to Turpie et al. (2006)[11] and suggested that rivaroxaban 10mg QD appears to be the most appropriate dose for further investigation.

Turpie et al. (2009)[14] compared rivaroxaban 10mg QD beginning 6-8 hours after surgery to the North American Enoxaparin dosing regimen, 30mg BID starting 12-24 hours post surgery, in the TKA patients population. Medication continued until venography at day 11-15. Treatment was followed for 30-35 days following final dose.
Rivaroxaban demonstrated superiority with respect to the primary endpoint with incidence in 6.7% of patients versus 9.3% of enoxaparin patients. Bleeding events occurred more often in the rivaroxaban group at 0.7% versus 0.3% with enoxaparin, however the difference was not statistically significant. No other safety concerns were identified.
The authors suggested further investigation to establish appropriate timing of initial Rivaroxaban dose.

Eriksson et al. (2008)[15], the RECORD 1 study, compared rivaroxaban 10mg QD started 6-8 hours post surgery to enoxaparin 40mg QD started pre surgery with dosing continued for 35 days in THA patients. Follow up visit occurred 30-35 days following final dose.

Rivaroxaban demonstrated superiority to enoxaparin with the primary endpoint observed in 1.1% of the rivaroxaban versus 3.7% of the enoxaparin intention-to-treat populations. Superiority of the secondary efficacy endpoint was reported with 0.2% occurrence in the rivaroxaban group compared to 2.0% of the enoxaparin patients. Major bleeding was similar with 0.3% in the rivaroxaban group and 0.1% in the enoxaparin group. Other adverse events were similar between both groups.

Kakkar et al. (2008)[16], the RECORD 2 study, compared rivaroxaban 10mg QD started 6-8 hours post op and continued for 31-39 days to enoxaparin 40mg QD stared pre surgery and continued for 10-14 days in THA patients. Patients were followed for 30-35 days after final dose.
Long term rivaroxaban was superior to enoxaparin with respect to the primary endpoint, with occurrences in 2.0% of rivaroxaban patients and 9.3% of enoxaparin patients, as well as the secondary endpoint with occurrences in 0.6% of rivaroxaban patients and 5.1% of enoxaparin patients. There was an extremely low occurrence of major bleeding, 0.1% for both groups, which was likely due to the definition of major bleeding. When major bleeding and clinically relevant non-major bleeding were combined, 3.4% of rivaroxaban patients had events compared to 2.8% of enoxaparin patients. Rivaroxaban patients had more cardiovascular adverse events at 0.7% compared to 0.3% of enoxaparin patients.
A limitation of RECORD 2 was fewer venograms were completed then anticipated and therefore further safety study is warranted in relations to bleeding risk and other adverse events.

Lassen et al. (2008)[17], the RECORD 3 study, compared rivaroxaban 10mg QD started 6-8 hours post op to the European enoxaparin dosing regimen, 40mg QD started pre surgery, in the TKA patient population.
Rivaroxaban was superior to enoxaparin with respect to the primary endpoint with occurrences in 9.6% of rivaroxaban patients versus 18.9% of enoxaparin patients. The secondary endpoint occurred in 1.0% of rivaroxaban patients versus 2.6% of the enoxaparin group. Major bleeding rates were low and similar at 0.6% for rivaroxaban versus 0.5% for enoxaparin patient groups. There were no significant differences in adverse events identified.

Eriksson et al. (2009)[18] completed a pooled analysis of the RECORD 1, 2 and 3 studies which showed that rivaroxaban significantly reduced the occurrence of the primary and secondary endpoints when compared to enoxaparin. The incidence of major bleeding, other bleeding and adverse events were similar.

Reviews and Opinions

This section presents some of the expert views regarding anticoagulation prophylaxis in elective arthroplasty. Information was obtained through both published reviews and consultation with local experts.

In general, the potential advantages of new oral anticoagulants are well documented including predictable action, dose-proportional pharmokinetics, rapid onset of activity, once-daily oral dosing, with no need for monitoring, no need for dose adjustment based on weight, gender, race etc[19,20]. Oral prophylaxis may provide increased convenience for patients and health care providers resulting in increased efficiency. However, the clinical trial results presented should be prefaced with some critical factors[21].

Haas et al. (2008)[22] identified the major challenge in clinical decision-makings related to anticoagulation:
"…**the use of anticoagulants requires the constant balancing of the risk of clots against the risk of bleeding."**
As such, studies have examined both efficacy and safety factors. However, the choice of venographic DVT for the primary efficacy endpoint has been criticized. Many surgeons indicate this measure correlates poorly with prevalence of death and symptomatic PE. As a result, these methodologies "…**generally favor aggressive pharmacologic prophylaxis…"**[22]**,** which surgeons relate to an increased prevalence of prolonged wound drainage.
The selection of venographic DVT has also been criticized for resulting in the exclusion of a large portion of patient results[23,16]. Although statistical analysis was undertaken to control for decreased outcome measures, a decrease in reliability of findings is possible.
The primary safety outcome - major bleeding – has been defined specifically within each study protocol. In some cases, the major bleeding definition appeared restrictive. Eriksson et al. (2008)[18] confirms the definition of major bleeding used across the RECORD trials "**excluded wound-related bleeding events, unless they led to a reoperation**"
Potentially confounding factors were identified as additional prophylactic anticoagulation methods such as aspirin[5] (BISTRO), and COX2 inhibitors[8,6] were permitted[21].

In 2004, Europe approved an oral anticoagulant (ximelagatran) for prophylactic use in arthroplasty. The medication was not approved by the FDA with liver toxicity and additional averse event rates (myocardial infarction, excess of death and PE during follow-up) cited as reasons for non-approval[24]. Long term impacts on liver function related to the currently approved oral anticoagulants are unknown.
Some authors have suggested further study to explore dosing related to weight, age, and renal status, as well as the possible interaction with other medications (NSAIDS)[21,25,26]. The lack of antidote and the difficulties associated with an oral administration method due to the potential for post-operative nausea are factors to consider. Mahaffey et al. (2006)[27] questioned the decision to proceed with phase III trials using the 10mg rivaroxaban dose. The author suggested examining both 5 and 10 mg doses to identify the most favorable risk-benefits profile.
In clinical practice, pre-operative assessment of bleeding and clotting risk is should be undertaken[21,22]. Care options, including treatment risks and benefits, should be discussed with patients in order to establish an appropriate, effective and acceptable treatment plan. One local expert suggested one available treatment option might be utilization of parenteral medications during inpatient period with oral medications prescribed upon at discharge thereby avoiding the possible difficulties of post-operative nausea and as well as the need for teaching parenteral injection methods to patients.

In 2008, orally administered anticoagulants were approved for prevention of VTE in elective hip and knee replacement patient. Currently, there is little published evidence regarding the either the early results of these methods or the long term health impacts. Local experts have indicated that active work is being done to gain approval for additional oral anticoagulant options (i.e. apixiban) as well as work to assess the risk-benefit profiles of the current chemical anticoagulant options.

Summary of Dabigatran Findings

Study	Dosing Regimens	Primary	Secondary	Bleeding Events		Summary Findings
				Major	Minor	
Ginsberg et al (2009)[7] RE-MOBILIZE	D 150mg QD D 220mg QD E 30 mg BID (D starts 6-12 hrs post; E starts 12-24 hrs post)	33.7% 31.1% 25.3%	3.0% 3.4% 2.2%	0.6% 0.6% 1.4%	2.7% 2.5% 2.4%	D failed to show non inferiority wrt primary and secondary efficacy measures No significant difference wrt bleeding events
Eriksson (2007)[8] RE-NOVATE	D 220mg QD D 150mg QD E 40mg QD (D start 1-4 hrs post; E starts pre op) Duration 28-35 days	6.0% 8.6% 6.7%	3.1% 4.3% 3.9%	2.0% 1.3% 1.6	6.1% 6.2% 6.4%	D (150 and 220mg) showed non inferiority to E wrt primary efficacy No significant difference wrt secondary efficacy No significant difference wrt bleeding
Eriksson et al (2007)[6] RE-MODEL	D 220mg QD D 150mg QD E 40mg QD (D starts 1-4 hrs post; E starts pre op)	36.4% 40.5% 37.7%	2.6% 3.8% 3.5%	1.5 1.5 1.3	8.8 6.8 5.3	Both D doses showed non inferiority to E No safety differences identified

Primary Efficacy Measure =composite of total VTE events (symptomatic or venographic DVT and symptomatic PE) and all cause mortality
Secondary Efficacy Measure = composite of major VTE (proximal DVT, PE, VTE related mortality); proximal DVT, incidence of total VTE; incidence of all-cause mortality during follow-up; the individual components of the primary efficacy outcome
D = Dabigatran
E = Enoxaparin

Summary of Rivaroxaban Findings

Study	Dosing Regimens	Primary	Secondary	Major Bleeding	Summary Findings
Eriksson et al (2007)[12]	R 2.5mg BID R 5mg BID R 10mg BID R 20mg BID R 30mg BID R 30mg QD E 40mg QD R start 6-8 hrs post E start pre surgery Duration 5-9 days	22.2% 23.8% 20.0% 10.2% 17.4% 15.1% 16.8%	11.1% 7.9% 3.6% 0% 4.3% 1.4% 4.7%	0% 2.5% 2.9% 6.5% 10.8% 4.5% 0%	Significant dose response relationship identified between R and major VTE. Correlation between major bleeding and increased dose.
Eriksson et al (2006)[11]	R 2.5 mg BID R 5 mg BID R 10 mg BID R 20 mg BID R 30 mg BID E 40 mg QD R start 6-8 hrs post, E start pre Duration 5-9 days	15.4 13.8 11.9 18.2 6.9 17.0	2.9 0.9 1.0 3.0 3.4 4.7	0.8 2.2 2.3 4.5 5.4 1.5	No dose response relationship for efficacy. Dose trend toward increased bleeding.
Eriksson et al (2006)[13]	R 5mg QD R 10mg QD R 20mg QD R 30mg QD R 40mg QD E 40mg QD R start 6-8 hrs post E start pre Duration 5-9 days	14.9 10.6 8.5 13.5 6.4 25.5	8.5 2.7 0.9 1.9 1.1 2.8	2.3 0.7 4.3 4.9 5.1 1.9	No significant dose response relationship wrt primary outcome. Significant dose response wrt secondary outcome. Significant rent to increased bleeding with increased dose.
Turpie et al (2005)[10]	R 2.5mg BID R 5 mg BID R 10mg BID R 20mg BID R 30 mg BID E 30mg BID R start 6-8 hrs post E start 12-24 post Duration 5-9 days	31.7 40.4 23.3 35.1 25.4 44.3	3.2 5.3 6.7 3.5 0 4.3	1.0 0 1.9 3.1 7.5 1.9	No significant dose relationship for efficacy. Significant trend toward increase bleeding with increased dose.

Summary of Rivaroxaban Findings, continued

Study	Dosing Regimens	Primary	Secondary	Major Bleeding	Summary Findings
Turpie et al (2009)[14]	R 10mg QD E 30mg BID R start 6-8 hrs post E start 12-24 post Duration 11-15 days	6.7% 9.3%	1.1% 1.5%	0.7% 0.3%	R demonstrated superior efficacy. No significant difference in bleeding
Eriksson et al (2008)[15] RE-CORD 1	R 10mg QD E 40mg QD R start 6-8hrs post E start pre surgery Duration 35 days	1.1% 3.7%	0.2% 2.0%	0.3% 0.1%	R superior wrt primary and secondary outcomes. Similar bleeding rates.
Kakkar et al. (2008)[16] RE-DORD 2	R 10mg QD E 40mg QD R start 6-8hrs post for 31-39 days E start pre surgery for 10-14 days	2.0% 9.3%	0.6% 5.1%	3.4% 2.8%	Long term R superior to short term E wrt primary and secondary outcomes
Lassen et al (2008)[17] RE-CORD 3	R 10 mg QD E 40 mg QD R start 6-8 hrs post E start pre surgery Duration 10-14 days	9.6% 18.9%	1.0% 2.6%	0.6% 0.5%	R superior wrt primary outcome. Similar bleeding rates.
Eriksson et al (2009)[18]	Pooled analysis of RE-CORD 1,2,3 studies				R reduced primary and secondary outcomes with similar bleeding and adverse event rates.

Primary Efficacy Measure = DVT, PE or all-cause mortality
Secondary Efficacy Measure = major VTE and symptomatic VTE
R = Rivaroxaban
E = Enoxaparin

Clinical Committee Comment

On October 15, 2009 the Hip and Knee Clinical Committee discussed the findings of this evidence review. Committee members agreed that the evidence was not strong enough to support the addition of new oral anticoagulants, specifically dabigatran and rivaroxaban, to the Hip and Knee Care Path. Additionally, neither dabigatran or rivaroxaban have been added to other published guidelines, such as the "Prevention of Pulmonary Embolism in Patients Undergoing Total Hip or Knee Arthroplasty" published by the American Academy of Orthopaedic Surgeons (AAOS). Committee members agreed to exclude new oral anticoagulants from the 2009 Hip and Knee Care Path release.

Care Path Recommendation

For the 2009 Hip and Knee Care Path release, new oral anticoagulants, specifically dabigatran and rivaroxaban, will not be recommended for use.

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Appendix 1 - ABJHI Hip/Knee Arthroplasty Search

1. exp *Arthroplasty, Replacement, Knee/
2. exp *Arthroplasty, Replacement, Knee/ae, mo, cl, nu, ct, px, ec, rh, ed, st, hi, sn, is, td, lj, ut, mt
3. 1 not 2
4. exp *Arthroplasty, Replacement, Hip/
5. exp *Arthroplasty, Replacement, Hip/ae, mo, cl, nu, ct, px, ec, rh, ed, st, hi, sn, is, td, lj, ut, mt, ve
6. 4 not 5
7. exp *Arthroplasty, Replacement, Knee/ae, mo, px, ec, rh, st, sn, td, ut
8. exp *Arthroplasty, Replacement, Hip/ae, mo, px, ec, rh, st, sn, td, ut
9. exp *Hip Prosthesis/
10. exp *Hip Prosthesis/ae, nu, cl, px, ct, rh, ec, st, ed, sn, hi, sd, is, td, mt, ut, mi, ve, mo
11. 9 not 10
12. exp *Hip Prosthesis/ae, px, rh, ec, st, sn, td, ut, mo
13. exp *Knee Prosthesis/
14. exp *Knee Prosthesis/ae, ps, cl, px, ct, rh, ec, st, hi, sn, is, sd, mt, td, mi, ut, mo, ve, nu
15. 13 not 14
16. exp *Knee Prosthesis/ae, px, rh, ec, st, sn, td, ut, mo
17. "hip replacement$".ti,ab.
18. ("knee replacement$" or "total joint arthroplast$").ti,ab.
19. (hip adj3 arthroplast$).ti,ab.
20. (knee adj3 arthroplast$).ti,ab.
21. 3 or 6 or 7 or 8 or 11 or 12 or 15 or 16 or 17 or 18 or 19 or 20
22. exp *ARTHROPLASTY/
23. exp *ARTHROPLASTY/ae, mo, cl, nu, ct, px, ec, rh, ed, st, hi, sn, is, td, lj, ut, mt, ve
24. 22 not 23
25. exp *ARTHROPLASTY/ae, mo, px, ec, rh, st, sn, td, ut
26. exp *OSTEOARTHRITIS/su
27. exp *prosthesis failure/su or exp *reoperation/
28. 24 or 25 or 26
29. exp hip/ or exp hip joint/ or exp knee/ or exp knee joint/
30. (hip or hips or knee or knees).ti,ab.
31. 29 or 30
32. 28 and 31
33. *orthopedics/
34. 21 or 32 or 33
35. limit 34 to animals
36. limit 34 to (animals and humans)
37. 35 not 36
38. 34 not 37

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is a standard of bone and joint health and health care that is the best in the world – a standard others will want to emulate.

Our mission

is to be the leading agent for continuous improvement in bone and joint health and health care.

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