New oral anticoagulants: One Step Closer to Replacing Warfarin

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Introduction

Anticoagulants are widely used for the prevention and treatment of venous and arterial thrombosis. The main indications for long-term anticoagulation therapy include treatment of venous thromboembolism (VTE), stroke prevention in atrial fibrillation (AF) and the prevention of valve thrombosis in patients with mechanical heart valves. For the past 65 years, vitamin K antagonists (VKA), such as warfarin, have been the only available oral anticoagulants. In North America, it is estimated that at least 2.5 million people receive warfarin each year for prevention of thromboembolism on the background of atrial fibrillation or mechanical heart valves [1]. Although effective, warfarin has multiple limitations that result in its underuse in eligible patients with atrial fibrillation. These limitations have prompted the development of new oral anticoagulants that target factor Xa or thrombin. Concentrating on these new drugs, this paper (a) outlines the limitations of warfarin, (b) describes how the new oral anticoagulants overcome these limitations, (c) reviews the pharmacology of the factor Xa and thrombin inhibitors, (d) describes the results of the clinical trials with the new oral anticoagulants, and (e) provides perspective on how these drugs will streamline long-term anticoagulant therapy.

Limitations of Warfarin

Although effective, warfarin has numerous drawbacks (Table 1). First, its onset of action is delayed. Consequently, warfarin must be overlapped with a parenteral anticoagulant, such as heparin or low-molecular-weight heparin (LMWH), until it produces a therapeutic anticoagulant response. Second, warfarin dose requirements vary from patient to patient. This variability reflects, at least in part, common genetic polymorphisms in enzymes responsible for warfarin metabolism. In addition, dietary intake of vitamin K and numerous drugs also influence warfarin metabolism and lead to a decrease or increase in its pharmacological effect. Because of this variability, monitoring of the international normalized ratio (INR) and frequent dose adjustments are necessary to maintain a therapeutic anticoagulant response. Such monitoring is inconvenient for patients and physicians and costly for the healthcare system [2].
Advantages of the New Oral Anticoagulants

The new oral anticoagulants target either factor Xa or thrombin, key enzymes involved in thrombin generation or fibrin formation, respectively. The advantages of these drugs over warfarin include a rapid onset of action, a predictable anticoagulant response that is minimally affected by food, and a low potential for drug-drug interactions. These properties permit administration of fixed doses without the need for coagulation monitoring [3,4].

From a mechanistic standpoint, the oral factor Xa inhibitors have a potential advantage over parenteral factor Xa inhibitors, such as heparin, LMWH or fondaparinux. The parenteral drugs are indirect inhibitors of factor Xa that exert their anticoagulant activity by binding to antithrombin in the plasma and accelerating its interaction with factor Xa. Although these agents inhibit free factor Xa, factor Xa incorporated within the prothrombinase complex is relatively protected from inhibition by the antithrombin/heparin complex [5]. In contrast, oral factor Xa inhibitors, which bind directly to factor Xa and block its active site, inhibit free factor Xa and factor Xa incorporated within the prothrombinase complex equally well [6]. This is a potentially important distinction because it is factor Xa assembled within the prothrombinase complex that propagates coagulation by converting prothrombin to thrombin.

The oral thrombin inhibitors also have potential advantages over heparin or LMWH. As direct inhibitors of thrombin, the oral thrombin inhibitors not only inhibit free thrombin but also inhibit thrombin bound to fibrin [7]. In contrast, fibrin-bound thrombin is relatively protected from inhibition by indirect thrombin inhibitors, such as heparin or LMWH [8]. The capacity of oral direct thrombin inhibitors to inhibit fibrin-bound thrombin may endow them with greater efficacy because fibrin-bound thrombin is an important trigger of thrombus growth.

Pharmacology of the New Oral Anticoagulants

Concentrating on drugs in the most advanced stages of clinical development, this review will focus mainly on rivaroxaban and apixaban, oral factor Xa inhibitors, and dabigatran etexilate, an oral direct thrombin inhibitor. A comparison of the pharmacological features of these agents is provided in Table 2.

Rivaroxaban: Rivaroxaban is a potent and specific inhibitor of factor Xa that binds reversibly to the active site of the enzyme [6]. The oral bioavailability of rivaroxaban is 60-80%. Peak drug levels are reached 3 hours after oral administration and the drug is cleared with a half life of about 5 to 9 hours in healthy young individuals, with a somewhat longer half life in the elderly. The drug exhibits a dual mechanism of excretion; about 66% is excreted via the kidneys, 33% of which reflects unaltered drug and the remainder inactive metabolites, while the remaining 34% is excreted in the feces. Rivaroxaban is metabolized in the liver and caution should be used in patients with either severe hepatic or renal impairment [3].

Apixaban: Like rivaroxaban, apixaban also is a potent and specific inhibitor of factor Xa. The oral bioavailability of apixaban is over 45% and peak drug levels are achieved within 3 hours. The half-life of apixaban is 9 to 14 hours. Apixaban is metabolized in the liver and
the drug exhibits a dual pathway of excretion with 25% via the kidneys and the remainder in the feces [9].

**Dabigatran Etexilate**: Dabigatran etexilate, a prodrug of dabigatran, has an oral bioavailability of 6%. Once absorbed, dabigatran etexilate is rapidly converted to dabigatran, which is a potent and reversible inhibitor of thrombin. Dabigatran levels peak in 2 hours and the drug is cleared with a half-life of 12 to 17 hours. About 80% of dabigatran is excreted unchanged by the kidneys [4,10,11].

**Clinical Trials with the New Oral Anticoagulants**

Rivaroxaban, apixaban and dabigatran are following parallel pathways of clinical development. All three drugs are being evaluated for thromboprophylaxis after hip or knee replacement surgery, treatment of established VTE, stroke prevention in patients with AF and for reduction of recurrent ischemic events in patients with acute coronary syndromes (ACS). Rivaroxaban and apixaban also are being evaluated for thromboprophylaxis in high-risk medical patients.

Rivaroxaban and dabigatran etexilate have been licensed for thromboprophylaxis after elective hip or knee replacement surgery in the European Union and in Canada based on the results of the trials summarized in Table 3. Apixaban is still undergoing phase 3 evaluation for this indication. Phase 3 clinical trials for the other clinical indications are underway.

**Rivaroxaban**:

(a) **VTE prevention in orthopedic surgery**: Rivaroxaban was compared with enoxaparin for VTE prevention after total hip replacement surgery (THR) in the RECORD 1 [12] and 2 [13] trials and after total knee replacement surgery (TKR) in the RECORD 3 [14] and 4 [15] trials. The rivaroxaban dose regimen was the same in all of the trials; 10 mg once-daily with the first dose given 6 to 10 hours after surgery. However, the treatment duration differed; rivaroxaban was given for about 35 days in RECORD 1 and 2, and for 10 to 14 days in RECORD 3 and 4. The enoxaparin regimen also differed among the trials. In RECORD 1, 2 and 3, enoxaparin was given at a dose of 40 mg once-daily with the first dose given on the evening prior to surgery. In RECORD 4, enoxaparin was given at a dose of 30 mg twice-daily with the first dose given 12 to 24 hours after surgery. Enoxaparin was given for 35 days in RECORD 1 and for 10 to 14 days in RECORD 2, 3 and 4.

All four trials used the same endpoints. The primary efficacy endpoint was total VTE, a composite of deep vein thrombosis (DVT), pulmonary embolism (PE) and all-cause mortality. Secondary efficacy endpoints included major VTE, a composite of proximal DVT, PE and VTE-related mortality, and symptomatic VTE. The primary safety endpoint was major bleeding. Of note, major bleeding from the surgical site was excluded in the RECORD program unless it triggered re-operation.
In the RECORD 1 trial, the rate of total VTE was 70% lower with rivaroxaban than with enoxaparin (1.1% and 3.7%, respectively; p<0.001), while the rate of major VTE was 88% lower (0.2% and 2.0%; p<0.001). The incidence of major bleeding was similar with rivaroxaban and enoxaparin (0.3% and 0.1%, respectively).

The RECORD 2 trial compared extended prophylaxis with rivaroxaban against shorter-term enoxaparin in patients undergoing THR. Rivaroxaban produced a 79% reduction in total VTE compared with enoxaparin (2.0% and 9.3%, respectively; p<0.0001). Symptomatic VTE also was 88% lower with rivaroxaban (0.6% and 5.1%, respectively; p<0.0001), while the rate of major bleeding was <0.1% in both groups. The findings of this trial confirm the benefit of extended thromboprophylaxis in patients undergoing THR.

In RECORD 3, the rate of total VTE was 49% lower with rivaroxaban than with enoxaparin (9.6% and 18.9%, respectively; p<0.001), while the rate of major VTE was 62% lower (1.0% and 2.6%, respectively; p=0.01). Rates of major bleeding were 0.6% and 0.5%, respectively. Even with the higher dose enoxaparin regimen used as the comparator in RECORD 4, the rate of total VTE was 32% lower with rivaroxaban than with enoxaparin (6.9% and 10.1%, respectively; p=0.012). The rate of major VTE was 1.2% with rivaroxaban and 2.0% with enoxaparin, a difference that did not reach statistical significance, while the rates of major bleeding were 0.7% and 0.3%, respectively.

(b) VTE prophylaxis in medical patients: The MAGELLAN trial (www.clinicaltrials.gov; NCT00571649) is comparing the efficacy and safety of extended prophylaxis with rivaroxaban (10 mg once-daily for up to 5 weeks) compared with short-term prophylaxis with enoxaparin in medically ill patients.

(c) VTE Treatment: The EINSTEIN DVT (www.clinicaltrials.gov; NCT00440193) and EINSTEIN PE (www.clinicaltrials.gov; NCT00439777) are multicentre, randomized, open-label studies in patients with acute symptomatic DVT or PE, respectively. Both studies are comparing the same rivaroxaban regimen (15 mg twice-daily for the first 3 weeks, followed by 20 mg once-daily for 3, 6 or 12 months), and then with LMWH followed by a VKA. The EINSTEIN EXT study randomizes VTE patients who have been treated for 6 or 12 months with rivaroxaban or a VKA to either rivaroxaban (20 mg once-daily) or placebo for an additional 6 to 12 months (www.clinicaltrials.gov; NCT00439725).

(d) Stroke prevention in AF: The ROCKET AF trial (www.clinicaltrials.gov; NCT00403767) is comparing fixed-dose rivaroxaban (20 mg once-daily) with warfarin (dose-adjusted to achieve an INR between 2 and 3) for stroke prevention in AF. A separate study, the J-ROCKET AF study, which is being conducted in Japan, is comparing a lower rivaroxaban dose (15 mg once-daily and 10 mg for patients with moderate renal impairment) with warfarin.

(e) ACS: A phase IIb study (ATLAS ACS TIMI 46, www.clinicaltrials.gov; NCT00402597) explored the utility of rivaroxaban in combination with ASA or ASA plus a
thienopyridine for secondary prevention in patients with ACS. Based on this study, rivaroxaban doses of 2.5 and 5 mg twice-daily will be compared with placebo in the phase III ATLAS 2-TIMI 51 trial.

**Apixaban:**

(a) **VTE prevention after orthopedic surgery:** Apixaban is being compared with enoxaparin in three trials; ADVANCE-1 and 2 in patients undergoing TKR and ADVANCE-3 in those having THR. The same apixaban regimen is used in all three trials; 2.5 mg twice-daily starting in the morning on the day after surgery to reduce the risk of bleeding. In ADVANCE-1 [16], this apixaban regimen was compared with enoxaparin 30 mg twice-daily starting 12–24 hours after surgery, with both treatment regimens continued for 12 days. The rates of total VTE with apixaban and enoxaparin were 8.99% and 8.85%, respectively, whereas rates of major bleeding were 0.69% and 1.39%, respectively (p=0.053). Despite the similar rates of total VTE, the pre-specified non-inferiority margin was not achieved because of the lower than expected rate of total VTE with enoxaparin. The ongoing ADVANCE-2 trial is comparing a 12-day course of apixaban with enoxaparin 40 mg once-daily in patients undergoing TKR (www.clinicaltrials.gov; NCT00452530), while in the ADVANCE-3 trial, a 35-day course of apixaban is being compared with enoxaparin 40 mg once-daily in patients undergoing THR (www.clinicaltrials.gov; NCT00423319).

(b) **VTE prophylaxis in medical patients:** In the ongoing ADOPT trial, a 30-day regimen of apixaban 2.5 mg twice-daily is being compared with enoxaparin 40 mg once-daily given for at least 7 days for the prevention of VTE in acutely ill medical patients (www.clinicaltrials.gov; NCT00457002) to explore the concept that medical patients remain at risk for VTE after hospital discharge. A phase II pilot study is investigating apixaban for the prevention of VTE in patients with metastatic cancer (www.clinicaltrials.gov; NCT00320255).

(c) **Treatment of VTE:** Building on the results of the phase 2 BOTICELLI trial in patients with confirmed DVT [17], the phase 3 AMPLIFY trial (www.clinicaltrials.gov; NCT00643201) is comparing a 6-month course of monotherapy with apixaban, at a dose of 10 mg twice-daily for one week followed by 5 mg twice-daily thereafter, with conventional anticoagulant therapy (enoxaparin followed by a VKA) in patients with objectively documented VTE. The AMPLIFY-EXT trial (www.clinicaltrials.gov; NCT00633893) will compare a 12-month course of apixaban at a dose of 2.5 or 5 mg twice-daily with placebo for extended secondary prevention of VTE.

(d) **Stroke prevention in AF:** Two phase 3 studies are underway. The ARISTOTLE trial (www.clinicaltrials.gov; NCT00412984) is comparing apixaban 5 mg twice-daily with warfarin dose-adjusted to achieve a target INR between 2 and 3 for the prevention of stroke or systemic embolism. The AVERROES trial (www.clinicaltrials.gov; NCT00496769) is comparing apixaban 5 mg twice-daily with aspirin in AF patients who have refused, or are unsuitable for, treatment with a VKA.
(e) **ACS:** The recently completed APPRAISE-1 study assessed the safety of various doses of apixaban in combination with anti-platelet therapy after ACS [http://www.clinicaltrials.gov; NCT00313300](http://www.clinicaltrials.gov). Building on these results, a phase 3 trial will compare apixaban (at doses of 2.5 or 5 mg twice-daily) with placebo in ACS patients receiving aspirin or aspirin plus clopidogrel.

**Dabigatran etexilate:**

(a) **VTE prevention in orthopedic patients:** Three phase 3 trials have been completed. All three trials compared the same regimens of dabigatran etexilate (150 or 220 mg once-daily, starting with a half-dose on the day of surgery) with enoxaparin. For both the RE-MODEL [18] and the RE-NOVATE [19] trials, dabigatran etexilate was started 1-4 hours after surgery and enoxaparin was administered at a dose of 40 mg once daily with the first dose given the evening prior to surgery. The RE-MODEL trial in TKR patients, found that, after a treatment duration of 6-10 days, both doses of dabigatran etexilate were non-inferior to enoxaparin for the primary efficacy endpoint of total VTE. Rates of major bleeding and the incidence of major VTE (proximal DVT and PE) were similar between both doses of dabigatran and enoxaparin. Likewise, the RE-NOVATE trial, which compared extended prophylaxis (28–35 days) with dabigatran etexilate or enoxaparin in THR patients, found that both doses of dabigatran etexilate were again non-inferior to enoxaparin for the primary efficacy endpoint of total VTE. The incidence of major VTE and the rates of major bleeding also were similar between both doses of dabigatran etexilate and enoxaparin. By contrast, the RE-MOBILIZE [20] trial in patients undergoing TKR, found that both doses of dabigatran etexilate failed to achieve non-inferiority compared with enoxaparin for the primary efficacy endpoint. The design of this trial differed from that of the RE-MODEL trial in several ways. Firstly, the initial dose of dabigatran etexilate was given later at 6–12 hours after surgery instead of 1–4 hours. Secondly, the dose of enoxaparin was higher: a 30 mg twice-daily regimen was used. Thirdly, the treatment duration was 12 – 15 days instead of 6–10 days. Therefore, the differing results from the RE-MODEL and RE-MOBILIZE trials may reflect the higher daily dose of enoxaparin used as a comparator and/or the delayed start of dabigatran etexilate in the RE-MOBILIZE trial.

A pre-planned pooled analysis of these trials revealed that major VTE and VTE-related death occurred in 3.3% of patients in the enoxaparin group versus 3.0% of patients in the higher dose dabigatran etexilate group and 3.8% in the lower dose dabigatran etexilate group. Major bleeding events were similar across all groups. Furthermore, no significant differences in the incidence of liver enzyme elevations or acute coronary events were observed [21]. Based on these findings, the 220 mg once-daily dose is recommended for most patients, while the 150 mg once-daily dose is reserved for elderly patients and those with moderate renal impairment (creatinine clearance of 30–50 ml/min).

(b) **VTE treatment:** The recently completed RE-COVER trial ([www.clinicaltrials.gov; NCT00291330](http://www.clinicaltrials.gov)) compared a 6-month course of dabigatran etexilate (150 mg twice-daily) with
dose-adjusted warfarin after 5 to 10 days of treatment with heparin or LMWH in patients with acute symptomatic VTE. A second phase 3 trial with a similar design has recently been initiated. The ongoing RE-MEDY trial (www.clinicaltrials.gov; NCT00558259) is comparing dabigatran etexilate (150 mg twice-daily) with dose-adjusted warfarin for secondary VTE prevention after a 3 to 6 month course of conventional anticoagulant therapy for acute symptomatic VTE.

(c) Stroke prevention in AF: The almost completed phase 3 RE-LY trial is comparing dabigatran etexilate doses of 110 or 150 mg twice-daily with dose-adjusted warfarin for stroke prevention in patients with atrial fibrillation (www.clinicaltrials.gov; NCT00262600). The trial has enrolled more than 18,100 patients and results will be reported in 2009.

(d) ACS: The ongoing phase 2 RE-DEEM study (www.clinicaltrials.gov; NCT00621855) is evaluating whether the addition of dabigatran etexilate to dual anti-platelet therapy with aspirin and clopidogrel reduces the risk of recurrent ischemia in ACS patients.

Conclusions and Future Directions

Although currently available parenteral and oral anticoagulants are widely used for prevention and treatment of venous and arterial thrombosis, the major unmet need is to find a replacement for VKA for long-term therapy. The introduction of LMWH and fondaparinux has simplified short-term anticoagulation because these drugs can be given in fixed or weight-adjusted doses without coagulation monitoring for both prevention and treatment purposes. For long-term treatment, however, oral anticoagulants are preferable. Although VKA are effective, their many limitations have prompted the development of new oral anticoagulants that are more convenient to administer. With limited potential for drug-drug interactions and no food effects, these novel agents produce a predictable anticoagulant response that obviates the need for coagulation monitoring or dose adjustment. Consequently, these drugs are more convenient to administer than VKA.

The recent introduction of rivaroxaban and dabigatran etexilate in Europe and Canada has simplified out-of-hospital prophylaxis for patients undergoing THR or TKR. These drugs are at least as effective as LMWH for thromboprophylaxis in the orthopedic setting, but are they as effective and safe as VKA for long-term use? This question will soon be answered when the results of the RE-LY and RE-COVER trials are presented later this year.

How do the oral factor Xa and thrombin inhibitors compare? This question is difficult to answer because head-to-head trials are lacking. Instead, clinicians will be guided by the clinical trial results. We already have a choice of agents and the list is likely to expand as newer agents enter the clinical development pathway. Unique pharmacological properties may render one drug a better choice than another depending on patient characteristics. Therefore, a thorough understanding of these new agents will be needed to make optimal treatment decisions.
What are some of the challenges facing the new oral anticoagulants? Although INR monitoring is cumbersome, such testing helps assess compliance with VKA therapy and ensures that a therapeutic anticoagulant response has been achieved. How will compliance be assessed with the new oral anticoagulants? Furthermore, even if routine coagulation monitoring is unnecessary with the new drugs, there will be situations where we will need to assess the level of anticoagulation. How will we do this when these agents have variable effects on routine tests of coagulation and the therapeutic levels are unknown?

The lack of a specific antidote is another challenge for the new oral anticoagulants. Although their relatively short half lives will limit the need for an antidote, there will be situations where rapid reversal is required to prepare patients for urgent surgery or to manage life-threatening bleeds. Hemodialysis or hemofiltration may be options for drugs that are not highly protein-bound, whereas the utility of procoagulants, such as recombinant factor VIIa, needs further exploration.

Despite the potential challenges, the new oral anticoagulants represent a major advance. The promising results in VTE prophylaxis bring us one step closer to finding a replacement for VKA.
TABLE 1

Limitations of Warfarin

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow onset of action</td>
<td>Overlap with a parenteral anticoagulant</td>
</tr>
<tr>
<td>Genetic variation in metabolism</td>
<td>Variable dose requirements</td>
</tr>
<tr>
<td>Multiple food and drug interactions</td>
<td>Frequent coagulation monitoring</td>
</tr>
<tr>
<td>Narrow therapeutic index</td>
<td>Frequent coagulation monitoring</td>
</tr>
</tbody>
</table>

TABLE 2

Comparison of the Features of New Oral Anticoagulants in Advanced Stages of Development

<table>
<thead>
<tr>
<th>Features</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran Etezilate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Xa</td>
<td>Xa</td>
<td>IIa</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>436</td>
<td>460</td>
<td>628</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Bioavailability (%) | 80 | 50 | 6
Time to peak (h) | 3 | 3 | 2
Half-life (h) | 9 | 9-14 | 12-17
Renal excretion (%) | 65 | 25 | 80
Antidote | None | None | None

TABLE 3
Major Efficacy and Safety Outcomes of Rivaroxaban versus Enoxaparin for Thromboprophylaxis Following Major Orthopedic Surgery

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration (days)</th>
<th>Total VTE (%)</th>
<th>Major VTE (%)</th>
<th>Major Bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECORDD1 [12] Total Hip Replacement</td>
<td>Rivaroxaban 10mg daily</td>
<td>30-35</td>
<td>1.1</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 40mg daily</td>
<td></td>
<td>3.7</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RECORDD2 [13] Total Hip Replacement</td>
<td>Rivaroxaban10mg daily</td>
<td>30-35</td>
<td>2.0</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 40mg daily</td>
<td>10-14</td>
<td>9.3</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RECORDD3 [14] Total Knee Replacement</td>
<td>Rivaroxaban 10mg daily</td>
<td>10-14</td>
<td>9.6</td>
<td>1.0</td>
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<tr>
<td></td>
<td>Enoxaparin 40mg daily</td>
<td></td>
<td>18.9</td>
<td>2.6</td>
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<tr>
<td></td>
<td>p-value</td>
<td></td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>RECORDD4 [15] Total Knee Replacement</td>
<td>Rivaroxaban 10mg daily</td>
<td>10-14</td>
<td>6.9</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 30mg BID</td>
<td></td>
<td>10.1</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td></td>
<td>0.012</td>
<td>0.124</td>
</tr>
</tbody>
</table>
### TABLE 4

Major Efficacy and Safety Outcomes of Dabigatran Etxililate versus Enoxaparin for Thromboprophylaxis Following Major Orthopedic Surgery

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration (days)</th>
<th>Total VTE (%)</th>
<th>p-value*</th>
<th>Major VTE (%)</th>
<th>p-value*</th>
<th>Major Bleeding (%)</th>
<th>p-value*</th>
</tr>
</thead>
</table>
| **RE-NOVATE**[18]
  Total Hip Replacement            | 28-35           | 36.4          | 0.0003   | 2.6           | 0.38     | 1.5                | not significant |
| Dabigatran 220mg daily           |                 |               |          |               |          |                    |           |
| Dabigatran 150mg daily           |                 | 40.5          | 0.017    | 3.8           | 0.82     | 1.3                | not significant |
| Enoxaparin 40mg daily            |                 | 37.7          |          | 3.5           |          | 1.3                |           |
| **RE-MODEL**[19]
  Total Knee Replacement           | 6-10            | 6.0           | <0.0001  | 3.1           | 0.33     | 2.0                | not significant |
| Dabigatran 220mg daily           |                 |               |          |               |          |                    |           |
| Dabigatran 150mg daily           |                 | 8.6           | <0.0001  | 4.3           | 0.71     | 1.3                | not significant |
| Enoxaparin 40mg daily            |                 | 6.7           |          | 3.9           |          | 1.6                |           |
| **RE-MOBILIZE**[20]
  Total Knee Replacement           | 12-15           | 3.4           | not significant | 31.1   | 0.02     | 0.6                | not significant |
| Dabigatran 220mg daily           |                 |               |          |               |          |                    |           |
| Dabigatran 150mg daily           |                 | 3.0           | not significant | 33.7   | 0.0009  | 0.6                | not significant |
| Enoxaparin 40mg daily            |                 | 2.2           |          | 25.3          |          | 1.4                |           |

* p-values reflect comparison of each dose of dabigatran with enoxaparin
References


