New Oral Anticoagulant (Rivaroxaban [Xarelto])

Rivaroxaban (Xarelto) was approved by the Food and Drug Administration (FDA) on July 1, 2011 for the prevention of deep vein thrombosis (DVT) in patients following hip or knee replacement surgery, and was recently added to the UIMCC formulary for use in this patient population. It is the first and only oral factor Xa inhibitor available for use in the United States. The recommended dose of rivaroxaban is 10 mg once daily for 12 days in patients undergoing knee replacement surgery and for 35 days in patients undergoing hip replacement surgery. Rivaroxaban exposure is increased in patients with renal impairment. Patients who have a creatinine clearance (CrCl) greater than 30 mL/min may receive rivaroxaban with careful monitoring; studies have not indicated an increased bleeding risk in these patients. However, those patients with a CrCl less than 30 mL/min have been excluded from clinical trials; thus, rivaroxaban use should be avoided in these patients at this time.

Efficacy Data for DVT prevention
Four phase 3 clinical trials known as the RECORD (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism) trials compared rivaroxaban 10 mg once daily to enoxaparin in patients undergoing hip or knee replacement surgery and found a reduced risk of the composite primary endpoint that included death, DVT, or pulmonary embolism (PE). Approval of rivaroxaban was based on data from the RECORD 1, 2, and 3 trials. In the RECORD 1, 2, and 3 trials, 4,487 patients were treated with rivaroxaban 10 mg/day and 4,524 were given subcutaneous (SC) enoxaparin 40 mg/day each given for a mean duration of 12 days. As with the data seen in the hip studies, use of rivaroxaban resulted in a significant RRR for total VTE and major VTE events. The rate of total VTE events was 9.7% in rivaroxaban-treated patients versus 1.8% in the enoxaparin group (RRR 81%, 95% CI 75-87, p<0.001) and major VTE events occurred in 1.0% and 2.5% of the groups, respectively (RRR 60%, 95% CI 14-81, p=0.024). Similar results were observed in the RECORD 4 trial, which compared rivaroxaban 10 mg/day with SC enoxaparin 30 mg twice daily, both given for 10 to 14 days, after knee replacement surgery. In this trial, the rate of total VTE in rivaroxaban-treated patients was 6.9% versus 10.1% in the enoxaparin group (RRR 31.4%, 95% CI 7.5-49.1, p=0.0160).

Future Uses
In addition to its use for DVT prevention in orthopedic surgery patients, rivaroxaban has also demonstrated efficacy for the prevention of stroke or systemic embolism in patients with atrial fibrillation (AF). One noninferiority trial, ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), compared rivaroxaban 20 mg daily (15 mg in patients with moderate renal impairment) to dose-adjusted warfarin in patients with nonvalvular AF. The primary composite endpoint of stroke or systemic embolism occurred in 1.7% of patients per year in the rivaroxaban group versus 2.2% of patients per year in the warfarin group (RRR 23%, 95% CI 5-38, p=0.009).
year in the warfarin group (hazard ratio [HR] 0.79, 95% CI 0.66 to 0.96, p<0.001 for noninferiority). Major and nonmajor bleeding events were similar between groups. In September, the FDA Cardiovascular and Renal Drugs Advisory Committee recommended approval of rivaroxaban for this indication. The decision has been criticized by some experts primarily because the warfarin-treated patients spent only 57.8% of the time in the therapeutic range. This time in the therapeutic range is lower than in the RE-LY study (see dabigatran story) which compared warfarin with dabigatran for prevention of stroke or systemic embolism in atrial fibrillation patients and potentially impacts both safety and efficacy results.

Other potential uses for rivaroxaban include treatment of acute DVT or PE, prevention of DVT in medically ill patients, and secondary prevention of acute coronary syndromes. The EINSTEIN-DVT trial showed rivaroxaban to be noninferior to the standard of care (enoxaparin followed by warfarin) in the treatment of acute DVT with a similar safety profile. EINSTEIN-PE is an ongoing phase 3 trial evaluating rivaroxaban in the treatment of acute PE. The MAGELLAN study assessed whether rivaroxaban 10 mg daily is noninferior or superior to SC enoxaparin 40 mg daily for 10 days for the prevention of VTE in patients 40 years or older who are hospitalized with a medical illness. Results from this study await publication; however, initial analysis indicate a lower risk of VTE, but increased risk of bleeding, with rivaroxaban. ATLAS-ACS 2 TIMI 51 is a phase 3 trial evaluating rivaroxaban for secondary prevention in patients with an acute coronary syndrome (ACS). Although no results have been released at this time, the study has met its primary endpoint and preliminary results are expected to be reported at an upcoming scientific session.

**Safety Considerations**

Several safety concerns have been noted with rivaroxaban including its use in patients with renal impairment, bleeding associated with its use, and its drug interaction potential. Rivaroxaban is primarily metabolized via cytochrome (CYP)3A4/3A5; CYP2J2 is involved to a lesser extent. In addition, rivaroxaban is a P-glycoprotein (P-gp) substrate and drug interactions are a concern. Drugs that are strong inhibitors of P-gp and CYP3A4 should not be used in combination with rivaroxaban. Patients with renal impairment who are receiving rivaroxaban should not receive a P-gp inhibitor or moderate or weak CYP3A4 inhibitors unless the benefit outweighs the potential increased bleeding risk. Drugs that strongly induce CYP3A4 should be avoided with rivaroxaban; in some cases a rivaroxaban dose increase may be considered.

Clinical trials indicate that rivaroxaban’s propensity for bleeding is similar to or greater than that of comparator drugs (enoxaparin or warfarin). This is especially concerning due to lack of a specific antidote to reverse its effects.

**Summary**

Rivaroxaban is the first oral factor Xa inhibitor approved by the FDA. Currently, it is approved for use in patients following hip or knee replacement surgery as DVT prophylaxis, and only approved on the UIMCC formulary for this indication. Rivaroxaban will likely be approved as an anticoagulant for the prevention of systemic embolism in patients with atrial fibrillation soon. It should be noted that the approved dose of rivaroxaban is 10 mg daily; however, the dose studied for atrial fibrillation is 20 mg daily. Rivaroxaban should not be used in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or concomitantly with strong inhibitors of CYP3A4 or P-gp.

**New Antiplatelet (Ticagrelor [Brilinta])**

A novel antiplatelet agent, ticagrelor (Brilinta) has recently been FDA approved to reduce the rate of thrombotic cardiovascular events in patients with ACS, including those with unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), and STEMI. It is currently being reviewed by the UIMCC Pharmacy and Therapeutics committee for formulary inclusion. Ticagrelor differs from both clopidogrel (Plavix) and prasugrel (Effient) in that it is a direct, reversible inhibitor of platelet activation and aggregation mediated by the P2Y12 ADP receptor. The drug does not require metabolic conversion to an active form and has a rapid onset and offset of action, with a half-life of approximately 12 hours. Ticagrelor has also been shown to produce greater inhibition of platelet aggregation compared with clopidogrel.

It is given as a 180 mg loading dose, followed by 90 mg twice daily. After the initial loading dose of aspirin (usually 325 mg), maintenance doses of aspirin must be kept between 75–100 mg/day. No dosage adjustments are required for patients with renal impairment or mild hepatic impairment, but it should be used cautiously in patients with moderate hepatic impairment and is contraindicated in those with severe hepatic impairment.

**Efficacy Data**

Approval was based on results from PLATO (Study of Platelet Inhibition and Patient Outcomes), a phase 3 study of 18,624 patients from 43 countries who were hospitalized with either STEMI or UA/NSTEMI. Patients who presented within 24 hours of onset of chest pain were randomized to either ticagrelor, given as a 180 mg loading dose followed by 90 mg twice daily (n=9,333), or clopidogrel, given as a 300 or 600 mg loading dose followed by 75 mg once daily (n=9,291). Patients could be included whether there was an intent to manage them medically or via an invasive procedure.

At baseline, the majority of patients in the 2 groups were male (72%) and white (92%); 43% were older than 65 years and 15% were older than 75 years. Median exposure to the study drug was approximately 277 days. At 12 months, the primary composite endpoint of first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke occurred in 9.8% of patients receiving ticagrelor and 11.7% of patients in the clopidogrel group (HR 0.84 [95% CI 0.77–0.92], p=0.0003). An analysis of prespecified secondary endpoints in PLATO revealed significant differences between ticagrelor and clopidogrel in terms of MI (5.8% vs. 6.9%, p=0.005), cardiovascular-related death (4.0% vs. 5.1%, p=0.001), and death from any cause (4.5% vs. 5.9%, p=0.0003). No difference was observed between groups with respect to strokes (1.5% vs. 1.3%, p=0.22). Among 11,289 patients who received either a drug-eluting or bare metal stent during the trial, use of ticagrelor was also associated with a lower risk of stent thrombosis compared with clopidogrel (1.3% vs. 1.9%, HR 0.67 [95% CI 0.50–0.91], p=0.0091).
No differences were noted in the rates of major bleeding between the 2 groups (11.6% ticagrelor vs. 11.2% clopidogrel), including coronary artery bypass graft (CABG)–related major bleeding. Although platelet inhibition is reversible with ticagrelor compared with clopidogrel, PLATO did not reveal an advantage when CABG-related major bleeding was assessed; similar results for major bleeding were observed when antiplatelet therapy was stopped 5 days before CABG. Other adverse events reported with ticagrelor compared with clopidogrel included dyspnea (13.8% vs. 7.8%), headache (6.5% vs. 5.8%), cough (4.9% vs. 4.6%), and dizziness (4.5% vs. 3.9%).

**Low-dose Aspirin Issue Explored**

When results from the rest of the world were compared with those from patients living in North America, a smaller effect was seen in patients living in the United States and Canada. Specifically, among the 1,800 patients from the United States and Canada who were included in PLATO, primary outcomes were worse in those receiving ticagrelor, although not significantly so (U.S.: HR 1.27 [95% CI 0.92–1.75]; Canada: HR 1.17 [0.59–2.31]). Analyses revealed that this was driven by the U.S. subset of patients, so a variety of baseline and procedural differences were examined.

The difference in the aspirin maintenance dose used in the United States versus other countries was identified as causing the variance in results. Approximately 8% of investigators in other countries used aspirin doses greater than 100 mg/day, and only 2% used doses above 300 mg/day, whereas 57% and 54% of patients in the United States received aspirin doses over 100 mg/day and 300 mg/day, respectively.

Overall efficacy results were better in patients who used lower aspirin maintenance doses, defined as 100 mg/day or less. As with any unplanned analysis, these results must be interpreted with caution. PEGASUS (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on Background of Aspirin), another ongoing trial with ticagrelor, should shed some light on this aspirin issue as only patients receiving aspirin (300 mg twice daily) were included. Approximately 8% of investigators in other countries used aspirin doses greater than 100 mg/day, and only 2% used doses above 300 mg/day, whereas 57% and 54% of patients in the United States received aspirin doses over 100 mg/day and 300 mg/day, respectively.

**Safety Considerations**

Ticagrelor was approved with a boxed warning describing its bleeding risk and a unique warning about appropriate aspirin dosing. According to the warning, maintenance doses of aspirin exceeding 100 mg/day reduce the effectiveness of ticagrelor and should be avoided; the basis for this warning is described above. In terms of bleeding, ticagrelor can cause serious, sometimes fatal bleeding events and should not be used in patients with active pathological bleeding or a history of intracranial hemorrhage. To educate health care providers about these risks, the drug was approved with a Risk Evaluation and Mitigation Strategy.

If surgery is planned, ticagrelor should be discontinued at least 5 days prior to any surgery. Other warnings include not using ticagrelor in patients with severe hepatic impairment and avoiding the concurrent use of strong CYP3A inhibitors and inducers. Ticagrelor also has the potential to cause dyspnea.
Recent Safety Concerns
In mid-August, the Japanese Ministry of Health, Labor, and Welfare issued a safety advisory for dabigatran following the deaths of 5 patients who were taking the drug. The advisory noted that since the launch of the drug in January 2011 and use in approximately 64,000 patients, there have been 81 cases of serious adverse events, including gastrointestinal bleeding. For the 5 deaths, 1 patient had kidney failure and the other 4 patients were over 80 years of age; although treatment with dabigatran could not be completely ruled out as the cause of death. Prescribers in that country are being reminded to carefully monitor for signs and symptoms of bleeding and anemia and to assess renal function before initiating dabigatran and during treatment. In addition, patient-related educational efforts are also underway aimed at informing patients to look for signs of abnormal bleeding such as blood in their stools or subcutaneous bleeding and to immediately report any abnormal bleeding to their healthcare provider.

Two cases reports of elderly women from France experiencing adverse events with dabigatran have also been published in the July 25 issue of Archives of Internal Medicine. In one case, an 84-year-old woman who weighed 40 kg and received dabigatran 75 mg twice daily developed massive rectal bleeding, had a cardiac arrest and died. In the second case, an 89-year-old woman who weighed 45 kg and received dabigatran 110 mg twice daily for 5 months had increased bleeding times, an elevated dabigatran plasma level, and recurrent epistaxis for about a week. Once treatment with dabigatran was discontinued, the patient had a favorable outcome. The authors of this case series concluded, “The risk of overdose is, however, much increased in this population [the elderly], with no way of detecting it with routine coagulation tests and no antagonist available. We therefore call for great caution before administering dabigatran etexilate in such patients and encourage physicians to declare bleeding events to drug regulatory agencies for close monitoring of adverse effects.”

Special Storage, Handling Requirements
On March 29, the FDA released a safety communication to alert health providers and patients about special storage and handling requirements for dabigatran. The drug must be stored in its original container, which has a desiccant cap, or in unit-of-use blister packaging to minimize product breakdown from moisture. The agency was concerned that these special storage and handling requirements were not commonly known or were not being followed by dabigatran users and pharmacies. In addition, the labeling for dabigatran states that the drug must be used within 30 days once opened; however, data have shown that no significant loss of potency occurs for up to 60 days after the bottle is opened as long as dabigatran is stored in the original bottle and the handling requirements are met.

Patients receiving dabigatran need to be educated to store the drug in the original bottle or blister package to protect it from moisture; not to store the product in any other container, such as pill boxes or pill organizers; and to remove only one capsule from the bottle at the time of use and to immediately close the bottle after use.

UIMCC Usage
Since its addition to the UIMCC formulary, inpatient use of dabigatran has been minimal primarily because of cost and insurance issues. Many patients have not been able to access the drug because of limitations imposed by their insurance companies, with many UIMCC patients having Medicaid or Medicare Part D plans. However, for new patients with AF whose insurance plans will pay for it, physicians have not been shy in prescribing the drug.

On the outpatient side, use of dabigatran has steadily increased. Current data show that all of its use has been 100% appropriate in terms of its indication and dose. Preliminary data indicate that 36 patients ages 35 to 92 years with either AF or atrial flutter have received the drug since May. A summary of these patient characteristics are presented in Table 1.

Summary
Based on the recent safety considerations for dabigatran, clinicians must exercise caution when using this agent in patients at a higher risk for bleeding such as those who are elderly, have renal impairment, low body weight, and/or are receiving concurrent medications that also affect bleeding. In addition, patients given the drug should be aware of its bleeding risks and when to report symptoms to their provider and dabigatran’s special storage and handling requirements.

It appears that inpatient usage at UIMCC has been minimal since its addition to the formulary; however, for those who did receive the drug in an outpatient setting, its use was appropriate. Only 3 patients with a CrCl between 15-30 mL/min were given the drug and no patients with a CrCl <15 mL/min received dabigatran (as recommended by the prescribing information). As expected, cardiology is the service which is most commonly prescribing this agent to their patients with AF or atrial flutter, although internal medicine and family medicine have had some minimal use as well. At this time, no outcome data are available in terms of cardiovascular events or safety measures; however, the appropriate use of this agent at our institution is reassuring.
What Methods are Available for Reversal of Dabigatran and Rivaroxaban?

Unlike well-established anticoagulants such as warfarin and unfractionated heparin, there are no clear antidotes for reversal of the anticoagulant effects of either dabigatran or rivaroxaban. Although both have relatively short half-lives (12 to 17 hours for dabigatran and 5 to 9 hours for rivaroxaban) there may be situations where urgent reversal of anticoagulant effects is needed (e.g., emergency surgery, overdose, or life-threatening bleeding).

Agents for reversal

Several publications are available with suggested approaches to reverse the anticoagulant effects of dabigatran and rivaroxaban. Both recombinant factor VIIa (rFVIIa) and prothrombin complex concentrates (PCCs) have been suggested as agents for reversal for both dabigatran and rivaroxaban. van Ryn and colleagues conducted an in vitro study using rFVIIa and a PCC (FEIBA which is an activated PCC containing nonactivated factors I, IX, X, and activated factor VII) to reverse the effects of high dose dabigatran in an animal model. Following administration of dabigatran, rFVIIa (0.5 or 1 mg/kg) and FEIBA (50 or 100 U/kg) were both found to reduce bleeding time from 1455 seconds to less than 186 seconds. Use of rFVIIa also reduced activated prothrombin time (aPTT) from 58.8 seconds to ~30 seconds; however, FEIBA had no effect on aPTT.

Eerenberg conducted a double-blind crossover trial to assess the effects of PCCs versus placebo in reversal of the effects of both dabigatran and rivaroxaban in healthy volunteers. Prothrombin complex concentrates are generally classified as 4-factor and 3-factor concentrates. In the United States, only 2 PCCs are available (Profilnine and Bebulin), both of which are 3-factor concentrates and contain lower concentrations of factor VII as compared to 4-factor concentrates.

Twelve healthy volunteers were randomized to either dabigatran (150 mg twice daily) or rivaroxaban (20 mg twice daily) for 2.5 days. On the third day, patients were given either a PCC or placebo (50 U/kg). The PCC used in this trial was Cofact, a nonactivated 4-factor concentrate containing factors II, VII, IX, and X; it is not available in the United States. After 11 days, patients were crossed-over to the alternate anticoagulant treatment and the study procedures repeated. The results are given in the Table 2. Overall, PCC had a significant effect on normalizing elevated coagulation parameters following rivaroxaban but had no effects on abnormal coagulation parameters following dabigatran.

Table 2. Effects of PCC on anticoagulation with dabigatran and rivaroxaban.

<table>
<thead>
<tr>
<th>Anti-coagulant</th>
<th>Reversal agent (change from posttreatment)</th>
<th>Baseline (after anticoagulant treatment)</th>
<th>Post-PPC treatment value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PT</td>
<td>aPTT</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>NA</td>
<td>59.4s</td>
<td>7.5m</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>15.8s</td>
<td>NA</td>
<td>51%</td>
</tr>
<tr>
<td></td>
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</tbody>
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|               |                                              |                                            |                         |
| Dabigatran    | NA                                         | 70.3s | 8.7m | IP  | 86s |
| Rivaroxaban   | 12.8s                                      | NA | 114% | NA  | NA |

*Thrombin generation tests assess the change in the thrombin generation by treatment. In this study, the effects of treatment on thrombin generation (as endogenous thrombin potential [ETP]) were measured as lag time to thrombin generation for dabigatran and the potential (as percentage) for thrombin generation for rivaroxaban. Effective reversal of dabigatran would be indicated by a shorter lag time to thrombin generation and an increase in percentage of potential for rivaroxaban.

**Significant change from baseline.**

Other interventions have been suggested for overdoses of dabigatran and rivaroxaban. van Ryn and colleagues have developed an algorithm for treatment of bleeding with dabigatran. For mild bleeding, a delay in dosing or discontinuation of the drug has been suggested. For patients with moderate to severe bleeding, treatment recommendations include mechanical compression, surgical...
intervention, fluid replacement, transfusion, oral charcoal (for ingestions < 2 h before), and hemodialysis. Use of either PCC, FVIIa, and fresh frozen plasma have been suggested by van Ryn and other authors for life-threatening bleeding, as well as charcoal filtration and hemodialysis. The PCCs have also been suggested for reversal of rivaroxaban, by providing more factor X and Xa. However, there is little clinical evidence for these interventions.

**Summary**
Currently, there are no definitive treatments for reversal of the effects of dabigatran or rivaroxaban. One available clinical trial supports the use of PCCs for rivaroxaban-associated bleeding. However, data are limited. Treatment of excess bleeding due to either of these agents needs to be individualized, with close monitoring of patient response.

**P&T Formulary Committee Action***

*The P&T Committee actions are effective when formulary changes have been implemented in the Cerner System.

**Additions**
- Lacosamide
- Rivaroxaban for its FDA approved indication of DVT prevention in patients underoing hip and knee replacement surgery.

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