Cleveland Clinic Pharmacotherapy Update
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Ticagrelor: A New Treatment for Acute Coronary Syndromes

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Introduction: Acute coronary syndrome (ACS) includes three conditions which involve the coronary arteries: unstable angina, non-ST elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). The primary cause of an ACS is erosion or rupture of an atherosclerotic plaque which incites platelet adherence, activation, and aggregation; this in turn, activates the clotting cascade and ultimately produces a clot-related cardiovascular event.[1] The American College of Cardiology/ American Heart Association (ACC/ AHA) joint practice guidelines recommend dual antiplatelet therapy with aspirin and clopidogrel for patients who have ACS with or without ST-segment elevation.[2,3] Clopidogrel (Plavix®; Bristol-Myers Squibb and Sanofi Pharmaceuticals), an oral irreversible platelet adenosine diphosphate (ADP) $P2Y_{12}$ receptor inhibitor, was approved by the Food and Drug Administration (FDA) in 1997. It has been shown to reduce the rate of cardiovascular events in patients with ACS, recent myocardial infarction (MI), recent stroke, and established peripheral arterial disease.[4] Some of the limitations of clopidogrel include: 1) pharmacologic activity dependent on conversion of an inactive parent prodrug to its active metabolite, 2) variable pharmacodynamic response due to different factors which can affect the drug's metabolism (e.g., genetic influences, drug interactions), 3) relatively slow onset of action (2 to 4 hours with a 300- to 600-mg loading dose) and 4) irreversible antiplatelet activity.[5,6] Some of these disadvantages have been overcome by prasugrel (Effient®; Eli Lilly and Company), a newer antiplatelet agent approved by the FDA in July 2009. Prasugrel provides cardiovascular protection in patients with ACS who are to be managed with percutaneous coronary intervention (PCI).[7] Like clopidogrel, prasugrel is an irreversible platelet inhibitor with pharmacologic effects dependent on its metabolic conversion to an active moiety. However, prasugel is much more rapidly converted to its active form than clopidogrel and therefore, has a faster onset of action (<30 minutes with 60 mg loading dose) and more consistent antiplatelet effect. Despite these advantages, prasugrel has been associated with a significantly increased risk of life-threatening and fatal bleeding, thus, limiting its use.[5,6] In response to the need for an ADP $P2Y_{12}$ receptor inhibitor with a better balance between efficacy and safety, ticagrelor (Brilinta™; AstraZeneca Pharmaceuticals) was developed and eventually approved by the FDA in July 2011. Ticagrelor, an oral reversible platelet ADP $P2Y_{12}$ receptor inhibitor, is indicated to reduce the risk of thrombotic cardiovascular events in patients with ACS. It is thought to have a more favorable pharmacokinetic and pharmacodynamic profile than clopidogrel and prasugrel.[5,6,8]

Mechanism of Action: Ticagrelor and its major metabolite reversibly

and noncompetitively bind to the ADP $P2Y_{12}$ receptor on the platelet surface which prevents ADP-mediated activation of the glycoprotein IIb/IIIa receptor complex leading to a reduction in platelet aggregation.[8,9] Since ticagrelor's antiplatelet action is reversible, recovery of platelet function is associated with the serum concentrations of ticagrelor and its major metabolite. In contrast, clopidogrel and prasugrel are irreversible ADP $P2Y_{12}$ inhibitors, which means their activity is maintained throughout the platelet's life-span; therefore, reversal of their pharmacodynamic effects is dependent on platelet turnover.[4,7]

Pharmacokinetics: Ticagrelor is rapidly absorbed following oral administration; its bioavailability is approximately 36%.[8] Food and high-fat meals do not affect its absorption; therefore, it can be taken with or without food. Ticagrelor is hepatically converted to the active metabolite AR-C124910XX by the cytochrome P450 (CYP) 3A4 enzyme system. Unlike prasugel and clopidogrel, ticagrelor does not require hepatic activation to exert its antiplatelet effect, since it is equally as potent at blocking the ADP $P2Y_{12}$ receptor as its active metabolite. The drug's peak antiplatelet activity occurs in about 2 hours. Ticagrelor and its active metabolite are highly protein bound (>99%). Although ticagrelor's primary route of elimination is via hepatic metabolism, it is also excreted in the urine and feces. The mean half-life of ticagrelor and its active metabolite are 7 and 9 hours, respectively.

Select Clinical Trials: Wallentin and colleagues conducted the **PLAT**elet Inhibition and Patient **O**utcome (PLATO) trial which evaluated the efficacy and safety of ticagrelor compared to clopidogrel.[6] This international Phase III, multicenter, randomized, double-blind study included patients (N=18,624) hospitalized for ACS with or without ST-segment elevation who experienced an onset of symptoms within 24 hours prior to randomization. For those with ACS without ST-segment elevation additional criteria needed to be met. Major exclusion criteria included any contraindication to clopidogrel, administration of a fibrinolytic agent within 24 hours of randomization, the need for maintenance oral anticoagulation, an increased risk of bradycardia, and concurrent use of a strong CYP3A4 inhibitor or inducer. Patients were randomized to receive a 180 mg oral loading dose of ticagrelor, followed by ticagrelor 90 mg twice daily, or a 300 mg oral loading dose of clopidogrel, followed by clopidogrel 75 mg daily for a 6 to 12 month period. Patients in the clopidogrel group who received a prior loading dose and maintenance therapy for at least 5 days were maintained on a 75 mg daily dosing regimen. All participants who were tolerant of aspirin received 75 to 100 mg daily; however, a 325 mg loading dose was given to those who had not been previously initiated on aspirin therapy and a daily 325 mg dose was given to patients for 6 months following stent placement. Depending on their treatment group designation, patients undergoing PCI after randomization were permitted either an additional dose of clopidogrel 300 mg or ticagrelor 90 mg. It was recommended that clopidogrel be held for 5 days and ticagrelor be held for 24 to 72 hours for those patients undergoing coronary artery bypass graft (CABG) surgery. The primary efficacy endpoint was the time to first occurrence of death from vascular causes, myocardial infarction (MI), or stroke. The primary safety endpoint was the time to first occurrence of any major life-threatening bleeding including CABG and non-CABG related bleeding, intracranial and other forms of fatal bleeding. The primary composite efficacy endpoint was significantly reduced in patients receiving ticagrelor compared to those receiving clopidogrel (9.8% versus 11.7%, respectively; $P<0.001$). The rate of stroke did not differ significantly between the two treatment groups. However, the ticagrelor-treated patients had a lower rate of MI than those treated with clopidogrel (5.8% versus 6.9%, respectively; $P=0.005$). Furthermore, the rate of death from vascular causes was significantly lower in the ticagrelor group than the clopidogrel group (4% versus 5.1%, respectively; $P=0.0005$). The overall rate of major life-threatening bleeding did not differ significantly between ticagrelor and clopidogrel (11.6% versus 11.2%, respectively; $P=0.43$). Additionally, the ticagrelor and clopidogrel arms did not differ significantly in the rate of CABG-related bleeding (5.3% versus 5.8%, respectively; $P=0.32$). However, there was a higher rate of non-CABG-related major bleeding with ticagrelor compared to clopidogrel (4.5% versus 3.8%, respectively; $P=0.03$). Although not statistically significant, more episodes of intracranial bleeding were associated with ticagrelor compared to clopidogrel (0.3% versus 0.2%, respectively; $P=0.06$). Furthermore, there were significantly more episodes of fatal intracranial bleeding associated with ticagrelor compared to clopidogrel (0.1% versus 0.01%, respectively; $P=0.02$). Nonetheless, there were significantly fewer episodes of other forms of fatal bleeding attributed to the ticagrelor compared to the clopidogrel (0.1% versus 0.3%, respectively; $P=0.03$). Dyspnea was more common in the ticagrelor group compared with clopidogrel group (13.8% versus 7.8%, respectively; $P<0.001$). Additionally, there was a higher incidence of ventricular pauses that were $\geq$3 seconds detected by Holter monitoring during the first week in the ticagrelor group compared with the clopidogrel group (13.8% versus 7.8%, respectively; $P=0.01$); however, after 1 month of the therapy the between-group incidence of this side effect was not statistically significant. The authors concluded that ticagrelor was more effective than clopidogrel in reducing the risk of death from vascular causes, MI, or stroke in patients with ACS and that ticagrelor's beneficial effects were not associated with an increased risk of major bleeding.

A subgroup analysis of the PLATO trial found that there was a significant correlation between treatment outcome and the patients' respective geographic regions ($P=0.045$).[10] Further evaluation demonstrated that ticagrelor had less of an

effect in reducing the risk of death in North American patients than in those residing in other areas of the world. Therefore, Mahaffey and associates performed another subgroup analysis to determine why North American patients in the PLATO trial experienced this lower response rate to ticagrelor. These investigators determined that more patients in the United States were treated with high-dose aspirin than their counterparts in other regions. Approximately 53.6% of patients in the United States compared to 1.7% of those in other areas of the world took a median aspirin dose ≥300 mg per day. The researchers could not find any other between-group differences which could explain the reduced clinical effects of ticagrelor in North American patients. Additionally, their analysis demonstrated that patients who took low-dose maintenance aspirin, including those in the United States, experienced better clinical outcomes with ticagrelor compared to clopidogrel. The authors concluded concurrent use of a low-dose (<300 mg/day) rather than a high-dose aspirin regimen with ticagrelor resulted in a more favorable clinical outcome.

A summation of other key clinical trials involving ticagrelor are located in Table 1.

Table 1: Key Clinical Trials

Name	Study Design	Objective	Conclusion
DISPERSE-2[11]	Phase II, randomized, double-blind, double-dummy	Compare the safety and initial efficacy of ticagrelor with clopidogrel in patients with NSTEMI	Ticagrelor has similar safety and efficacy compared with clopidogrel.
Comparison of Ticagrelor with Clopidogrel in Patients with a Planned Invasive Strategy for ACS[12]	Subgroup analysis of the PLATO trial	Compare the safety and efficacy of clopidogrel in patients with planned PCI	Ticagrelor demonstrated significant and clinically relevant reduction in cardiovascular events with similar safety compared with clopidogrel in patients undergoing PCI.
The Onset/Offset Study[13]	Multicenter, randomized, double-blind, double-dummy, parallel group	Compare the onset and offset of antiplatelet effects of ticagrelor compared with clopidogrel	Ticagrelor achieved rapid and greater onset and faster offset compared with clopidogrel.

ACS= Acute Coronary Syndrome, NSTEMI=Non-ST Elevation Myocardial Infarction, PCI=Planned Coronary Intervention

Adverse Reactions: The most common adverse reactions associated with ticagrelor were dyspnea, headache, cough, dizziness, nausea, atrial fibrillation, and hypertension (≥3%).[8] In the PLATO trial, dyspnea was reported in 14% of patients on ticagrelor compared with 8% of patients on clopidogrel; this resulted in 0.9% of ticagrelor group discontinuing the medication.[6] The cause of dyspnea associated with ticagrelor is unknown. However, it is speculated that the mechanism may be related to modulation of adenosine metabolism.[14] Bradyarrythmias, including ventricular pauses of ≥3 seconds, were also reported with ticagrelor in the PLATO trial.[6] More specifically, the reported ventricular pauses of ≥3 seconds occurred in approximately 6% of patients. Bleeding is the most serious adverse effect of ticagrelor. In the PLATO trial, there were more intracranial bleeds in the ticagrelor-treated patients compared to clopidogrel-treated patients, 26 (0.3%) patients and 14 (0.2%) patients, respectively. Additionally, fatal intracranial bleeding occurred in 11 patients receiving ticagrelor and in 1 patient receiving clopidogrel. Finally, ticagrelor was associated with a greater risk of non-CABG bleeding compared to clopidogrel, however, there was no difference with CABG-related bleeding. In the PLATO trial, laboratory abnormalities were also reported. Serum uric acid levels increased approximately 0.6 mg/dL from baseline for the ticagrelor group and approximately 0.2 mg/dL for the clopidogrel group (P<0.001). The difference resolved upon discontinuation of the medication within 30 days. Also, a greater than 50% increase in serum creatinine levels from baseline was reported in patients receiving ticagrelor. This increase did not progress with treatment and decreased to baseline with continued therapy.[6, 8]

Drug Interactions: Daily maintenance doses of aspirin >100 mg have been shown to reduce ticagrelor's clinical effects and therefore, should be avoided.[8] Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5; so concurrent use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin) or potent CYP3A4 inducers (e.g., rifampin, carbamazepine, and phenobarbital) is not recommended. Ticagrelor can inhibit the metabolism of simvastatin and lovastatin via the CYP3A4 enzyme system; therefore, doses >40 mg of either drug should be avoided during concomitant use with ticagrelor. Since ticagrelor can inhibit the P-glycoprotein transporter, digoxin levels should be monitored with initiation or after any change in ticagrelor therapy. In contrast, clopidogrel is extensively metabolized via CYP2C19 to its active metabolite.[4] Therefore, concomitant use of CYP2C19 inhibitors and inducers with clopidogrel should be avoided. Prasugrel is metabolized by CYP3A4 and CYP2B6 to its active metabolite.[7] Thus, the use of strong CYP3A4 inhibitors with prasugrel is not recommended.

Pregnancy and Lactation: Ticagrelor is classified as Pregnancy-Risk Category C, since there are no adequate and well-controlled studies which evaluated the use of this drug in pregnant women.[8] However, it has been shown that at approximately 5 to 7 times the maximum human dose, ticagrelor produced structural abnormalities in animal offspring. Therefore, ticagrelor should only be given to a pregnant woman if the potential maternal benefit outweighs the risk to the fetus. On the other hand, clopidogrel and prasugrel are classified as Pregnancy-Risk Category B, since supratherapeutic doses of these medications have not demonstrated fetal harm in animal studies.[4,7] However, it is still recommended that neither drug be taken during pregnancy unless the benefit to the mother exceeds any potential risk to the fetus. It is not known if ticagrelor or its active metabolites pass into human breast milk. Since many drugs are excreted in human milk and have the potential to cause serious adverse reactions in nursing infants, the manufacturer recommends either discontinuing breastfeeding or ticagrelor, taking into account the importance of the drug to the mother.[8]

Monitoring Parameters: Signs of bleeding, hemoglobin and hematocrit levels, and renal function should be monitored during ticagrelor therapy.[8] Uric acid levels should also be followed, especially in patients with gout or at risk of hyperuricemia. Additionally, all ticagrelor-treated patients should be assessed for signs and symptoms of dyspnea.

Dose and Administration: The recommended dose of ticagrelor is 180 mg oral loading dose followed by 90 mg orally twice daily as a maintenance dose.[8] After the initial loading dose of aspirin 325 mg, the recommended daily maintenance dose of aspirin is 75- to 100-mg daily. Ticagrelor can be administered with or without regard to food. No dosage adjustments are recommended for patients with renal or mild/moderate hepatic impairment However, the drug is contraindicated in patients with severe hepatic dysfunction.

Cost and Formulary Status: Ticagrelor is available as a 90 mg tablet. Its average wholeprice (AWP) sale is $4.35 per tablet. Therefore, a 180 mg loading dose is $8.70, and a 30 day supply is $261.00.[15] Ticagrelor has been added to the CCHS Formulary.

Conclusion: Ticagrelor is a novel antiplatelet agent which is FDA-approved to reduce the rate of thrombotic cardiovascular events in patients with ACS. Some advantages of ticagrelor compared to clopidogrel and prasugrel, include its reversible antiplatelet effect, more rapid onset and offset of action, and pharmacologic activity not dependent on the production of an active metabolite. The recommended time period for discontinuation prior to an invasive procedure or surgery listed in the product labeling is 5 days for both clopidogrel and ticagrelor and 7 days for prasugrel. However, some experts believe that the ticagrelor can be stopped 72 hours before these events without increasing the risk of bleeding. The PLATO trial demonstrated that ticagrelor was more effective in reducing cardiovascular-related mortality than clopidogrel with a similar risk of major bleeding. Some side effects in the trial which occurred more commonly with ticagrelor than clopidogrel were dyspnea and bradyarrthymias, including ventricular pauses ≥3 seconds. A potential disadvantage of ticagrelor is its twice daily dosing regimen compared with clopidogrel and prasugrel which only need to be given once daily. Furthermore, ticagrelor is more expensive than either clopidogrel or prasugrel. Key differences between these $P2Y_{12}$ inhibitors are summarized in Table 2.

Table 2: Key Differences Between Oral Platelet ADP $P2Y_{12}$ Receptor Inhibitors [4,7,8,15]

Feature	Clopidogrel (Plavix®)	Prasugrel (Effient®)	Ticagrelor (Brilinta ™)
FDA-approved indications	ACS Prevention of acute CV events following: MI, stroke, or PAD	ACS Prevention of acute CV events in patients to be managed with PCI	ACS
Manufacturer	Bristol Myers Squibb/ Sanofi Aventis	Eli Lilly	AstraZeneca
Reversible platelet inhibition	No	No	Yes
Loading dose	300-600 mg	60 mg	180 mg
Maintenance dose	75 mg once daily	10 mg once daily*	90 mg twice daily
Prodrug	Yes	Yes	No
Metabolism	CYP2C19 and CYP3A4	CYP3A4 and CYP2B6	CYP3A4 and CYP3A5
Dyspnea and ventricular pauses	No	No	Yes
Average Wholesale Price	75 mg: $7.29/ tablet $2,624/year	10 mg: $7.28/tablet $2,620/year	90 mg: $4.35/tablet $3,132/year

ACS= Acute Coronary Syndrome, CV=Cardiovascular, MI=Myocardial Infarction, PAD=Peripheral Artery Disease, PCI=Percutaneous Coronary Intervention

*Manufacturer recommends a maintenance dose of 5 mg once daily in patients weighing <60 kg.

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Acetaminophen (Tylenol®) Concentrated Infant Drops Alert

There has been a long history of safety concerns associated with the availability of multiple strengths of acetaminophen products. In May 2011, an FDA Advisory Panel recommended that liquid, chewable, and tablet forms of acetaminophen be made in only one strength to help minimize the risk of medication dosing errors. The Panel also promoted standardization of dosing devices utilized to measure liquid acetaminophen products. Consequently, manufacturers have decided to voluntarily phase out the acetaminophen 100 mg/mL concentrated infant drops. Furthermore, the Consumer Healthcare Products Association, a trade group representing over-the-counter pharmaceutical companies, is supporting the conversion of all acetaminophen liquid concentrations to 160 mg/5mL. Additionally, the pharmaceutical industry is voluntarily standardizing the units of measure on dosing devices (e.g., cups, spoons) which accompany liquid acetaminophen-containing products as milliliters rather than teaspoonfuls or cubic centimeters. Further information about this matter can be found on this website: http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM264038.pdf.

In order to ensure patient safety, the Pediatric Institute decided to remove all remaining 100 mg/mL acetaminophen products on September 7, 2011. Acetaminophen 160 mg/5 mL cups will be available in all Pyxis machines. Order sets and preference lists will be automatically updated to reflect this change. Cleveland Clinic Ambulatory Pharmacies will be removing the concentrated infant drops to ensure continuity and patient safety.

Formulary Update

The CCHS Medical Staff Pharmacy and Therapeutics Committee met on October 4, 2011, and the Cleveland Clinic Local Pharmacy and Therapeutics Committee met on October 13, 2011, and the following decisions were made:

Additions to the CCHS Adult Formulary:

Antimicrobials:

1. **Oxacillin (generic)** will once again be the antistaphylococcal penicillin of choice on the CCHS Formulary. The switch from nafcillin to oxacillin is needed because there are a number of drug interactions which occur with nafcillin, but not oxacillin.
2. **Quinupristin/dalfopristin (Synercid™)**: It is an antimicrobial agent used primarily for coverage of multidrug resistant gram-positive organisms including vancomycin-resistant *enterococci* (VRE). Although this was removed from the Main Campus formulary several years ago due to availability of other agents with improved side effect and drug interaction profiles; it is needed once again because of the increasing number of daptomycin-nonsusceptible VRE. Quinupristin/dalfopristin is a potent inhibitor of CYP3A4.
    a. Quinupristin/dalfopristin is **restricted** to Infectious Diseases.

Hematology/Oncology:

1. **Brentuximab (Adcetris®)**: It is an antibody drug conjugate targeting the CD30 receptor that is FDA-approved for patients with Hodgkin lymphoma who have failed at least 2 prior chemotherapy regimens (in patients ineligible for transplant) or after stem cell transplant failure; and for the treatment of systemic anaplastic large cell lymphoma (sALCL) after failure of at least 1 prior chemotherapy regimen. The usual dose of brentuximab is 1.8 mg/kg administered as an IV infusion over 30 minutes every 3 weeks to a maximum of 16 cycles. The dose for patients weighing >100 kg should be calculated for 100 kg (i.e., the maximum dose is 180 mg).
    a. Brentuximab is **restricted** to the Department of Hematology and Oncology for use in the **outpatient setting only**.
2. **Peginterferon alfa-2a (Pegasys®)**: It is FDA-approved for the treatment of chronic hepatitis C and chronic hepatitis B; however, the drug was reviewed by the CCHS Hematology/Oncology Specialty Panel specifically for an off-label indication, the treatment of myelofibrosis. Currently, there are no FDA-approved medications for the treatment of myelofibrosis. The dose of peginterferon alfa-2a for myelofibrosis is 90 mcg weekly administered via subcutaneous injection which is lower than the usual dose for hepatitis B and C. It is important to note that peginterferon alfa-2a is a weak inhibitor of CYP1A2 and patients receiving theophylline, ribavirin, methadone, and zidovudine should be monitored closely for increased adverse effects due to the potential for increased substrate drug levels.

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Neurosciences:

1. **Lurasidone (Lutada®)**: It is an atypical antipsychotic indicated for the treatment of schizophrenia. The starting dose is 40 mg per day with a maximum recommended dose of 80 mg daily. Dosage adjustments are necessary for renal and hepatic impairment. The daily dose should be administered with food (at least 350 calories) in order to ensure adequate absorption. Lurasidone is metabolized by CYP3A4 and dosage adjustments may be required in patients on concomitant therapy with inducers or inhibitors of CYP3A4.
    a. Lurasidone is **restricted** to initiation by Psychiatry; however, continuation of therapy from home is not restricted.
2. **Asenapine (Saphris®)**: It is an atypical antipsychotic indicated for the acute or maintenance treatment of schizophrenia and for the acute treatment of mixed or manic episodes associated with bipolar I disorder in adults. Due to extensive first pass metabolism, when ingested orally, this agent is available as a sublingual tablet. The usual dose for schizophrenia is 5 mg sublingual twice daily and 10 mg sublingual twice daily for bipolar disorder. The sublingual tablets should be placed under the tongue and allowed to disintegrate. The tablets should not be chewed, crushed, or swallowed and eating or drinking should be avoided for at least 10 minutes after administration. Asenapine is a weak inhibitor of CYP2D6 and a substrate of CYP1A2.
    a. Asenapine is **restricted** to initiation by Psychiatry; however, continuation of therapy from home is not restricted.

Critical Care/Surgery/Anesthesia

1. **Roflumilast (Daliresp®)**: It is a selective phosphodiesterase type 4 (PDE4) inhibitor FDA-approved to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD. The usual dose is 500 mcg orally once daily. Roflumilast is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh class B or C) and it should not be used for acute exacerbations of COPD or acute bronchospasms. Roflumilast is a major substrate of CYP3A4 and a minor substrate of CYP1A2.
    a. Rofumilast is **restricted** to continuation of therapy from home (i.e., no initiation of therapy in hospital).
2. **Aerosolized epoprostenol (Flolan®)**: It is a prostacyclin vasodilator FDA-approved for the treatment of pulmonary hypertension and the intravenous formulation is available on the Formulary. Inhaled epoprostenol is considered to be an off-label route of administration for the commercially available intravenous formulation; however, its use has been described for the treatment of refractory hypoxemia associated with acute respiratory distress syndrome, severe pulmonary hypertension and acute right ventricular failure after cardiac surgery. Rationale for use of inhaled epoprostenol include: less systemic side effects (e.g. hypotension and pulmonary shunting) versus intravenous epoprostenol, decreased side effects vs. inhaled nitric oxide (NO), and cost savings due to reduction in use of NO. There is a specific protocol and procedure for use of inhaled epoprostenol.
    a. Aerosolized epoprostenol is **restricted** to the ICUs and must be ordered by an ICU physician.
3. **Intravenous acetaminophen (Ofirmev®)**: It is FDA-approved for the management of mild to moderate pain; management of moderate to severe pain as an adjunct to opioid therapy, and reduction of fever. Dosing of intravenous (IV) acetaminophen in adults weighing ≥50 kg is 1000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4000 mg per day (4 hours is the minimum dosing interval). Dosing for adults weighing < 50 kg is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. The drug can be administered undiluted; however, all doses must be administered as a 15 minute intermittent infusion. **For doses less than 1000 mg, the appropriate dose must be withdrawn from the vial and placed into a separate empty, sterile, container (e.g., glass bottle, plastic intravenous container, or syringe) prior to administration in order to avoid the inadvertent delivery and administration of the total volume of the commercially available container (e.g., 1000 mg/100 ml).** The product only has a stability of 6 hours once the vial is punctured or the medication is transferred to another container.
    a. Intravenous acetaminophen is **restricted as follows** in order to ensure appropriate use as IV acetaminophen is more expensive compared to oral and rectal acetaminophen as well as generic ketorolac**:**
        i. Must be prescribed by a Staff/Attending Physician
        ii. Must not be used as first-line therapy
        iii. Must have specific indication for use (e.g., patient is NPO, cannot receive NSAID due risk of bleeding)
        iv. CPOE drug file will be for 24 hours only (however, drug can be re-ordered each day if needed).
        v. It will not be stocked in any automated dispensing cabinet (e.g., Pyxis machine).
    b. Cost Comparison (Approximate Cleveland Clinic Acquisition Cost):
        i. Acetaminophen injection 1000 mg = $ 10
        ii. Oral acetaminophen 1000 mg = $ 0.04
        iii. Rectal acetaminophen 650 mg = $ 0.12
        iv. Ketorolac injection 30 mg = $ 0.49

Cardiovascular/Thrombosis:

1. **Rivaroxaban (Xarelto™)**: It is an oral anticoagulant that directly antagonizes factor Xa and is a reversible inhibitor of the factor Xa active site**.** It is FDA-approved for prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. The recommended dose is 10 mg orally daily for DVT prophylaxis. Caution is recommended in patients with moderate renal function (CrCl 30 – 49 mL/min) although no specific dosage adjustment is recommended. The drug should not be used in patients with severe renal impairment (CrCl <30 mL/min) or moderate to severe hepatic impairment (Child-Pugh classes B and C) and patients with hepatic disease associated with coagulopathy. Drug interaction concerns exist with p-glycoprotein and CYP3A4 inhibitors and inducers. Therefore, if rivaroxaban must be administered as a crushed tablet via a feeding tube, it must be administered through a tube ending in the stomach; which would most commonly be an orogastric (OG) or nasogastric (NG) feeding tube.
    a. Rivaroxaban is **restricted** as follows:
        i. For use as thromboprophylaxis after orthopedic surgery
        ii. For use by Vascular Medicine
2. **Ticagrelor (Brilinta™)**: It is an agent that reversibly and noncompetitively binds the adenosine diphosphate (ADP) $P2Y_{12}$ receptor on the platelet surface which prevents ADP-mediated activation of the glycoprotein (GP) IIb/IIIa receptor complex, therefore, inhibiting platelet aggregation. It is FDA-approved to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) as well as in patients treated with percutaneous coronary intervention (PCI). The recommended dose of ticagrelor is a 180 mg oral loading dose followed by 90 mg orally twice daily as maintenance. Concomitant aspirin dosing should be 75- to 100-mg daily after an initial loading dose of 325 mg. Drug interaction potential exists because ticagrelor is metabolized by CYP3A4 and to a lesser extent CYP3A5.

Adults:

Not Added to the CCHS Formulary:

1. **Fidaxomicin (Dificid™)**: It is indicated for the treatment of Clostridium difficile-associated diarrhea (CDAD) and was not added to the formulary due to availability of other treatment options.
2. **Degarelix (Firmagon®)**: It is a long-acting gonadotropin-releasing hormone (GnRH) antagonist approved for use in patients with advanced prostate cancer; however, it has no advantage over current formulary medications.
3. **Mometasone/formoterol (Dulera®)**: It is a combination inhaler containing a synthetic corticosteroid and selective long-acting beta-2 adrenergic receptor agonist indicated for the treatment of asthma and was not added due to lack of advantage over current formulary medications (e.g., Advair® [fluticasone/salmeterol] and Symbicort® [budesonide/formoterol]).
4. **Alvimopan (Entereg®)**: It is an opioid receptor antagonist indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis. Due to lack of efficacy in decreasing length of stay as per a drug use evaluation performed at the Main Campus, the CCHS Medical Staff Pharmacy and Therapeutics Committee has decided to remove this agent from the Main Campus Formulary and it is considered non-formulary at all CCHS hospitals.

Adults:

Deletion from the CCHS Formulary:

1. **Oral alcohol** (e.g., gin, scotch, vodka, whiskey, and bourbon) is being removed from the CCHS Formulary. There will be no dispensing of oral alcohol for any medical use at any CCHS hospital. The rationale for this decision is that there are other treatment modalities to manage alcohol withdrawal. **Oral alcohol will be non-formulary and not available after November 16, 2011.** The EPIC drug file for alcoholic beverage will be removed from the preference list. If providers do not know how to manage alcohol withdrawal any other way, they can consult Psychiatry for assistance. At the Main Campus, Dietary and Food Services has carried beer and wine for purposes of dietary preference; however, they will be contacted and it will be recommended that they remove oral alcohol as well.

Children's Hospital/Pediatrics:

Additions to the CCHS Pediatric Formulary:

Antimicrobials:

1. **Oxacillin** will once again be the antistaphylococcal penicillin of choice on the CCHS Formulary. The switch from nafcillin to oxacillin is needed because there are a number of drug interactions which occur with nafcillin, but not oxacillin.
2. **Quinupristin/dalfopristin (Synercid™)**: This is an antimicrobial agent used primarily for coverage of multidrug resistant gram-positive organisms including vancomycin-resistant *enterococci* (VRE). Although this was removed from the Main Campus formulary several years ago due to availability of other agents with improved side effect and drug interaction profiles; it is needed once again because of the increasing number of daptomycin-nonsusceptible VRE. Quinupristin/dalfopristin is a potent inhibitor of CYP3A4.
    a. Quinupristin/dalfopristin is **restricted** to Infectious Diseases.

Miscellaneous:

1. **Intravenous acetaminophen (Ofirmev®)**: It is FDA-approved for the management of mild to moderate pain; management of moderate to severe pain as an adjunct to opioid therapy, and reduction of fever in adults and children ≥2 years of age. Dosing recommendations for children ≥ 2 to 12 years old and adolescents <50 kg are 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day (4 hours is the minimum dosing interval). Dosing for adolescents > 50 kg is the same as adult dosing 1000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4000 mg per day (4 hours is the minimum dosing interval). The drug can be administered undiluted; however, all doses must be administered as a 15 minute intermittent infusion. **For doses less than 1000 mg, the appropriate dose must be withdrawn from the vial and placed into a separate empty, sterile, container (e.g., glass bottle, plastic intravenous container, or syringe) prior to administration in order to avoid the inadvertent delivery and administration of the total volume of the commercially available container (e.g., 1000 mg/100 ml).** The product only has a stability of 6 hours once the vial is punctured or the medication is transferred to another container.
    a. Intravenous acetaminophen is **restricted as follows:**
        i. Must be prescribed by a Staff Physician from Pediatric Anesthesia, Pediatric Pain Service, or Pediatric ICU.
        ii. Prescribers will need to document the indication for IV acetaminophen in Epic (See below)
        iii. Can only be prescribed for 24 hours (however, drug can be re-ordered each day if needed)
        iv. The drug will not be stocked in any automated dispensing cabinet

        Indications for Pain:

        1. Obstructive sleep apnea
        2. Mitochondrial cytopathy
        3. High-risk of postoperative nausea and vomiting (PONV):
            a. Tonsillectomy and Adenoidectomy
            b. Strabismus Surgery
            c. Ophthalmologic procedures
            d. Testicular procedures
            e. Middle ear surgery
        4. Pyloromyotomy
        5. Neurosurgical procedures
        6. Bowel surgery with expected postoperative NPO status and likely bowel absorption derangement
        7. Patient is NPO or has PONV and cannot receive rectal acetaminophen (neutropenic, bowel absorption derangement after surgery or due to inflammatory bowel disease)
        8. Patient with severe constipation or other adverse side effects related to opioids for whom ketorolac use is either contraindicated or not fully effectual in controlling pain
        9. Patient is not a candidate for ketorolac: renal pathology or bleeding diathesis and for whom multimodal analgesia as per WHO guidelines is the best practice approach for pain control
        10. Patient with intolerance to opioids, contraindication to ketorolac, and NPO who requires improved pain control

        Indications for Antipyrexia:

        1. Patient is NPO or has PONV and cannot receive rectal acetaminophen either because of neutropenia, rectal trauma, patient refusal for rectal administration, bowel absorption derangement as related to surgery or inflammatory bowel condition.

Children's Hospital/Pediatrics:
Additions to the CCHS Pediatric Formulary

Intravenous acetaminophen (Ofirmev®) (continued):
Can only be used first-line for specific indications/patient populations:

1. High-risk of PONV:
    a. Tonsillectomy and Adenoidectomy
    b. Strabismus Surgery
    c. Ophthalmologic procedures
    d. Testicular procedures
    e. Middle ear surgery
2. Pyloromyotomy
3. Neurosurgical Procedures
4. Bowel surgery with expected postoperative NPO status and likely bowel absorption derangement

Deletion to the CCHS Pediatric Formulary:

1. Remove Plasma-Lyte from the CCHS Pediatric Formulary and CCHS Labor and Delivery due to no advantage over other formulary agents (e.g. Lactated Ringers).