Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Oral Antiplatelet Agents***
May 2015

The NPTC performed a class review of oral antiplatelet agents at the May meeting. This class of medications was last reviewed in March 2011. Since that time, ticagrelor received FDA approval. Oral antiplatelet agents include aspirin, clopidogrel, prasugrel, ticlopidine, and ticagrelor. Ticlopidine is no longer recommended as a first line agent as it has many life threatening hematologic adverse reactions, and thus, was not included in the review. Aspirin was also not included in the review. Clopidogrel is the only (non-aspirin) oral antiplatelet agent currently named on the National Core Formulary (NCF).

Discussion:
All three agents reviewed are FDA-approved for thrombosis prophylaxis of acute coronary syndrome (ACS) managed with percutaneous coronary intervention (PCI). Ticagrelor and clopidogrel are also approved for thrombosis prophylaxis in ACS managed without PCI. Clopidogrel has the most FDA-approved indications, including ACS, acute ST-segment elevation myocardial infarction (STEMI), stroke, recent myocardial infarction (MI) and peripheral arterial occlusive disease. Clopidogrel is the only agent studied in patients undergoing fibrinolysis. Both prasugrel (Wiviott, 2007) and ticagrelor (Wallentin, 2009) have been associated with lower rates of cardiovascular (CV) events and stent thrombosis than clopidogrel. Prasugrel has shown a marked benefit over clopidogrel in patients with diabetes. Prasugrel is also associated with a higher rate of bleeding than clopidogrel. Patients with a history of stroke/transient ischemic attack (TIA), weight less than 60 kilograms or age greater than or equal to 75 years should not receive prasugrel because risks outweigh the benefits. The overall risk of major bleeding with ticagrelor is not greater than that with clopidogrel, although there is a higher rate of non-CABG related bleeding. Ticagrelor is associated with a 22% lower rate of death from any cause than clopidogrel. This is an effect that is not observed in studies with prasugrel versus clopidogrel. Ticagrelor has a slightly different adverse reaction profile than the other two, notably ventricular pauses that are rarely symptomatic and usually only during the first week of treatment and an increase in serum uric acid levels. Ticagrelor is contraindicated in severe hepatic impairment. Ticagrelor is dosed twice daily versus once daily for clopidogrel and prasugrel. When used as dual antiplatelet therapy (DAPT) with ticagrelor, it is recommended to use no greater than 100mg of aspirin daily.

Literature Review:
The following guidelines were reviewed: 2011 European Society of Cardiology (ESC) guidelines for the management of ACS in patients presenting without persistent ST-segment elevation, the 2012 ESC guidelines for the management of acute MI in patients presenting with ST-segment elevation, the 2013 American College of Cardiology/America Heart Association (ACC/AHA) guidelines for the management of ST-elevation MI, and 2014 ACC/AHA guidelines for the management of patients with non-ST-elevation ACS. ESC guidelines recommend the use of ticagrelor or prasugrel over clopidogrel whereas the AHA/ACC guidelines do not state a preferential agent as a Class I recommendation. The ACC/AHA guidelines do give a Class II recommendation stating that it is “reasonable” to use one agent over the others based on patient/disease characteristics.

Primary literature was introduced through the above guidelines. The TRITON-TIMI 38 study evaluated prasugrel and clopidogrel. This multi-centered, international, double-blinded study enrolled 13,608 patients with moderate to high risk ACS who received PCI. Randomized study participants received either prasugrel 60mg load followed by a 10mg daily maintenance dose or clopidogrel 300mg load followed by a 75mg daily maintenance dose for 6 to 15 months. Both treatment arms also took aspirin daily. The primary outcomes measured were death from CV causes, nonfatal MI or nonfatal stroke. DAPT with prasugrel/ASA showed significantly reduced rates of death from CV causes, nonfatal MI and stent thrombosis versus clopidogrel/ASA. Prasugrel had an increased risk of major bleeding versus clopidogrel. The study also reported that patients who are over 75 years, who weigh less than 60 kg, or have a prior history of TIA/stroke may not benefit from prasugrel. Patients with diabetes mellitus or who have suffered STEMI may benefit from prasugrel.

The Study of Platelet Inhibition and Patient Outcomes (PLATO) was a multicenter, double blind, randomized trial that compared ticagrelor and clopidogrel for the prevention of CV events in 18,624 patients admitted to the hospital with ACS, with or without ST-segment elevation. The primary endpoint (composite of death from vascular causes, MI, or stroke) was significantly less in the ticagrelor group versus clopidogrel at 12 months. The difference was apparent within the first 30 days and persisted throughout the study period. For those patients enrolled in North America, the benefit of ticagrelor appeared attenuated. A sub-analysis attributed this to higher doses of ASA (325mg) used in North America versus lower doses (75-100mg) used in Europe. Other groups in which the benefit also appeared attenuated were those weighing less than the median weight for their sex and those not taking lipid-lowering medications at randomization. No differences in rates of major bleeding were noted between the two agents. However, a non-significant higher rate of non-CABG related major bleeding and more episodes of intracranial bleeding were seen in the ticagrelor group.

A 2014 systematic review from the Agency on Healthcare Research and Quality (AHRQ) entitled "Antiplatelet and Anticoagulant Treatments for Unstable Angina/Non-ST Elevation Myocardial Infarction" was also reviewed. This document evaluated the effectiveness and safety of antiplatelet agents used to treat UA/NSTEMI in an early invasive approach, an initial conservative approach, and after hospitalization. In patients on antiplatelet therapy treated with early invasive or PCI-based strategy, findings were consistent with published guidelines and meta-analyses. Prasugrel and ticagrelor were both associated with significant reduction in ischemic endpoints compared with clopidogrel. Ticagrelor did not have a significantly higher incidence of major bleeding compared with clopidogrel at one year as noted with prasugrel. Studies looking at initial conservative treatment utilized injectable glycoprotein IIb/IIIa inhibitors and anticoagulants rather than oral antiplatelet agents. Findings reviewing treatment after discharge were also consistent with current published guidelines. Dual antiplatelet therapy, typically aspirin and another antiplatelet agent, has better outcomes than single antiplatelet therapy but questions remain about the optimal duration of treatment. There is inconsistent data to draw conclusions about use of triple antiplatelet therapy. Additionally, there is a lack of direct comparison of prasugrel and ticagrelor. Safety and efficacy data is lacking for mixed treatment approaches. The duration of DAPT needs to be better defined and requires further study on aspirin doses in DAPT.

Findings:
Although there is evidence to support the use of all three antiplatelet agents reviewed, NPTC retained clopidogrel as the sole (non-aspirin) oral antiplatelet agent on the NCF. Prasugrel and ticagrelor were not added as their use is dependent on diagnosis, procedure, concomitant disease states and preference by local cardiologists. There are currently no head-to-head studies comparing prasugrel versus ticagrelor.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

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