Efficacy of Triple Oral Antithrombotic Therapies

Early evidence showed improved outcomes associated with long-term aspirin therapy after acute coronary syndromes. In more recent years, the efficacy of dual anti-platelet therapy (DAPT) with aspirin plus a P2Y₁₂ receptor inhibitor (e.g., clopidogrel) is beneficial for the treatment of acute coronary syndrome (ACS) and non-ST-elevation myocardial infarction (NSTEMI). A 20% reduction in composite ischemic events over 12 months was observed with aspirin plus clopidogrel vs. aspirin plus placebo. More potent DAPT regimens produced an even greater reduction in the incidence of stent thrombosis; however, an increase in major bleeding risk could be observed. Due to the higher incidence of ischemic stroke after an ACS, more information needs to be evaluated to determine if triple oral antithrombotic therapy following an ACS is appropriate. This issue of CLIPS briefly summarizes a review article that evaluates triple oral antithrombotic therapies following an ACS event or percutaneous coronary intervention (PCI) procedure. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Cilostazol
- Phosphodiesterase inhibitor that decreases platelet aggregation.
- Treatment is not recommended by the ACC/AHA or ESC guidelines for ST elevation myocardial infarction (STEMI), unstable angina / non ST-elevation myocardial infarction (UA/NSTEMI) or percutaneous coronary intervention (PCI). It is not approved for acute coronary syndrome (ACS) or post-PCI in the USA or Europe.
- Cilostazol, aspirin, and clopidogrel have been evaluated against aspirin and clopidogrel in patients receiving a PCI with stent implantation.
- Triple therapy was associated with a lower rate of revascularization (RR, 0.65; 95% CI, 0.55 – 0.77) and less angiographic restenosis (RR, 0.54; 95% CI, 0.45 – 0.65; P <0.00001); however, no significant differences in myocardial infarction (MI) (RR, 0.92; 95% CI, 0.63 – 1.34) or all cause-death (RR, 0.77; 95% CI, 0.5 – 1.09) with triple antiplatelet therapy compared to DAPT.

Thrombin receptor inhibitors

Atopaxar
- Protease-activated receptor (PAR-1) antagonist that is being evaluated in clinical trials.
- No differences between atopaxar groups and placebo for bleeding in patients treated in clinical trials in patients with Non ST-elevation Acute Coronary Syndrome (NSTE-ACS).
- No differences between the composite ischemic outcomes (CVD, MI, stroke, or recurrent ischemia) were observed between atopaxar and placebo.
- Development of atopaxar was suspended due to dose-dependent increases in liver enzymes and QT prolongation.

Vorapaxar
- Oral PAR-1 receptor antagonist that was evaluated in two large randomized phase III trials.
- In the first trial, 12,944 patients with NSTE-ACS received vorapaxar or placebo + DAPT. No differences in the combination of CVD, MI, stroke, recurrent ischemia with rehospitalization or urgent coronary revascularization was observed through 2 years. The frequency of bleeding was significantly greater in the vorapaxar group; an increased risk of intracranial hemorrhage (ICH) was observed in the vorapaxar group.
- In the second trial, 26,449 patients with a history of MI or ischemic stroke or peripheral artery disease received vorapaxar or placebo with background aspirin therapy. The study was discontinued due to the increased risk of ICH. With the primary endpoint of CVD, MI, or stroke, a significant reduction in the primary outcome occurred compared to placebo (9.3% vs. 10.5%; HR, 0.87; 95% CI, 0.80 – 0.94).

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Thrombin Inhibitors

Ximelagatran
- Ximelagatran with aspirin therapy was evaluated in patients with recent myocardial damage and ximelagatran was associated with a lower frequency of death, MI, or recurrent severe ischemia compared with placebo (12.7 vs. 16.3%; HR, 0.76; 95% CI, 0.59 – 0.98). A significant increase in major bleeding was not observed.
- Ximelagatran was associated with hepatic toxicity and development was discontinued.

Dabigatran
- Oral, direct thrombin inhibitor with a half-life of 12-17 hours. Therapy was evaluated in patients with acute coronary syndrome.
- Patients were receiving dabigatran or aspirin and clopidogrel. A total of 1,861 patients with ACS within the last 14 days and planned treatment with DAPT were randomized to dabigatran or placebo. The incidence of CV death, MI, or ischemic stroke was similar between dabigatran and placebo.

Darexaban
- Oral Factor Xa inhibitor with a half-life of 14-18 hours.
- One clinical trial was conducted in which the efficacy and safety of the agent in ACS was evaluated with background DAPT therapy.
- The primary endpoint was bleeding and it occurred in 3.1% of patients with placebo and between 6.2% and 9.3% with darexaban treatment.
- A similar frequency of the outcome for death, MI, stroke, or recurrent ischemia was observed with darexaban vs. placebo.

Apixaban
- Direct oral factor Xa inhibitor with a half-life of 12 hours.
- The Apixaban for Prevention of Acute Ischemic Events-1 (APPRAISE-1) clinical trial was conducted in which 1,715 patients with recent ACS (within 7 days) and with at least one cardiovascular risk factor, received placebo or apixaban for 6 months. DAPT use was documented in 81% of the patients.
- Two of the apixaban doses (10 mg BID or 20 mg daily) were discontinued due to increased bleeding risk.
- Lower doses of apixaban was associated with dose-dependent, higher rates of International Society of Thrombosis and Hemostasis (ISTH) major or clinically relevant non-major bleeding (HR, 1.78; 95% CI, 0.91 – 3.48).
- Although lower rates of death, MI, ischemic stroke or recurrent severe ischemia were observed for apixaban 2.5 mg twice daily and 10 mg daily, no statistically significant reductions were observed.
- APPRAISE-2 was conducted in 7,392 patients and was prematurely discontinued due to an increase in major bleeding.

Rivaroxaban
- Direct, oral factor Xa inhibitor with a half-life of 5-7 hours was evaluated in Anti-Xa Therapy to lower cardiovascular events in addition to Aspirin with our without thienopyridine therapy in Subjects with ACS-Thrombolysis in Myocardial Infarction trial (ATLAS ACS-1).
- Dose dependent increases in bleeding were observed with rivaroxaban with no difference in the primary endpoint of death, MI, stroke, or severe recurrent ischemia between rivaroxaban and placebo.
- ATLAS ACS-2 trial included patients with a recent ACS event and 87% of patients were receiving DAPT therapy.
- Significant reductions in CV death, MI or stroke were observed compared to placebo.
- TIMI major bleeding not related to coronary artery bypass grafting and ICH was increased with rivaroxaban doses.
- Rivaroxaban was approved for post-ACS in Europe, but not the US.

Summary
- Small treatment benefits (e.g., ischemic event reduction) appear to be associated when adding a third antithrombotic agent to DAPT after ACS or PCI; however, increased risk of bleeding is observed.
- Additional oral antithrombotic agents are on the horizon that may provide ways to intensify therapy.
- Appropriate patient and dose selection are needed to ensure optimal outcomes.

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