DUAL ANTIPLATELET THERAPY

Dual antiplatelet therapy has been recognized as effective for prevention of adverse events due to acute coronary syndrome and is recommended for at least 12 months; however, the benefits of dual antiplatelet therapy beyond 12 months or extended antiplatelet therapy are unknown. This issue of *CLIPs* briefly summarizes an article that describes clinical trials regarding dual antiplatelet for prevention of thrombosis and reviews the benefits and harms of extending dual antiplatelet therapy. If you need further information, please contact the Center for Healthcare Innovation and Patient Outcomes Research (CHIPOR) at chipor@samford.edu.

Lincoff M. Dual Antiplatelet therapy for acute coronary syndromes: How long to continue? *CCJM*. **2016;83(9):675-688.**

Pathogenesis of platelet aggregation in acute coronary syndromes
- Exposure of subendothelial thrombogenic collagen and von Willebrand factor to blood leads to adhesion of platelets to endothelial collagen by binding of the GP Ib-IX-V receptor on platelets and leads activation of the extrinsic coagulation cascade which releases thrombin activating the platelet receptor GP IIb/IIIa.
- Adhesion to the GP Ib-IX-V receptor on platelets leads to a conformational change and activation of the platelets and releasing of autocrine and paracrine mediators including adenosine diphosphate and thromboxane.
- Binding of adenosine diphosphate to the platelet receptor $P2Y_1$ and thromboxane A_2 to the platelet receptor $P2Y_{12}$ activate the platelet receptor GP IIb/IIIa.
- GP IIb/IIIa facilitates platelet aggregation by binding to fibrinogen and forming a stable platelet thrombus.

Types of stents and their susceptibility to stent thrombosis
- Balloon angioplasty was associated with elastic vascular recoil and smooth muscle cell proliferation both of which leads to restenosis.
- Bare-metal stents eliminated vascular recoil, but are associated with an increased growth of vascular smooth muscle cells or growth of smooth muscle cells that may close the stent that cannot be treated with anticoagulants.
- Drug-eluting stents coated with anti-proliferative and anti-inflammatory polymers suppressed the initial vascular smooth-muscle proliferative response, but were still associated with late and very late stent thrombosis.
- Second-generation drug-eluting stents are believed to encourage more complete re-endothelialization, reducing the rates of stent thrombosis.

Antiplatelet agents: Mechanism of action
- Aspirin irreversibly inhibits cyclo-oxygenase from catalyzing the conversion of arachidonic acid to thromboxane A_2.
- Clopidogrel is a thienopyridine agent that irreversibly inhibits the $P2Y_{12}$ receptor.
- Prasugrel is a more potent thienopyridine agent that irreversibly inhibits the $P2Y_{12}$ receptor.
- Ticagrelor directly and reversibly inhibits the $P2Y_{12}$ receptor.

Clinical Trials
- CAPRIE, ISAR, STARS, CURE, CREDO, CLARITY-TIMI 28, and COMMIT/CCS 235
  - These trials led to the establishment of dual antiplatelet therapy as safe and effective for prevention of adverse events due to acute coronary syndromes.

- CHARISMA
  - In patients with more stable ACS characteristics, clopidogrel added to aspirin compared with aspirin alone showed no benefit in patients with established vascular disease (secondary prevention) or risk factors for vascular disease (primary prevention). However, in the large subgroup of patients with established atherosclerotic vascular disease, dual antiplatelet therapy showed an overall reduction in absolute risk of 1.5% (RR [Relative Risk] 0.88, P = .046) over a median follow-up of 27.6 months. The Relative Risk Reduction (RRR) was 17.1% (P = .01) and an Absolute Risk Increase (ARI) of 1.5% in those patients with prior myocardial infarction, stroke, or peripheral artery disease. The rate of severe bleeding was greater in the clopidogrel-plus-aspirin group compared with the placebo-plus-aspirin (RR 1.25 [95% CI 0.97–1.61, P = .09].
- PEGASUS-TIMI 54
  - In patients with stable coronary artery disease who had had a myocardial infarction 1 to 3 years earlier, ticagrelor 60- 90 mg plus aspirin resulted in a significantly lower incidence of the ischemic primary efficacy end point of cardiovascular death, myocardial infarction, and stroke when compared to placebo plus aspirin (7.85% vs 9.04%; hazard ratio (HR, 0.85, 95% confidence interval [CI] 0.75–0.96, P = .008). The rate for the ticagrelor 60 mg-plus-aspirin group was 7.77% vs 9.04% for the placebo-plus-aspirin group (HR 0.84, 95% CI 0.74–0.95, P = .004). However, the rates of all TIMI major and minor bleeding, as well as, bleeding requiring transfusion or discontinuation of the study drug, were significantly higher in both ticagrelor dosing groups than in the placebo group (P < .01 for both groups vs placebo).
- SECURITY, EXCELLENT, OPTIMIZE, and RESET
  - All these trials reported that short-duration therapy (6 months) was not inferior to standard-duration therapy (12 months). However, these studies were underpowered to definitively demonstrate the relative efficacy of 6-months vs 12-months of dual antiplatelet therapy.
- PRODIGY
  - This trial found that 6 months of dual antiplatelet therapy compared with 24 months of antiplatelet therapy was not significantly different for the primary outcome.
- ARCTIC-Interruption and DES-LATE
  - These trials assessed a composite of death due to cardiovascular cause nonfatal myocardial infarction, stroke, or stent thrombosis. Extended dual antiplatelet therapy beyond 12 months did not demonstrate any benefit when compared with the standard 12-month duration of dual antiplatelet therapy for these outcomes.
- DAPT
  - This study also sought to examine the benefit of dual antiplatelet therapy beyond 1 year and was designed so that it included a sufficient number of patients (n= 9,961) for definitive detection of difference. A significant reduction of the risk of stent thrombosis was observed at an additional 18 months in patients who received drug-eluting stents and who had been on 12 months of dual antiplatelet therapy for stent thrombosis (HR 0.29, 95% confidence interval [CI] 0.17–0.48) and the composite ischemic end point (HR 0.71, 95% CI 0.59–0.85) when compared with placebo plus aspirin. However, the risk of bleeding was higher in the dual antiplatelet therapy group during the treatment period (2.5% vs 1.6%, P = .001).
- WOEST
  - Double therapy with anticoagulant and clopidogrel resulted in significantly fewer bleeding events within 1 year when compared to triple therapy with additional aspirin following percutaneous coronary intervention.

Conclusion
- Dual antiplatelet therapy is effective for suppressing coronary ischemic complications resulting from both thrombosis due to spontaneous plaque rupture following acute coronary syndromes and thrombosis due to percutaneous coronary intervention.
- The two trials with the longest duration studies of dual antiplatelet therapy, DAPT and PEGASUS, indicate that there is benefit to dual antiplatelet therapy beyond 12 months or extended antiplatelet therapy.
- Since the rates of ischemic efficacy and the rates of bleeding are major consideration with any antithrombotic and antiplatelet therapy, the three largest trials discussed (CHARISMA, PEGASUS, and DAPT), suggest that dual antiplatelet therapy has a net benefit and that for longer-term therapy clopidogrel may be superior to ticagrelor or prasugrel.
- If dual antiplatelet therapy was interrupted due to an acute event such as surgical procedure, it is reasonable to restart long-term dual antiplatelet therapy.