"Antiplatelet therapy post coronary stenting: What drugs and for how long?"

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Disclosures

- None
PCI and Arterial Injury

- Endothelial damage and plaque rupture
- Thrombin generation and platelet activation
- Platelets serve as the center of clot formation
- Mimics or propagate the thrombotic milieu of ACS
Continued risk of thrombus formation until endothelialization is complete

DAT and Stent Thrombosis

The STARS Trial

Bleeding requiring transfusion 1.8% ASA, 6.2% ASA+warfarin, 5.5% ASA+ticlopidine (P<0.001 for the comparison of all three groups)

Leon MB, et.al., NEJM ’98;339:1665-71
Drivers for Type and Duration of DAT

- Risk of recurrent ischemic events/stent thrombosis vs. bleeding risk
- Clinical indication for stenting
  - ACS
  - Stable CAD
- Type of stent
  - Bare metal (BMS)
  - Drug Eluting (DES)
Optimal Duration of DAT Post-stenting

- **Short answer**
  - 12 months DAT for all PCI patients independent of stent type or procedural indication
  - Lifelong continuation of single antiplatelet agent

- **Caveats**
  - Patients (all or selected) may benefit from a more prolonged course of DAT
  - Risk of bleeding outweighs the anticipated benefit of thienopyridine therapy, earlier discontinuation should be considered (BMS 1 month, SES 3 months, PES/EES/ZES 6 months)
  - Risk of early discontinuation lower in BMS patients
  - Unclear if 12 months is superior to shorter duration DAT

ACC/AHA guidelines PCI update 2009
Hazard of Premature Discontinuation of Antiplatelet Therapy in DES Patients

Overall stent thrombosis = 1.3% ($P=0.09$, $N=2229$)

- Unstable angina: 1.4%
- Thrombus: 2.0%
- Diabetes: 2.5%
- Unprotected left main: 3.3%
- Bifurcation: 3.6%
- Renal failure: 6.2%
- Prior brachy Rx: 8.7%
- Premature antiplatelet discont: 29.0%

Registry Data: Prolonged Duration of DAT Beneficial in DES?

24 Month Events in Patients who Discontinued or did not Discontinue Clopidogrel at 6 Months Stratified by Stent

- **DES**
  - 24 month: 637
  - 6 month: 579
  - P = 0.02
  - RRR: 50%

- **BMS**
  - 24 month: 417
  - 6 month: 1,976
  - P = 0.50

Eisenstein EL et al, JAMA 2007
Dual Antiplatelet Therapy (DAPT) Study

DES n = 15,245
BMS n = 5,400

1:1 Randomization at month 12

All patients on aspirin + open-label thienopyridine therapy for 12 months

50% of patients continue on Dual Antiplatelet Therapy

50% of patients receive aspirin + placebo

Total 33 month patient evaluation including additional 3-month follow-up
Which antiplatelet agents post-stenting?

- **Aspirin**
  - 81-325 mg daily up to 6 months
  - 81-162 mg after 6 months

- **P2Y12 ADP-receptor inhibitor**
  - Thienopyridine
    - Ticlopidine (Ticlid) 250mg BID
    - Clopidogrel (Plavix) 75 mg daily
    - Prasugrel (Effient) 10 mg daily (5 mg daily)
      - ACS
  - Cyclopentyltriazolopyrimidine
    - Ticagrelor (Brilique) 90 mg BID
      - ACS
Limitations of Clopidogrel

- Delayed onset of action due to pro-drug metabolism
  - 4 to 5 days after daily administration of 75 mg clopidogrel
  - 2-6 hours after loading dose
- Substantial inter-individual variability in platelet inhibition
  - Extent of metabolism of the pro-drug
  - Drug-drug interactions (PPIs)
  - Genetic Polymorphisms
- Non or hypo-responders have higher risk of ischemic events
- Irreversible
  - Problem for patients who need to undergo CABG
Prasugrel vs Clopidogrel in ACS: TIMI38

CV Death / MI / Stroke

138 events
HR 0.81
(0.73-0.90)
P=0.0004
NNT = 46

TIMI Major
NonCABG Bleeds

35 events
HR 1.32
(1.03-1.68)
P=0.03
NNH = 167
Ticagrelor vs Clopidogrel in ACS: PLATO Study

- Randomized double-blind study 18,624 patients
- Composite of CV death, MI, or stroke
  - 9.8 vs 11.7% HR 0.84 (0.77, 0.92) 0.0003
- Lower risk of stent thrombosis
  - 1.3 vs 1.9% HR 0.67 (0.50-0.91) p=0.0091
- Adverse events ticagrelor vs clopidogrel
  - HR for major bleeding: 1.04 (0.95 to 1.13) NS
  - Major or minor bleeding: 1.11 (1.03–1.20) 0.008
  - Dyspnea 1.84 (1.68–2.02) <0.001
    - Drug discontinuation 6.12 (3.41–11.01) <0.001
  - Ventricular pauses ≥3 sec 5.8 vs 3.6%, p 0.01
    - trend towards higher rate syncope
Cautions with New Agents

Prasugrel
- Higher bleeding risk
  - Contraindicated in patients with prior stroke
  - Caution age >75, weight <60kg (5 mg daily)
- Irreversible, slow offset of action
  - CABG bleeding risk higher than clopidogrel

Ticagrelor
- Metabolized by CYP3A, avoid or dose adjust drugs with similar metabolism (simva/pravachol)
- Low dose aspirin recommended 100mg or less
- Contraindicated: prior ICH, active bleeding, liver failure
- Side effect to monitor dyspnea 14% and bradycardia/pauses 6%
- Reversible, faster offset of action
  - CABG bleeding risk same as clopidogrel
Conclusions

- DAT should be given for 12 months in patients with low risk of bleeding until further studies are available
- ASA/clopidogrel combination indicated for non-ACS patients
- ACS patients weigh risks and benefits of more potent antiplatelet agents
  - High bleeding risk: ASA/clopidogrel
    - Prior GI bleed, stroke, advanced age, malignancy, anemia/thrombocytopenia, concurrent use of anticoagulants, steroids, or NSAIDS
  - High ischemic risk: ASA/prasugrel or ASA/ticagrelor
    - STEMI, DM, PAD, complex PCI incl. LM, bifurcation
- Cost
PPIs and Thienopyridines

- Clopidogrel alone, aspirin alone, and their combination are all associated with increased risk of GI bleeding.
- Patients with prior GI bleeding are at highest risk for recurrent bleeding on antiplatelet therapy.
  - Advanced age; concurrent use of anticoagulants, steroids, or nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin; and Helicobacter pylori infection.
- Use of a PPI or histamine H2 receptor antagonist (H2RA) reduces the risk of upper GI bleeding compared with no therapy. PPIs are superior to H2RAs.
- PPIs are recommended to reduce GI bleeding among patients with a history of upper GI bleeding. PPIs are appropriate in patients with multiple risk factors for GI bleeding who require antiplatelet therapy.
- Routine use of either a PPI or an H2RA is not recommended for patients at lower risk of upper GI bleeding.
- Pharmacokinetic and pharmacodynamic studies, using platelet assays as surrogate endpoints, suggest that concomitant use of clopidogrel and a PPI reduces the antiplatelet effects of clopidogrel. Controversial whether clinically meaningful differences exist.
- Clinical decisions regarding concomitant use of PPIs and thienopyridines must balance overall risks and benefits, considering both CV and GI complications.