Antiplatelet Therapy and Cardiac Surgery: A Challenge?

The use of aspirin and clopidogrel in cardiac surgery
Overview

- Indications of DAPT
- Pharmacology
  - Aspirin
  - P2Y$_{12}$ Receptor blockers
- Perioperative use
  - Benefit
  - Risk
- Practical Recommendations
Indications for DAPT

- **CHARISMA Trial:**
  - No benefit in primary prevention
  - No benefit in stable CAD

- **CURE trial:**
  - Benefit for NSTEMI or Unstable Angina without PCI

- **CLARITY-TIMI 28 trial:**
  - Benefit of DAPT auxiliary to thrombolytics

- **PCI-CURE trial/ CREDO trial:**
  - Benefit of DAPT for STEMI

- **Multiple Trials/ FDA:**
  - BMS 1 years or at least 1 month
  - DES: at least 1 year

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**Table 1. Recommendations for Dual Antiplatelet Therapy**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dual Therapy Recommended</th>
<th>Duration of Dual Therapy</th>
</tr>
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<tbody>
<tr>
<td>Coronary artery disease primary prevention</td>
<td>no</td>
<td>NA</td>
</tr>
<tr>
<td>secondary prevention</td>
<td>no</td>
<td>NA</td>
</tr>
<tr>
<td>NSTEMI/UA without PCI</td>
<td>yes</td>
<td>1 y (minimum 3 mo)</td>
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<tr>
<td>STEMI without PCI</td>
<td>yes</td>
<td>up to 28 days while hospitalized</td>
</tr>
<tr>
<td>PCI[13,26,27]</td>
<td>yes</td>
<td>BMS: 1 y (minimum 1 mo)</td>
</tr>
<tr>
<td>Stroke</td>
<td>no</td>
<td>NA</td>
</tr>
<tr>
<td>atherosclerotic ischemic stroke (primary and secondary prevention)</td>
<td>no</td>
<td>NA</td>
</tr>
<tr>
<td>cardioembolic (AF)</td>
<td>no</td>
<td>NA</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; BMS = bare metal stent; DES = drug-eluting stent; NA = not applicable; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.
Pharmacology: ASPIRIN

- COX-1 inhibition
  - Preventing platelet activation and aggregation
- Impair Secondary Haemostasis
- Influences interaction between platelets, neutrophils and erythrocytes
- Augments endothelial functions

Aspirin inhibition of COX-1 decreases TXA2 production. Source: Gasparyan, A. Y. et al. J Am Coll Cardiol 2008;51:1829-1843
Pharmacology: P2Y$_{12}$ Receptor Inhibitors

- **General**
  - Preventing ADP binding to P2Y$_{12}$ Receptor
  - Inhibition of activation, aggregation and thrombin generation
  - Inhibition of CRP and TNF release
  - Inhibition of platelet-neutrophil aggregates

- **Clopidogrel**
  - Prodrug
  - Slow onset and variable inhibition

- **Prasugrel**
  - Prodrug
  - More rapid and less variable inhibition
  - Higher risk for bleeding

- **Ticagrelor**
  - Reversible
  - Fast onset and off-set
  - More consistent inhibition

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Perioperative use of Aspirin: Benefits vs Risk

**BENEFITS**
- Lower all cause mortality in secondary prevention
  - Sung et al.
- Decrease in post-op MI after cardiac surgery and in-hospital mortality
  - Hastings et al.
- Cardioprotective effect immediately post-op in CABG setting

**RISKS**
- Rebound Phenomenon
  - Bieving et al./ Vial et al.: Dose dependent
  - Increased risk of cardiovascular events
  - O’Riodan et al: Cessation has gloomy prognosis
- Increased bleeding risk
  - POISE-2: 23% relative increase
  - Burger et al: Increase bleeding complications, not severity
Perioperative use of Clopidogrel: Benefits vs Risk

**BENEFITS**
- Reduction of cardiovascular ischemic events
  - ACUITY trial: stopping clopidogrel 5 days before surgery
  - Miceli et al: Time frame of 5 days

**RISKS**
- Increased bleeding risk
  - ACUITY trial: Dependent on timing of last dose
  - CURRENT-OASIS 7: Effect of loading dose
- Increased Mortality and Post-op MI
  - Siller-Matula et al: related to increased bleeding
  - Vorobcsuk et al: similar results
  - Miceli et al: cessation less than 5 days
Perioperative use of Prasugrel and Ticagrelor

**Prasugrel**
- **TRITON-TIMI 38:**
  - greater bleeding risk than clopidogrel group
  - Lower 13 month mortality

**Ticagrelor**
- **PLATO trial:**
  - no raise in CABG related bleeding
  - Lower rate of post CABG mortality

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**Figure 3.** Relative risk ratios of death for comparison between preoperative versus no preoperative use of prasugrel, ticagrelor or clopidogrel in PLATO and TRITON-TIMI 38 studies in patients undergoing coronary artery bypass surgery. CI: confidence interval

Practical recommendations: Cessation of drugs

- **Aspirin:**
  - Continued in perioperative surgery except for high-bleeding risk surgeries
  - ACC/AHA guideline: stop Aspirin 7-10 days before cardiac surgery
  - Guideline by European Journal of Cardio-Thoracic surgery:
    - Stop aspirin 2-10 days before elective cardiac surgery
    - Urgent cardiac surgery: continue aspirin up to the day of surgery
    - Restart Aspirin as soon as possible post-operative

- **Clopidogrel/Ticagrelor:**
  - Stop 5-7 days before elective cardiac surgery
  - Urgent CAGB: stop 24 hours if possible
  - Bridging therapy with GP IIb/IIIa receptor inhibitors: requires further research

- **Prasugrel:**
  - Stop 7-10 days before elective cardiac surgery
Practical recommendations: Reduction of blood loss

- Prophylactic Platelet transfusion
  - Rapid reversal
  - Risk of reversal of clinical benefit

- Use of Antifibrinolytics
  - Aprotinin: renal dysfunction and end-organ damage
  - Tranexamic acid:
    - reduces blood loss, need for transfusion and re-operation
    - Can be used safely

- In vitro platelet function testing: Additional studies recommended
  - Recognizing patients had higher bleeding risk
  - Fixing optimal window for surgery
  - Predictive value and guide for transfusion
Fig 2. A proposed algorithm for the use of antiplatelet therapy in patients undergoing CABG surgery. (ACS = acute coronary syndrome; CAD = coronary artery disease; CABG = coronary artery bypass graft.)
Questions & Discussion
References


