Topics in Anti-platelet Therapy

DAPT and ASA Primary Prevention

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Disclosures

- None
Objectives

• Review data and recommendations on:
  – ASA in primary prevention among men and women
  – Anti-platelet therapy: clopidogrel, prasugrel, ticagrelor, cangrelor
  – Duration of DAPT in ischemic heart disease
  – Discontinuing DAPT for surgery
Case Presentation

- 55 man with no hx CAD and no sx of ischemic heart disease, routine physical
- PMH: Hypertension, obesity
- SH: Never smoked
- FH: No premature CAD
- Medication: Chlorthalidone
- BP 140/79, unremarkable PE
- TC 201, Tri 150, LDL 160, HDL 41

- Should he start on ASA for primary prevention of cardiovascular disease?
ASA Primary Prevention

What do the guidelines say?

• 2012 Guidelines from the American College of Chest Physicians (ACCP) suggest low dose ASA (75-100mg) for patients >50 without sx CVD (includes impact of Cancer and mortality)

• 2012 Guidelines from European Society of Cardiology (ESC) advise against ASA in patients without sx CAD/CVD due to risk of major bleeding

• 2009 Guidelines from US Preventative Task Force encourage ASA in select patients (men 45-79, women 55-79) considering relative CAD/CVD benefit vs bleeding risk
ASA Primary Prevention

- Absolute risk reduction with ASA is small since events are infrequent in primary prevention population
- Pooled data from RCT
  - 20% RRR in non-fatal MI
  - No sig effect on non-fatal stroke (Women have risk reduction for CVA)
  - 12% RRR in cancer incidence, potentially greater with long-term use
  - 50% increase in RR major non-fatal extra-cranial bleeding
  - Possible 6-8% RRR in overall mortality
- In 1000 patients, age 60, average 10 year risk (10-20%)
  - 17 fewer non-fatal MI
  - No reduction in CVA
  - 6 fewer cancers
  - 16 more major bleeding events
  - 6 fewer deaths

Lancet 2009; 373: 1849-60
ASA Primary Prevention – Women

- Most RCT primarily men and meta-analysis shows 20% RRR non-fatal MI*
- Women have RRR in CVA but not CAD
- Relative benefit of ASA similar in patients with and without DM

*References
Lancet 1998;351:233-41
Lancet 1998;351:1755-62

39,876 Women, 45 or older
17% RRR CVA
24% RRR ischemic CVA
No effect on MI
No effect on death
40% inc risk GIB

ASA Primary Prevention

- Patients at higher risk for CV events derive greater benefit
- In general, patients at higher CV risk are also at higher bleeding risk
- Online risk calculators available
- Shared decision making encouraged with patients
- Consider cancer benefit
- 5 ongoing RCT studying ASA in primary prevention

Risk level at which CVD events prevented (benefit) exceeds GI harms

USPTF 2009

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td>10-year CHD risk</td>
<td>10-year stroke risk</td>
<td></td>
</tr>
<tr>
<td>Age 45-59 years</td>
<td>≥4%</td>
<td>Age 55-59 years</td>
</tr>
<tr>
<td>Age 60-69 years</td>
<td>≥9%</td>
<td>Age 60-69 years</td>
</tr>
<tr>
<td>Age 70-79 years</td>
<td>≥12%</td>
<td>Age 70-79 years</td>
</tr>
</tbody>
</table>

2014 Position paper ESC working group

Step 1: Assess 10 year risk of major CV events
- <10%
- 10-20%
- >20%

Step 2: History of bleeding without reversible causes, concurrent use of other medications that increase bleeding risk

Consider family history of GI (especially colon) cancer / patient values and preferences

Stop
Go ahead with caution
Proceed

Low-dose aspirin

J Am Coll Cardiol. 2014;64(3):319-327
Case Presentation - conclusion

- 10 year cardiovascular risk 11%
- CV event reduction on ASA in 10 years 5%
- Bleeding risk due to ASA in 10 years 2.4%

NHLBI online risk calculator: http://cvdrisk.nhlbi.nih.gov

<table>
<thead>
<tr>
<th>Age</th>
<th>55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>male</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>201 mg/dL</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>41 mg/dL</td>
</tr>
<tr>
<td>Smoker</td>
<td>No</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>140 mm/Hg</td>
</tr>
<tr>
<td>On medication for HBP</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Risk Score* 11%
Means 11 of 100 people with this level of risk will have a heart attack in the next 10 years.

Based on guidelines reasonable to consider ASA after discussing risks and benefits with patient
Case Presentation - DAPT

- 65M with HTN, HLD, DM, non-smoker presents to PCP for routine physical
- Hx NSTEMI 10 months ago, Tn 15, TTE with mild HK mid to distal ant wall, EF 45%.
- Coronary angiography revealed 80% prox LAD stenosis; treated with 2.75 x 16mm Promeus Premier DES
- Treated with ASA, prasugrel, statin
- How long should he continue DAPT?
In-stent Restenosis vs. Stent Thrombosis

**In-Stent Restenosis**

Mechanisms:
- Denuded endothelium and disrupted medial tissue leads to platelet activation and microthrombi
- Microthrombi and stretch injury attracts macrophages and lymph
- Inflammatory cells produce cytokines lead to smooth muscle proliferation
- Neointimal layer forms and matrix deposition occurs over months
- ISR Associated with small lumen size, stent length, poor coronary flow, Stent malapposition and geographic miss

**Stent thrombosis**

Mechanisms:
- Both BMS and DES induce platelet adhesion, activation and thrombus Formation
- Carries a mortality rate up to 45%
- As endothelial cells cover stent struts risk of ST decreases
**Bare Metal Stents vs Drug Eluting Stents**

**RAVEL Study – NEJM 2002**

- Early ST accounted for 60% of cases
- Late ST accounted for 40%
- Late ST occurred steadily at rate of 0.6%/yr
- DAPT stopped in 13% early ST and 77% late ST
- DM and ACS independent predictors of ST

**Early and Late ST in (1st generation) DES – Lancet 2007**

- DES reduce risk of restenosis and TVR
- SIRIUS Trial looked at more complex lesion and patients - DM, small vessels, longer lesions, overlapping stents - 8.9% restenosis in SES arm and 36.3% in BMS p<0.0001

- Sirolimus and Paclitaxel eluting stents
- Early ST accounted for 60% of cases
- Late ST accounted for 40%
- Late ST occurred steadily at rate of 0.6%/yr
- DAPT stopped in 13% early ST and 77% late ST
- DM and ACS independent predictors of ST

Several reports between 2006-2008 questioned long-term safety of DES leading to reduction in use and prolonged dual anti-platelet therapy (DAPT)
2\textsuperscript{nd} Generation DES

- New DES designed to improve safety and efficacy
  - Thin, malleable cobalt chromium struts (81\textmu m)
  - Polymer coating: Thromboresistant flurocopolymer
  - Anti-proliferative agent (elutes more quickly, allows vascular healing)

- Xience Prime and Xience V CE mark approval for DAPT 3 months
- Resolute Integrity zotarolimus CE marked for 1 month DAPT
Review of P2Y12 Receptor Inhibitors

- **Clopidogrel**
  - 2nd gen thenopyridine
  - Studied in UA, NSTEMI, STEMI, with or without PCI, lytics
  - Variable anti-platelet response due to CYP2C19 metabolism
  - Irreversible inhibition; stop 5 days prior to surgery
Prasugrel
- 3rd gen thienopyridine
- Efficient metabolism, faster onset, more potent inhibition, less variability
- Particular benefit in DM and STEMI
- Increased risk of bleeding
- Only for invasive strategy
- Avoid in age>75, hx CVA/TIA and wt <60kg
- Irreversible inhibition; stop 7 days prior to surgery
Review of P2Y12 Receptor Inhibitors

- Ticagrelor
  - Cyto-pentyl-triazolo-pyrimidine.
  - Faster onset, more potent inhibition, less variability
  - Invasive or conservative tx
  - No increased risk overall bleeding, but more fatal intracranial
  - Contra-indicated in hepatic dysfunction
  - Only with ASA 81mg daily
  - Dyspnea common 13.8% vs 7.8%
  - BID dosing
## P2Y12 Receptor Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Cangrelor</th>
<th>Ticagrelor</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td>IV</td>
<td>PO</td>
<td>PO</td>
<td>PO</td>
</tr>
<tr>
<td><strong>Pro-drug</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>P2Y12 Inhibition</strong></td>
<td>Reversible</td>
<td>Reversible</td>
<td>Irreversible</td>
<td>Irreversible</td>
</tr>
<tr>
<td><strong>Renal Considerations</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Hepatic Considerations</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Time to Peak Platelet Inhibition</strong></td>
<td>2 min</td>
<td>120 min</td>
<td>60-90 min</td>
<td>60 min</td>
</tr>
<tr>
<td><strong>Half-Life</strong></td>
<td>3-6 min</td>
<td>8 hours</td>
<td>7 hours</td>
<td>6 hours</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$700/vial</td>
<td>$352/month</td>
<td>$420/month</td>
<td>$213/month</td>
</tr>
</tbody>
</table>
Intermountain Anti-platelet Guidelines - PCI

- STEMI → Prasugrel or Ticagrelor preferred
- NSTEMI/UA→ Prasugrel or Ticagrelor preferred
- Stable CAD → Clopidogrel
- Switching → If Cost prohibitive consider switching to Clopidogrel after 1-3 months
- Cangrelor – FDA approved but not on formulary due to excessive cost ($700/vial)
Duration of DAPT after PCI?

- ACC/AHA recommend 12 months DAPT after placement of DES
- European Society of Cardiology recommends 6-12 months DAPT after DES
- Tremendous practice variation with many providers continuing DAPT for >12 months
- Observational data showed mixed results for continued DAPT beyond 1 year
DAPT Trial – NEJM 12/14

- US FDA requested post-market study to address question of DAPT duration. Study sponsored by 4 stent manufacturers and 4 antiplatelet manufacturers. Conduct and analysis of study by HCRI.

- 9961 patients who received DAPT after DES (stable angina, UA, NSTEMI, STEMI) were randomly assigned to continue DAPT after 1 year.

- Co-primary efficacy endpoint ST and composite MACE (death, MI, CVA).

- Primary safety endpoint: Moderate or severe bleeding.

Based on results a DAPT trial a score was developed to predict combined ischemic and bleeding events.
Case Presentation

Patient Characteristics

Age
Between 65 and 74

Diabetes Mellitus

Cigarette Smoking Within Last Two Years

Prior Myocardial Infarction or Percutaneous Coronary Intervention

History of Congestive Heart Failure or Left Ventricular Ejection Fraction < 30%

Index Procedure Characteristics

Myocardial Infarction at Presentation

Stenting of Vein of Graft

Stent Diameter < 3mm

http://www.daptstudy.org/for-clinicians/score_calculator.htm
Stopping Anti-platelet Therapy for Surgery

First three months after Percutaneous Coronary Intervention (PCI) with Stent (BMS or DES)

a. Request cardiology consult
b. Surgery ONLY for immediate life-threatening conditions or benefit outweighs risk
c. If aspirin and P2Y12 inhibitor can be continued during surgery (preferable)
   (1) Proceed with surgery
   (2) Discontinue P2Y12 inhibitor 5-7 days before surgery, or at least until VerifyNo P2Y12 Assay is >240 PRU.
   (3) Restart P2Y12 inhibitor (with standard load) ASAP after surgery.
   (4) Consider pre-op tirofiban bridging per cardiologist.
d. If aspirin can be continued during surgery, but not P2Y12 inhibitor
   (1) Continue aspirin through surgery
   (2) Discontinue P2Y12 inhibitor 5-7 days before surgery, or at least until VerifyNo P2Y12 Assay is >240 PRU.
   (3) Restart P2Y12 inhibitor (with standard load) ASAP after surgery.
   (4) Consider pre-op tirofiban bridging per cardiologist.
e. If neither aspirin nor P2Y12 inhibitor can be given during surgery
   (1) Discontinue aspirin and P2Y12 inhibitor 5-7 days before surgery or at least upon VerifyNow P2Y12 Assay is >240 PRU
   (2) Restart aspirin and P2Y12 inhibitor (with standard load) ASAP after surgery.
   (3) Consider pre-op tirofiban bridging per cardiologist.

More than three months after PCI

a. If still on aspirin and P2Y12 inhibitor
   (1) If aspirin and P2Y12 inhibitor can be continued during surgery
      (a) Proceed with surgery
   (2) If aspirin can be continued during surgery, but not P2Y12 inhibitor
      (a) Continue aspirin through surgery
      (b) Discontinue P2Y12 inhibitor 5-7 days before surgery, or at least until VerifyNow P2Y12 Assay is >240 PRU.
      (c) Restart P2Y12 inhibitor (with standard load) ASAP after surgery.
   (3) If neither aspirin nor P2Y12 inhibitor can be given during surgery
      (a) Discontinue aspirin and P2Y12 inhibitor 5-7 days before surgery or at least until VerifyNow P2Y12 Assay is >240 PRU
      (b) Restart aspirin and P2Y12 inhibitor (with standard load) ASAP after surgery.

b. If still on aspirin but not P2Y12 inhibitor
   (1) If aspirin can be continued during surgery
      (a) Do so
   (2) If aspirin cannot be given during surgery
      (a) Discontinue aspirin 5 days before surgery
      (b) Restart aspirin ASAP after surgery

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**Antiplatelet therapy after stenting**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPT is indicated for at least 1 month after BMS implantation.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>DAPT is indicated for 6 months after DES implantation.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Shorter DAPT duration (&lt;6 months) may be considered after DES implantation in patients at high bleeding risk.</td>
<td>IIb</td>
<td>A</td>
</tr>
<tr>
<td>Life-long single antiplatelet therapy, usually ASA, is recommended.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Instruction of patients about the importance of complying with antiplatelet therapy is recommended.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>DAPT may be used for more than 6 months in patients at high ischaemic risk and low bleeding risk.</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>
Final thoughts

• Decision for using ASA for primary prevention requires weighing risk vs benefits; ongoing clinic trials will further help clarify who benefits
• 2nd generation stents have lower risk of ISR and low rates of ST
• Multiple P2Y12 inhibitors are available; decision on which to use depends on presentation, clinical variables, bleeding risk, adverse reactions and cost
• Duration of anti-platelet therapy is still area of active study but >1 year DAPT may be beneficial in some patients; a risk score has been developed to help identify patients who will benefit
• Stopping anti-platelet therapy for surgery prior to 3 months year requires full cardiology consult; 3-6 months reach out to cardiologist.