PRIMER ON SECONDARY PREVENTION OF CORONARY ARTERY DISEASE
CCPN Atlantic Fall Conference
September 29, 2015
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Disclosure
- Regional Delegate, Canadian Cardiovascular Pharmacists’ Network
- Advisory Board – Hospital Pharmacy in Canada Survey/Report, Eli Lilly Canada
- Advisory Board – Fresenius Kabi Group

Learning Objectives
By the end of this session, participants will be able:
• To identify contemporary, evidence-informed therapies for secondary prevention in patients post-acute coronary syndrome (ACS)
• To familiarize with an online toolkit designed to assist in educating patients about ACS

Case
• M.G. is 50-year-old African-Canadian male
• Developed typical RSCP at rest or on exertion 3 times in 24 hrs → to ED & referred for cath/PCI
• Dx: Inferior Non-STEMI, BMS to RCA
• PMHx:
  • No prior hx HTN, chol or DM
  • Obesity, depression, smoker, 12-15 beer/wk
  • FHx premature CAD: father CHD 50s, brother stroke age 38
  • NKDA, no home medications
  • M.G. concerned about drug costs & activity limits

Case (cont.)
• Seen in cardiac rehab 4 mos. post-MI
• New dx HTN (180/90 mmHg in ED during ACS)
• BP & lipids at target
• Pt is willing to quit smoking, reduce beer intake, get more active & attend cardiac rehab
• Rx regimen:
  • ASA 81mg daily
  • Clopidogrel 75mg daily (x 12 mos.)
  • Bisoprolol 5mg daily
  • Perindopril 4mg daily
  • Atorvastatin 80mg daily

Acute Coronary Syndromes in Atlantic Canada
• Atlantic Canadian population is oldest in Canada – more ACS occurs in old vs young patients
• Of all ACS in this region, ~50% NSTEMI, ~25% UA & ~25% STEMI
• Distance from initial treatment centre to cardiac cath lab in Atlantic Canada
• Cardiovascular mortality: higher vs rest of Canada, 33% vs 30%

StatsCan 2012; AAPI 2012
Guidelines for Secondary Prevention of Myocardial Infarction

- CCS: Antiplatelet Guideline Update, 2012
- Also 2011 Canadian perspective on ACS guidelines from ACC/AHA
- Atlantic:
  - Atlantic Antiplatelet Initiative (AAPI), Apr 14, 2012


ABCs of Secondary Prevention Therapy

- A: Antiplatelets, ACEI/ARB/AA, Anti-Anginals
- B: Beta-Blockers
- C: Cholesterol-Lowering

A = Antiplatelet Agents

ASA

- Benefits:
  - Prevents platelet adhesion & clots
  - Prevents NFMI (NNT=77) & death (NNT=333)
- Risks: GI bleeding (major, NNH=400)
- Dose: 160-320 mg load then 81-325 mg daily indefinitely for all patients without contraindications
  - 81 mg preferred (lower bleed risk)

Can J Cardiol 2013;29:1334-45 / CURRENT-OASIS 7

Learning Objectives

- Goals of therapy (post-discharge)
  - Prevent recurrent MI, need for revascularization, death
  - Manage modifiable CV risks: BP, HR, lipids, body weight, etc.

- ABCs of Secondary Prevention Therapy
  - A: Antiplatelets, ACEI/ARB/AA, Anti-Anginals
  - B: Beta-Blockers
  - C: Cholesterol-Lowering

P2Y12 Receptor Antagonists: Comparison

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loading dose</strong></td>
<td>300-600 mg*</td>
<td>60 mg</td>
<td>180 mg</td>
</tr>
<tr>
<td><strong>Maintenance dose</strong></td>
<td>75 mg OD</td>
<td>10 mg OD</td>
<td>90 mg BID</td>
</tr>
<tr>
<td><strong>Reversible binding</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Estimated time to 50% IPA</strong></td>
<td>NA†</td>
<td>30-45 min</td>
<td>30-45 minutes</td>
</tr>
<tr>
<td><strong>% Platelet inhibition at steady state</strong></td>
<td>40-60%</td>
<td>69-74%</td>
<td>74-96%</td>
</tr>
<tr>
<td><strong>Duration of platelet inhibition</strong></td>
<td>5-7 days</td>
<td>5 days</td>
<td>3 days</td>
</tr>
</tbody>
</table>

IPA: inhibition of platelet activation. * Based on in vitro assays with 20 μM ADP. † 50%IPA was not achieved with clopidogrel 300 mg or 600 mg using the 20 μM ADP assay.

ABCs

- Goals of therapy (post-discharge)
  - Prevent recurrent MI, need for revascularization, death
  - Manage modifiable CV risks: BP, HR, lipids, body weight, etc.

- ABCs of Secondary Prevention Therapy
  - A: Antiplatelets, ACEI/ARB/AA, Anti-Anginals
  - B: Beta-Blockers
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Clinical Considerations with Antiplatelet Therapies

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>MI, Stroke, PAD, ACS, AFB</td>
<td>Increased bleeding in those ≥75yrs and also in those less than 60yrs (risk/benefit assessment)</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacological Considerations</strong></td>
<td>CYP2C19 genetic polymorphisms may decrease efficacy</td>
<td>CYP344A1 inducers (i.e. rifampin)</td>
<td>CYP344A1 inhibitors (i.e. clarithromycin)</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>Bleeding, Rash, Diarrhea</td>
<td>Bleeding, Contusion, Rash</td>
<td>Bleeding, Dyspnea, Headache, Ventricular pauses</td>
</tr>
<tr>
<td><strong>Perioperative Considerations</strong></td>
<td>Hold at least 5-7 days prior to surgery if possible</td>
<td>Hold at least 7 days prior to surgery if possible</td>
<td>Hold at least 5 days prior to surgery if possible</td>
</tr>
</tbody>
</table>

Can J Cardiol 2013;29:1334-45 / CURRENT-OASIS 7 / Medicines Canada
**Stent Thrombosis**

- ST is rare (0.5-1% in year following PCI) but serious complication, sometimes fatal
- Usually presents as acute MI & requires urgent reperfusion in cath lab
- ST associated with 30-day mortality of 10-25%
- 20% of pts who have ST will develop a second ST within 2 years
- Most common factor associated with ST is premature cessation of or non-adherence to antiplatelet therapy

*Circulation 2011;124;1283-7*

**Ticagrelor:**

**NB Hospital Formulary Criteria for Use**

In combination with ASA 75-150 mg daily for patients with ACS:

(a) STEMI
- STEMI patients undergoing primary PCI

(b) NSTEMI or UA
- Presence of high risk features irrespective of intent to perform revascularization:
  - High GRACE risk score (>140)
  - High TIMI risk score (5-7)
  - Second ACS within 12 months
  - Complex or extensive coronary artery disease e.g. diffuse three-vessel disease
  - Definite documented cerebrovascular or peripheral vascular disease
  - Previous CABG
  - OR
  - Undergoing PCI + high risk angiographic anatomy

**A = ACEI / ARB / AA**

**RAAS Inhibitors**
- Favorable impact on ventricular remodeling, improvement in hemodynamics, & reductions in CHF

**ACE inhibitors**
- Decrease risk of recurrent MI by ~20%
- Indefinitely in all patients with LVEF less than 40% and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated
A = ACEI / ARB / AA

Angiotensin receptor blockers (ARB)
- In patients with HF or MI with LVEF less than 40% who are ACEI-intolerant
- Reasonable in other patients with CVD who are ACEI-intolerant

ACEI & ARB
- Risks: cough (ACEI), renal impairment, hyperkalemia, hypotension, rash, angioedema
- Dose (target):
  - Ramipril 10 mg, perindopril 8 mg, lisinopril 10 mg
  - Valsartan 160 mg (bid), candesartan 32 mg
  “But I don’t have high blood pressure?”

A = Anti-Anginal

Nitroglycerin
- Rescue therapy as sublingual spray or tablet
- Chronic therapy as long-acting oral or transdermal patch
- Patient education on proper use is important

- Beta blocker and/or calcium channel blocker may also be used for managing angina

B = Beta-Blocker

- Relieve ischemic pain, reduce need for analgesics, reduce infarct size and life-threatening arrhythmias
- Start oral beta blockers within 24 hrs of AMI in absence of:
  - Signs of heart failure
  - Evidence of a low output state
  - Increased risk for cardiogenic shock
  - Other relative contraindications (PR interval > 0.24 sec, 2nd or 3rd degree AV block, or reactive airway disease)
- Reasonable to continue BB in patients with normal LVEF

Beta Blockers (cont.)

- Duration of therapy
  - Recommended for at least 1 year for all hemodynamically stable patients to relieve chest pain, reduce risk of re-infarction & ventricular arrhythmias
  - Most trials involving BB were conducted prior to current revascularization therapies & modern post-AMI care
  - Chronic use of BB may not confer mortality benefit in low risk patients, e.g. single artery, successful revascularization, preserved LVEF, young age, no arrhythmias or residual ischemia

- Calcium channel blockers
  - In absence of contraindications, non-DHP (diltiazem, verapamil) may be used for ischemic symptoms when BB are not working, contraindicated or not tolerated

A = ACEI / ARB / AA

Aldosterone Antagonists
- In those without significant renal dysfunction or hyperkalemia who are receiving ACEI & beta-blocker, & have LVEF less than 40%, diabetes or HF
- Benefits: 30% lower risk of CV death & HF progression, decreased risk of hospitalization for HF
- Risks: renal impairment, hyperkalemia, breast pain & gynecomastia (males on spiro)
- Dose: Spironolactone 12.5-25 mg daily, eplerenone 25-50 mg daily

A = Anti-Anginal

Nitroglycerin
- Rescue therapy as sublingual spray or tablet
- Chronic therapy as long-acting oral or transdermal patch
- Patient education on proper use is important

- Beta blocker and/or calcium channel blocker may also be used for managing angina

ACC/AHA Guidelines / RALES & EPHESUS trials

ACC/AHA Guidelines

ACC/AHA Guidelines

Kehraashvile et al. Curr Cardiol Rev 2012
C = Cholesterol-Lowering

- Goal of therapy (surrogate) in secondary prevention is to reduce LDL to 2.0 mmol/L or less (or 50% drop in initial LDL)
- Statins may also possess anti-inflammatory & other pleotropic properties to assist in healing during early post-MI stage
- Dose: Post-MI intensive statin dosing (atorvastatin 80 mg) lowers risk of recurrent MI & death significantly more than lower dosing regimens
- “But I don’t have high cholesterol!”

Other Considerations

- Risk reduction
  - Manage BP, cholesterol, diabetes, smoking
  - Lifestyle – activity, nutrition, stress, mood
- Cardiac rehabilitation
- Immunization – seasonal influenza, pneumococcal
- Need for chronic pain therapy – NSAID use & risk of bleed or CV harm
- Gastroprotection – when consider higher risk of GI bleed

Secondary Prevention: Potential Cumulative Benefit of Therapies

<table>
<thead>
<tr>
<th>RRR</th>
<th>2-Year Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>8%</td>
</tr>
<tr>
<td>ASA</td>
<td>6%</td>
</tr>
<tr>
<td>Beta-Blockers</td>
<td>4.5%</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>3.0%</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Cumulative relative risk reduction if all four drugs are used is about 75%

Summary: In-Hospital and/or Discharge Medications

- ASA – all pts unless CI
- DAPT: Clopidogrel or ticagrelor (with ASA)
- ACEI – ACS pts with LVEF<40%
- Consider for all ACS pts to prevent recurrent MI
- ARB – ACS pts intolerant of ACEI with LVEF<40%
- Aldosterone antagonist – ACS pts with LVEF<40%
- Anti-anginal – rescue & chronic (if needed) nitrates
- Beta blockers – most ACS pts esp with LV dysfunction or residual coronary stenosis
- Statin – all pts independent of lipid profile to maximize LDL lowering
- Influenza vaccine – All ACS pts

Role of Pharmacist in Management of Patient with ACS

- Assist in obtaining or review history of medical conditions & medication use (may reveal precautions or contra-indications to management options)
- Advocate for evidence-based therapies in ACS in patients at high ischemic risk, e.g. elderly, diabetes, renal dysfunction, past CABG, etc.
- Review & adjust patient drug therapies as needed based on associated bleeding risk, e.g. age, renal, body wt, bleed hx

Role of Pharmacist in Management of Patient with ACS

- Consider lifestyle behaviours (smoking cessation, etc.) & secondary prevention therapies appropriate for patient condition & other factors (drug coverage, potential for adherence, etc.
- Educate patients on benefits & risks of post-MI therapies to enhance their knowledge & identify/address adherence issues
- Educate all patients with stents on importance of avoiding discontinuation of dual antiplatelet regimens to minimize risk of in-stent thrombosis
ACS Patient Education Toolkit

- CCPN developed toolkit for education of patients with ACS
- Open access on CCPN website in English or French

CCPN website → www.ccpn.ca

Patient Needs re: ACS & PCI

Disease Information

Medication Information

Lifestyle Information
Case Follow-Up

- M.G.'s rx regimen at 6 months after discharge:
  - ASA 81 mg daily
  - Clopidogrel 75 mg daily (x 12 mos. total)
  - Bisoprolol 7.5 mg daily
  - Perindopril 8 mg daily
  - Atorvastatin 80 mg daily

- Does M.G. warrant change from clopidogrel to ticagrelor?

- Would you add any other preventative therapies?

Thank you!

Questions?

Clopidogrel

- 2nd generation P2Y12 inhibitor
- Mainstay of treatment & secondary prevention of CAD (usually combined with ASA) for over a decade
- CURE study design
  - PC, DB, RCT of 12,000+ pts with UA or NSTEMI
  - Subjects rec'd clopidogrel 300mg LD/75mg daily or matching placebo; ASA 75-325mg/d & other medical therapy at discretion of treating physician
  - Mean duration of treatment was 9 mos

DAPT: ASA + Clopidogrel

The CURE trial:
Clopidogrel is beneficial, but increases the risk of bleeding

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>CLOPIDOGREL (N=6,296)</th>
<th>PLACABO (N=6,294)</th>
<th>RELATIVE RISK</th>
<th>PVALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome (any of the following)</td>
<td>8.1%</td>
<td>11.3%</td>
<td>0.72</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>5.5%</td>
<td>5.5%</td>
<td>0.97</td>
<td>.77</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>5.5%</td>
<td>5.5%</td>
<td>0.97</td>
<td>.77</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.2%</td>
<td>1.4%</td>
<td>0.86</td>
<td>.46</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.1%</td>
<td>2.0%</td>
<td>2.1</td>
<td>.46</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>2.2%</td>
<td>1.8%</td>
<td>1.21</td>
<td>.30</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>3.0%</td>
<td>2.8%</td>
<td>1.06</td>
<td>.46</td>
</tr>
<tr>
<td>All bleeding</td>
<td>6.5%</td>
<td>5.0%</td>
<td>1.3</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

**Prasugrel:**

TRITON TIMI-38: Efficacy and Safety Outcomes

- CV Death, MI, Stroke
- Median follow-up 14.5 months

**Major Bleeding**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clopidogrel (N=6,795)</th>
<th>Prasugrel (N=6,813)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRB</td>
<td>HR 1.32, 95% CI 1.11–1.58, p=0.001</td>
<td>HR 1.41, 95% CI 1.12–1.75, p=0.003</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>0.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>GI bleed</td>
<td>0.8%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

**Incidence at 1 year (%)**

- Ticagrelor: PLATO: Secondary Efficacy Outcomes

- Ticagrelor reduced mortality in ACS

**Cardiovascular Death**

- Months After Randomization

**How to Choose P2Y12 Inhibitor?**

- **Clopidogrel**
  - If other agents not available or contraindicated
  - If not high risk

- **Ticagrelor**
  - High CV risk
  - Switch after PCI
  - Not high bleed risk, no past ICH
  - No COPD or bradycardia

- **Prasugrel**
  - High CV risk
  - Planned PCI
  - Preferably diabetics
  - No prior CVA/TIA, <75 yo, >60 kg

- **Median follow-up** 277 days
- **Major Bleeding**

- Cumulative Incidence (%)
  - Ticagrelor: N=9,333
  - Clopidogrel: N=9,291

- **Incidence at 1 year (%)**

- **HR 0.79, 95% CI 0.69–0.89, p=0.001**

- **HR 0.78, 95% CI 0.69–0.89, p=0.001**