Anti-thrombotic and anti-platelet therapy in primary and secondary prevention

How thin can you go?

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Dr. John Graham – Presenter

Topic: Antithrombotic therapy in primary and secondary prevention

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- Patents: N/A
- Other: N/A
Educational Objectives

- Discuss indications for anti-platelet and anti-thrombotic therapy
  - Primary and secondary prevention
  - Combination therapy
- Targeted review of literature
- Tie this in with CCS guidelines
- Caveat
  - Moving target – this talk will likely be outdated in a month
  - Importance of individually tailored therapy being recognized
  - Recent research data of single anti-platelet therapy post ACS
WHAT IS PREVENTION?

1. **Primary Prevention**—intervening before health effects occur, through measures such as vaccinations, altering risky behaviors (poor eating habits, tobacco use), and banning substances known to be associated with a disease or health condition

2. **Secondary Prevention**—screening to identify diseases in the earliest stages, before the onset of signs and symptoms (e.g. BP testing, CT angio, etc)

3. **Tertiary Prevention**—managing disease post diagnosis to slow or stop disease progression through measures such as chemotherapy, rehabilitation, and screening for complications.

https://www.cdc.gov/pictureofamerica
PRIMARY PREVENTION

- Observed benefit counterweighed by risk of complications (primarily bleeding)
- For anti-platelets, no convincing evidence of role in primary prevention
- Most recent statement from CCS is from 2011 pocket guide
PRIMARY PREVENTION – More Recent Data

ASCEND Trial

Eligibility: Age ≥ 40 years, any DIABETES and no baseline cardiovascular disease

Participants: 15,480 UK patients

Factorial randomization: Aspirin 100 mg daily vs placebo (& to omega-3 fatty acid supplements vs placebo)

Follow-up: Mean 7.4 years, >99% complete for morbidity and mortality

Adherence: Average difference in anti-platelet use between groups 69%

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Male</td>
<td>63%</td>
<td>63%</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>Diabetes duration, median years</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62%</td>
<td>62%</td>
</tr>
<tr>
<td>Statin use</td>
<td>76%</td>
<td>75%</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Glycated haemoglobin, mmol/mol</td>
<td>55 (7.2%)</td>
<td>55 (7.2%)</td>
</tr>
</tbody>
</table>
ASCEND Trial

Efficacy – Effect on SVE

- **Aspirin**: 658 (8.5%)
- **Placebo**: 743 (9.6%)

Rate ratio: 0.88 (0.79-0.97)

\( P = 0.01 \)

Safety – Rates of Major Bleeding

- **HR**: 1.29 [1.09-1.52]
- **p**: 0.003
ASCEND Trial

Efficacy – Effect on SVE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Participants</th>
<th>Event Rate</th>
<th>Rate Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>658 (8.5%)</td>
<td>86 (13.2%)</td>
<td>0.88 (0.79-0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Placebo</td>
<td>743 (9.6%)</td>
<td>89 (11.9%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Safety – Rates of Major Bleeding

HR 1.29 [1.09-1.52]  
p=0.003
ASCEND Trial - higher risk patients will benefit?

<table>
<thead>
<tr>
<th>Baseline 5-year serious vascular event risk</th>
<th>SVE/revasc</th>
<th>Bleed</th>
<th>SVE/revasc</th>
<th>Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>Less: 6 ± 4</td>
<td>More: 3 ± 3</td>
<td>Less: 13 ± 6</td>
<td>More: 9 ± 3</td>
</tr>
<tr>
<td>≥5%, &lt;10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SECONDARY PREVENTION

- Post ACS, large body of evidence regarding use of anti-platelet therapy
- Aspirin for all plus P2Y12 inhibitor
  - Clopidogrel
  - Prasugrel
  - Ticagrelor
Anti-thrombotic therapy: Primary/Secondary Prevention

2018 CCS Guidelines: STEMI/ NSTEACS

PCI for STEMI or NSTEACS

DAPT for 1 year
ASA 81 mg OD +
Ticagrelor 90 mg BID or Prasugrel 10 mg OD
preferred over
Clopidogrel 75 mg OD

At 1 year, determine bleeding risk

Not at high risk of bleeding
Continue DAPT for up to 3 years
ASA 81 mg OD +
Ticagrelor 60 mg BID or
Clopidogrel 75 mg OD

High risk of bleeding
SAPT
ASA 81 mg OD
or
Clopidogrel 75 mg OD

1 Factors associated with increased bleeding risk include: need for OAC in addition to DAPT, advanced age (> 75 years), frailty, anemia with hemoglobin < 110 g/dL, chronic renal failure (creatinine clearance < 40 mL/min), low body weight (< 60 kg), hospitalization for bleeding within the last year, prior stroke/intracranial bleed, regular need for NSAIDS or prednisone
2 Instead of ticagrelor or clopidogrel, prasugrel 5-10 mg daily is also an option (weak recommendation)

Ticagrelor/Prasugrel > Clopidogrel

- Preference for these agents stems from TRITON-TIMI 38 and PLATO trials
- Shown to be more effective than clopidogrel WRT combined primary end-point (MI, CVA, death)
  - Marked benefit in rates of stent thrombosis
  - Similar benefit with RRR approx. 20%
  - Excess bleeding with more potent agents
- CCS Guidelines:
  - “These recommendations place greater emphasis on reduction of major CV events and stent thrombosis vs an increase in bleeding complications.”
2018 CCS Guidelines: Elective PCI

- Reflect latest generation of drug eluting stents
  - Thinner struts
  - Biodegradable/ ‘inert’ polymer
- Awareness of lower ischemic event risk
Is Ticagrelor the same as Prasugrel?

• RRR in trials comparing these agents against clopidogrel were similar (approx. 20% for MACE)

• In TRITON-TIMI 38, signals seen in certain subgroups with Prasugrel
  • Low body weight (<60kg) – No benefit
  • Age >75 yrs – No benefit
  • Prior CVA/TIA – evidence of harm

• TRITON-TIMI 38 – treatment was started after coronary anatomy was known (i.e. after angiography)
  • Very US-centric practice
  • Not the case in Canada and Europe (treatment given before anatomy known)

• CCS guidelines reflected these issues with Ticagrelor favoured over prasugrel in majority of cases
Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes

- ISAR-REACT5 study
- Investigator initiated study comparing Ticagrelor with Prasugrel in ACS patients
- 4018 patients randomized (Germany/Italy)
- End-point
  - Primary – Composite of death/MI/stroke at 1 year
  - Secondary – Bleeding safety endpoint

Anti-thrombotic therapy: Primary/Secondary Prevention

Results

**Efficacy**

- Hazard ratio, 1.36 (95% CI, 1.09–1.70) for Ticagrelor vs. Prasugrel, P=0.006

**Safety**

- Hazard ratio, 1.12 (95% CI, 0.83–1.51) for Ticagrelor vs. Prasugrel, P=0.46

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**All-cause mortality, MI, CVA**

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Ticagrelor</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1877</td>
<td>1892</td>
</tr>
<tr>
<td>2</td>
<td>1857</td>
<td>1877</td>
</tr>
<tr>
<td>4</td>
<td>1835</td>
<td>1862</td>
</tr>
<tr>
<td>6</td>
<td>1815</td>
<td>1839</td>
</tr>
<tr>
<td>8</td>
<td>1801</td>
<td>1829</td>
</tr>
<tr>
<td>10</td>
<td>1722</td>
<td>1803</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor</td>
<td>1989</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>1773</td>
</tr>
</tbody>
</table>

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**Bleeding**

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Ticagrelor</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor</td>
<td>1441</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>1465</td>
</tr>
</tbody>
</table>
I’m Glad that the Concept of DAPT is Sacred Or is it in its TWILIGHT?

Ticagrelor with or without Aspirin in High-Risk Patients after PCI


• Post PCI – treated with ASA/Ticagrelor for 3/12
• At 3/12, if no ischemic/bleeding endpoints, randomized:
  • Ticagrelor + placebo, vs
  • Ticagrelor + ASA
• End-point:
  • Primary - BARC type 2, 3 or 5 bleeding (actionable, Hgb drop or fatal)
  • Secondary - All-cause mortality, MI, CVA

Ticagrelor with or without Aspirin in High-Risk Patients after PCI


<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor plus aspirin</td>
<td>3564</td>
<td>3454</td>
<td>3357</td>
<td>3277</td>
<td>3213</td>
</tr>
<tr>
<td>Ticagrelor plus placebo</td>
<td>3555</td>
<td>3474</td>
<td>3424</td>
<td>3366</td>
<td>3321</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.56 (95% CI, 0.45–0.68)  
P<0.001

Anti-thrombotic therapy: Primary/Secondary Prevention

Ticagrelor with or without Aspirin in High-Risk Patients after PCI


Hazard ratio, 0.99 (95% CI, 0.78–1.25)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Ticagrelor plus aspirin</th>
<th>Ticagrelor plus placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3515</td>
<td>3524</td>
</tr>
<tr>
<td>0 months since randomization</td>
<td>3466</td>
<td>3457</td>
</tr>
<tr>
<td>3 months since randomization</td>
<td>3415</td>
<td>3412</td>
</tr>
<tr>
<td>6 months since randomization</td>
<td>3361</td>
<td>3365</td>
</tr>
<tr>
<td>9 months since randomization</td>
<td>3320</td>
<td>3330</td>
</tr>
</tbody>
</table>

Enough about Anti-platelets; what about anti-thrombtics?

ACS – APPRAISE-2 & ATLAS ACS2

Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

Jessica L. Mega, M.D., M.P.H., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., Jean-Pierre Bassand, M.D., Deepak L. Bhatt, M.D., M.P.H., Christoph Bode, M.D., Paul Burton, M.D., Ph.D., Marc Cohen, M.D., Nancy Cook-Bruns, M.D., Keith A.A. Fox, M.B., Ch.B., Shinya Goto, M.D., Sabina A. Murphy, M.P.H., et al., for the ATLAS ACS 2–TIMI 51 Investigators*


Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome

John H. Alexander, M.D., M.H.S., Renato D. Lopes, M.D., Ph.D., Stefan James, M.D., Ph.D., Rakhi Kilaru, M.S., Yaohua He, M.D., Ph.D., Puneet Mohan, M.D., Ph.D., Deepak L. Bhatt, M.D., M.P.H., Shaun Goodman, M.D., Freek W. Verheugt, M.D., Ph.D., Marcus Flather, M.D., Kurt Huber, M.D., Danny Liaw, M.D., Ph.D., et al., for the APPRAISE-2 Investigators*

Anti-thrombotic therapy: Primary/Secondary Prevention

Anti-thrombotic Post ACS

• **ATLAS ACS2** – >15,000 patients. Rivaroxaban reduced rate of MACE but at expense of major bleeds (inc. IC hemorrhage). Bleeding worse with 5mg bid dose.

• **APPRAISE2** – terminated prematurely after 7,000 patients. No reduction in ischemic events
Anti-thrombotic therapy: Primary/Secondary Prevention

Anti-thrombotics-Secondary Prevention with Rivaroxaban

COMPASS Trial Design

Stable CAD or PAD
2,200 with a primary outcome event

Rivaroxaban 2.5 mg bid
+ aspirin 100 mg od

Rivaroxaban 5 mg bid

Run-in (aspirin)

Aspirin 100 mg od

Expected follow up
3-4 years

Major bleeding increased: HR 1.70 (95% CI 1.40-2.05) p<0.001
Chronic Therapy – Personal biases/thoughts

<table>
<thead>
<tr>
<th></th>
<th>P2Y&lt;sub&gt;12&lt;/sub&gt; receptor inhibitor</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvascular disease</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Recurrent MI/PCI</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Complex PCI</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Prior stent thrombosis</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Time of MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 yrs ago</td>
<td></td>
<td>? ✔</td>
</tr>
<tr>
<td>&gt;3 yrs ago</td>
<td></td>
<td>? ✔</td>
</tr>
</tbody>
</table>
SUMMARY

• As in most fields of cardiology, there is a large body of evidence regarding the use of anti-platelets and anti-thrombotics

• Currently no evidence for net benefit with ‘true’ primary prevention for anti-platelets

• DAPT has been established as standard of care over the last 2 decades
  • Recent TWILIGHT study has questioned this
  • ISAR REACT 5 may renew interest in Prasugrel

• Concomitant use of anti-thrombotics is beneficial:
  • ACS – not firmly established (excess bleeding)
  • Chronic – clear benefit

• As with any effective anti-platelet/anti-thrombotic, the cost is in excess bleeding and must be weighed up individually
THANK YOU

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@docjohnnyg