Acute coronary syndromes

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## Disclosures

<table>
<thead>
<tr>
<th>Company name</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
<td>Research grant, honoraria, consultant</td>
</tr>
<tr>
<td>Idorsia</td>
<td>Consultant</td>
</tr>
<tr>
<td>Bayer</td>
<td>Consultant</td>
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<tr>
<td>Bristol Myers Squibb / Pfizer</td>
<td>Consultant, honoraria</td>
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<td>Haemonetics</td>
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<td>Novartis</td>
<td>Consultant</td>
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<tr>
<td>Thromboserin</td>
<td>Consultant</td>
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</table>
Common modifiable and relatively unmodifiable CVD risk factors

<table>
<thead>
<tr>
<th>Modifiable Risk Factors*</th>
<th>Relatively Fixed Risk Factors†</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hypertension</td>
<td>- CKD</td>
</tr>
<tr>
<td>- Current cigarette smoking, secondhand smoking</td>
<td>- Family history</td>
</tr>
<tr>
<td>- Diabetes mellitus</td>
<td>- Increased age</td>
</tr>
<tr>
<td>- Dyslipidaemia/hypercholesterolaemia</td>
<td>- Low socioeconomic/educational status</td>
</tr>
<tr>
<td>- Overweight/obesity</td>
<td>- Male sex</td>
</tr>
<tr>
<td>- Physical inactivity/low fitness</td>
<td>- Obstructive sleep apnea</td>
</tr>
<tr>
<td>- Unhealthy diet</td>
<td>- Psychosocial stress</td>
</tr>
</tbody>
</table>

*Factors that can be changed and, if changed, may reduce CVD risk.
†Factors that are difficult to change (CKD, low socioeconomic/educational status, obstructive sleep apnea, cannot be changed (family history, increased age, male sex), or, if changed through the use of current intervention techniques, may not reduce CVD risk (psychosocial stress).
CKD indicates chronic kidney disease; and CVD, cardiovascular disease.

Targets in post-ACS management

• Thrombosis risk
• Lipids
• Blood pressure
• Left ventricular dysfunction/heart failure/arrhythmia risk
• Glycaemic control
Targets in post-MI management

• Thrombosis risk
• Lipids
• Blood pressure
• Left ventricular dysfunction/heart failure/arrhythmia risk
• Glycaemic control
Oral antithrombotic mechanisms

Adapted with permission from Storey RF. Curr Pharm Des 2006
Overlap between placebo and clopidogrel effects

Ticagrelor vs. placebo
PEGASUS-TIMI 54 substudy

- Ticagrelor vs. placebo
- PEGASUS-TIMI 54 substudy

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Ticagrelor 60mg</th>
<th>Ticagrelor 90mg</th>
</tr>
</thead>
</table>

0 | 100 | 200 | 300 | 400
Pre-dose | Post-dose

PRU = 208

P = 0.34
P = 0.73

Ticagrelor vs. clopidogrel
STEEL PCI study

- Ticagrelor vs. clopidogrel
- STEEL PCI study

<table>
<thead>
<tr>
<th>Clopidogrel 60mg</th>
<th>Ticagrelor 60mg</th>
<th>Ticagrelor 90mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel 90mg</td>
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</tr>
</tbody>
</table>

0 | 100 | 200 | 300 | 400
Pre-dose | Post-dose

PRU = 208

*** | *** | ***

P = 0.07

Storey RF et al. J Am Coll Cardiol 2016

Orme R, Storey RF et al. Circulation 2018
Sheffield observational study

Adjusted mortality rates in 9,570 patients

Gosling R et al. Platelets 2017 online

Ticagrelor vs. clopidogrel:
Adjusted HR 0.82 (95% CI 0.71-0.96)
p = 0.01
Sheffield observational study

Adjusted definite stent thrombosis rates

Ticagrelor vs. clopidogrel:
Adjusted HR 0.51 (95% CI 0.29-0.89)
p = 0.02

**PEGASUS-TIMI 54: Primary endpoint**

- **Event rate (%)** vs **Months from randomization**
- **Placebo**
- **Ticagrelor 90 mg bid**
- **Ticagrelor 60 mg bid**

**HR**
- Ticagrelor 60 mg vs placebo: HR 0.84 (95% CI 0.74–0.95) *p*=0.004
- Ticagrelor 90 mg vs placebo: HR 0.85 (95% CI 0.75–0.96) *p*=0.008

**Event rates**
- Placebo: 9.04%
- Ticagrelor 90 mg bid: 7.85%
- Ticagrelor 60 mg bid: 7.77%
PEGASUS-TIMI 54: Primary Safety Endpoints

PEGASUS-TIMI 54: Estimates of first efficacy and bleeding events prevented and caused Ticagrelor 60 mg bd

PEGASUS TIMI 54: MACE and other events with ticagrelor 60mg vs placebo in patients with multivessel disease

**Bansilal S et al. JACC 2018**

![Graph showing event rates for different endpoints with ticagrelor vs placebo.](image)

**Note:**

§ Note: The secondary endpoint of coronary death (CHD death) did not meet statistical significance in the primary PEGASUS-TIMI 54 study analyses. The secondary endpoint of stent thrombosis was not explored in the primary PEGASUS-TIMI 54 study analyses.

† In the primary PEGASUS analysis, 3-year KM estimates of death from CHD were 1.72% for Ticagrelor 60 mg + ASA vs 2.08% for ASA alone (HR 0.80, 95% CI 0.62–1.04; P=0.09).
Decision algorithm for DAPT duration post MI

Admission with MI and treated with DAPT
- Coronary angiography
  - CABG
    - Up to 12 months DAPT
  - PCI
    - Conservative treatment
      - Multivessel/extensive CAD with DM, PAD, CKD or recurrent MIs OR very severe multivessel CAD
        - Yes
      - Intolerance to ticagrelor (not bleeding related)
        - No
      - History of ischaemic stroke
        - No
      - Indication for oral anticoagulation (e.g. atrial fibrillation) OR high-risk features for life-threatening bleeding: anaemia, history of spontaneous major bleed, bleeding diathesis or thrombocytopenia, severe liver disease, intracranial vascular abnormality or neoplasm, extreme old age or frailty
    - No

Prolonged DAPT with aspirin + ticagrelor (downtitrate from 90 mg to 60 mg BD from 1 year post MI)

Adapted from Sumaya W et al. Thromb Haemost 2019 online
COMPASS trial: primary endpoint

Rivaroxaban+aspirin vs. aspirin alone
Hazard ratio, 0.76 (95% CI, 0.66–0.86)
P<0.001

Rivaroxaban alone vs. aspirin alone
Hazard ratio, 0.90 (95% CI, 0.79–1.03)
P=0.12

Eikelboom JW et al. NEJM 2017
### COMPASS Primary components

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban 2.5mg bd + Aspirin (N=9,152)</th>
<th>Aspirin (N=9,126)</th>
<th>Rivaroxaban + Aspirin vs. Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>CV death</td>
<td>160 (1.7%)</td>
<td>203 (2.2%)</td>
<td>0.78 (0.64-0.96)</td>
</tr>
<tr>
<td>Stroke</td>
<td>83 (0.9%)</td>
<td>142 (1.6%)</td>
<td>0.58 (0.44-0.76)</td>
</tr>
<tr>
<td>MI</td>
<td>178 (1.9%)</td>
<td>205 (2.2%)</td>
<td>0.86 (0.70-1.05)</td>
</tr>
</tbody>
</table>

Eikelboom JW et al. NEJM 2017
The challenge of AF and ACS

How do you treat coronary thrombosis

....and prevent cardiac thromboembolism?

Images provided courtesy of Professor Storey.

ACS: acute coronary syndrome; AF: atrial fibrillation.
Dropping aspirin from triple therapy combination after PCI is an option in selected patients

GRACE: global registry of acute coronary events; HAS-BLED: hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, Labile INR, elderly, drug/alcohol usage; OAC: oral anticoagulant; LAD, left anterior descending coronary artery; mo: months; TTR, time in therapeutic range.
AUGUSTUS primary outcome
Major or clinically-relevant non-major bleeding

AUGUSTUS secondary outcome
Death or Hospitalization

VKA + Placebo (27.3%)
Apixaban + Placebo (22.0%)
Apixaban + Aspirin (24.9%)
VKA + Aspirin (27.5%)

Apixaban + Placebo vs. VKA + Aspirin: 5.5% absolute risk reduction (NNT=18)

### AUGUSTUS
Ischaemic Outcomes
Aspirin vs. Placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Aspirin (N=2307)</th>
<th>Placebo (N=2307)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death / Ischemic Events (%)</td>
<td>6.5</td>
<td>7.3</td>
<td>0.89 (0.71–1.11)</td>
</tr>
<tr>
<td>Death (%)</td>
<td>3.1</td>
<td>3.4</td>
<td>0.91 (0.66–1.26)</td>
</tr>
<tr>
<td>CV Death (%)</td>
<td>2.3</td>
<td>2.5</td>
<td>0.92 (0.63–1.33)</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>0.9</td>
<td>0.8</td>
<td>1.06 (0.56–1.98)</td>
</tr>
<tr>
<td>Myocardial Infarction (%)</td>
<td>2.9</td>
<td>3.6</td>
<td>0.81 (0.59–1.12)</td>
</tr>
<tr>
<td>Definite or Probable Stent Thrombosis (%)</td>
<td>0.5</td>
<td>0.9</td>
<td>0.52 (0.25–1.08)</td>
</tr>
<tr>
<td>Urgent Revascularization (%)</td>
<td>1.6</td>
<td>2.0</td>
<td>0.79 (0.51–1.21)</td>
</tr>
<tr>
<td>Hospitalization (%)</td>
<td>25.4</td>
<td>23.4</td>
<td>1.10 (0.98–1.24)</td>
</tr>
</tbody>
</table>

AF and PCI
General principles

• Assess risk of cardiac thromboembolism - DAPT alone may suffice if CHA$_2$DS$_2$-VASc is low
• Determine the risk of stent thrombosis based on patient and lesion characteristics and procedural outcome – higher thrombosis risk if stent deployment is suboptimal
• Determine which factors are present that increase the risk of bleeding
• Use NOAC in preference to warfarin unless poor renal function
• Stop aspirin early after PCI if stent thrombosis risk is low or bleeding risk outweighs the stent thrombosis risk
• If using aspirin, clopidogrel and warfarin, minimise duration of combined therapy and take care over INR control (2.0-2.5)
Targets in post-MI management

- Thrombosis risk
- Lipids
- Blood pressure
- Left ventricular dysfunction/heart failure/arrhythmia risk
- Glycaemic control
Mechanisms in atherothrombosis

Cytokine release & leukocyte recruitment

Platelet adhesion & activation

Leukocyte adhesion, rolling & migration

Fibrous cap & foam cell accumulation

Plaque rupture & thrombosis

Shear stress

SELECTINS & ADHESION MOLECULES

LDL

NITRICOXIDE++

VSMC migration & proliferation

Healthy vasculature

Endothelial activation

Early lesion

Advanced lesion

Atherothrombosis

ATHEROGENESIS
Reduction in CVD events is related to absolute reduction in LDL-C

*defined as coronary death, confirmed nonfatal acute MI, or cardiac arrest with resuscitation or stroke.

1 mmol/L = ~40 mg/dL.

PCSK9 Inhibitors

Mullard A. Nature Reviews Drug Discovery 2012; 11: 817-819
PCSK9 inhibition following ACS

ODYSSEY OUTCOMES study

Alirocumab vs placebo

Primary endpoint: CHD-related death, nonfatal MI, nonfatal or fatal ischaemic stroke, or unstable angina requiring hospitalisation

ODYSSEY OUTCOMES
Primary endpoint according to baseline LDL-cholesterol

Targets in post-MI management

- Thrombosis risk
- Lipids
- Blood pressure
- Left ventricular dysfunction/heart failure/arrhythmia risk
- Glycaemic control
SPRINT study primary outcome

Hazard Ratio = 0.75 (95% CI: 0.64 to 0.89)

During Trial (median follow-up = 3.26 years)
Number Needed to Treat (NNT) to prevent a primary outcome = 61

Sprint Research Group. NEJM 2015
### Categories of BP in Adults*

<table>
<thead>
<tr>
<th>BP Category</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120 mm Hg</td>
<td>&lt;80 mm Hg</td>
</tr>
<tr>
<td>Elevated</td>
<td>120–129 mm Hg</td>
<td>&lt;80 mm Hg</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>130–139 mm Hg</td>
<td>80–89 mm Hg</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥140 mm Hg</td>
<td>≥90 mm Hg</td>
</tr>
</tbody>
</table>

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category. BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.)
Targets in post-MI management

• Thrombosis risk
• Lipids
• Blood pressure
• Left ventricular dysfunction/heart failure/arrhythmia risk
• Glycaemic control
Aldosterone antagonists

Spironolactone
Eplerenone

Competitive antagonist of the aldosterone receptor
(myocardium, arterial walls, kidney)

- Retention $\text{Na}^+$
- Retention $\text{H}_2\text{O}$
- Excretion $\text{K}^+$
- Excretion $\text{Mg}^{2+}$

Oedema
Arrhythmias

Collagen Deposition
- Fibrosis
  - myocardium
  - vessels
Targets in post-MI management

• Thrombosis risk
• Lipids
• Blood pressure
• Left ventricular dysfunction/heart failure/arrhythmia risk
• Glycaemic control
SGLT2 Inhibitors in Patients with Diabetes

- Decrease renal glucose reabsorption
- Increase urinary glucose excretion
  - Reduce rate of hyperglycaemia, lower HbA1c ~0.6-1%
  - Reduce blood pressure ~3-5mmHg
  - Loss of calories and modest weight loss ~2-3kg

EMPA-REG OUTCOME study

Conclusions

• Addressing modifiable risk factors has a profound effect on prognosis after ACS
• Long-term dual antiplatelet/antithrombotic therapy is indicated in patients at high ischaemic risk who don’t have high bleeding risk conditions
• LDL-cholesterol: aim low for best risk reduction
• Blood pressure: manage to target; ambulatory monitoring can be very helpful
• LVSD/heart failure: beta-blockers, ACEi and aldosterone antagonist for medical therapy; devices for LVEF <35%
• Diabetes: use of new agents (SGLT-2i, liraglutide) with appropriate counselling can improve clinical outcomes