The Clinical Unmet need in the patient with Diabetes and ACS

Professor Kausik Ray (UK)
BSc(hons), MBChB, MD, MPhil, FRCP (Ion), FRCP (ed), FACC, FESC, FAHA
Disclosures

- Kausik Ray has participated in
- Advisory Boards for Sanofi/Regeneron, Amgen, Pfizer, Roche, MSD, Kowa, BI, Takeda;
- Acted as a speaker for AZ, Pfizer, Sanofi Regeneron, Amgen, Kowa, Algorithm, Cipla, BI, Takeda
- Received research grant support from Sanofi/Regeneron, Pfizer, Amgen & MSD; CME lectures at Symposia for Sanofi/Regeneron, Amgen, Pfizer, AZ & MSD;
- NLI/SC member for Odyssey- (Sanofi/Regeneron), Roche; PI for ORION 1 (Medicines Company), Cerenis, Lilly, Esperion, Kowa, AZ, Resverlogix
Diabetes is a global public health challenge and outcomes remain poor compared to those without Diabetes.
Prevalence of diabetes in 2030

<table>
<thead>
<tr>
<th>Total number of people with diabetes (age 20-79)</th>
<th>2010</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of diabetes (age 20-79)</td>
<td>6.6 %</td>
<td>7.8 %</td>
</tr>
</tbody>
</table>
Diabetes doubles the risk of vascular events
Emerging Risk Factors Collaboration

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of cases</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary heart disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary death</td>
<td>11,556</td>
<td>2.31 (2.05–2.60)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>14,741</td>
<td>1.82 (1.64–2.03)</td>
</tr>
<tr>
<td><strong>Cerebrovascular disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>3799</td>
<td>2.27 (1.95–2.65)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1183</td>
<td>1.56 (1.19–2.05)</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>4973</td>
<td>1.84 (1.59–2.13)</td>
</tr>
<tr>
<td><strong>Other vascular deaths</strong></td>
<td>3826</td>
<td>1.73 (1.51–1.98)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; MI, myocardial infarction.

Estimated life years lost among those with Diabetes

Seshasai, NEJM. 2011;364(9):829-841
Life expectancy is reduced by ~12 years in diabetes patients with previous CVD*

Modelling of years of life lost by disease status of participants at baseline compared with those free of diabetes, stroke and MI

*Male, 60 years of age with history of MI or stroke

7 Year Risk of Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke in IMPROVE IT

![Chart showing LDL-C levels and 7-year risk in different groups](Cannon Et al NEJM 2015)
Reducing CV risk in T2D may need a multifactorial approach

CV risk

Control of dyslipidaemia

Antihypertensive therapy

Weight loss and lifestyle intervention*

Glycaemic control

Antiplatelet therapy

Targeting additional pathways (inflammation, complement activation, Activated vasculature Reverse cholesterol transport

CV, cardiovascular; T2D, Type 2 Diabetes.
*Includes smoking cessation.

What else is perturbed and which could be a target for therapy?
Perturbed Vasculature
A perturbed vasculature predicts recurrent events Post ACS

Ray AJC 2006
The risk from a perturbed vasculature may be attenuated by treatments that reduce LDL-C and inflammation.
The presence of heightened inflammation or a perturbed vascular is associated with greater risk in those with DM vs those without – OPUS TIMI 16

Figure 1

A

CRP

B

MCP-1

C

vWF

Non-DM Low CRP

Non-DM High CRP

DM Low CRP

DM High CRP

Non-DM Low MCP-1

Non-DM High MCP-1

DM Low MCP-1

DM High MCP-1

Non-DM Low vWF

Non-DM High vWF

DM Low vWF

DM High vWF

HR of Death or MI

HR of Death or MI

HR of Death or MI

Ray EHJ 2012
Validation of the greater impact of inflammation on adverse outcomes among those with DM vs those without DM in TACTICS-TIMI 18
Potential mechanism of increased risk is an interaction between dysglycaemia and inflammation in DM

Figure 3

HR per 1 mmol increase in glucose after adjustment for diabetes

Low CRP

High CRP

HR 1.02, 95% CI 0.97-1.06, p=0.5

P interaction 0.045

HR 1.07, 95% CI 1.03-1.11, p<0.0001
Targeting HDL function
Is HDL-C causal? No

Estimate of the association of genetically raised LDL cholesterol or HDL cholesterol and risk of myocardial infarction using multiple genetic variants as instruments

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (95% CI) per SD increase in plasma lipid based on observational epidemiology*</th>
<th>Odds ratio (95% CI) per SD increase in plasma lipid conferred by genetic score†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
<td>1.54 (1.45–1.63)</td>
<td>2.13 (1.69–2.69), p=2x10^{-10}</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.62 (0.58–0.66)</td>
<td>0.93 (0.68–1.26), p=0.63</td>
</tr>
</tbody>
</table>

*Observational epidemiology estimates derived from more than 25,000 individuals from prospective cohort studies; †LDL genetic score consisting of 13 SNPs, and HDL genetic score consisting of 14 SNPs

SNP, single nucleotide polymorphism

Is low HDL-C a risk marker? Yes

Potential atheroprotective effects of HDL

- Anti-apoptotic
- Anti-inflammatory
- Antithrombotic
- Cholesterol transport
- Endothelial repair
- Protection against oxidation
- Modulation of endothelial function
- Cholesteryl ester donor
HDL cholesterol efflux capacity and incident cardiovascular events

Atherosclerotic cardiovascular disease

<table>
<thead>
<tr>
<th>Year</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Participants with event (%)

P=0.002 by log-rank test

Hazard ratio

<table>
<thead>
<tr>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>0.74 (0.48–1.13)</td>
</tr>
<tr>
<td>Q2</td>
<td>0.49 (0.31–0.79)</td>
</tr>
<tr>
<td>Q3</td>
<td>0.44 (0.27–0.73)</td>
</tr>
</tbody>
</table>

Other Potential Pathways
Relationship of Proteinuria, eGFR and Mortality

Where is the highest risk / Unmet need?

• Patients with ACS
• Patients with ACS and DM
• Patients with ACS, DM and low HDL

• Very high event rate!
Apabetalone Biomarker Changes Accompanied by MACE Reduction in Phase 2 Studies

MACE: Major Adverse Cardiac Events including: death, myocardial infarction, stroke, coronary revascularization, hospitalization for acute coronary syndrome or heart failure.

Note: Patients were censored at 30 days after the last dose of study medication.

**Key inclusion criteria**

- T2DM
  - HbA1c > 6.5% or history of diabetes medications
- CAD event 7 days - 90 days prior to Visit 1
  - MI, UA or PCI
- HDL < 1.04 for males and < 1.17 for females

**Primary Objective**

To evaluate if treatment with apabetalone as compared to placebo increases time to the first occurrence of triple MACE. Triple MACE is defined as a single composite endpoint of CV death or non-fatal MI or stroke.

**Primary Endpoint**

Time from randomization to the first occurrence of adjudication-confirmed triple MACE defined as a single composite endpoint of CV Death or Non-fatal MI or Stroke.

**Secondary Endpoint**

Time from randomization to the first occurrence of adjudication-confirmed MACE including revascularization and UA

Changes in apoA-I, apoB, LDL-C, HDL-C, and TG

Changes in HbA1c, fasting glucose, and fasting insulin

Changes in ALP and eGFR
The study is an event-based trial and continues until 250 events have occurred.
Summary

• T2D is a major public health challenge
• CV events are highest in patients with T2D and ACS
• Beyond current therapies targeting several novel pathways known to be perturbed post ACS may offer novel solutions to current unmet need