Diabetes and Cardiovascular Disease: Time for multifactorial approach

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Monday 27 August 2018
Professor John Deanfield: Disclosures

- Received CME honoraria and/or consulting fees from Amgen, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk, Bayer
- Member of Study Steering Committees for Novo Nordisk
- Research grants from British Heart Foundation, MRC(UK), NIHR, PHE, MSD, Pfizer, Aegerion, Colgate, Roche
- No conflicts of interest for this presentation
Diabetes Is Associated With Significant Loss of Life Years

On average, a 50-year old with diabetes but no history of vascular disease is ~6 years younger at time of death than a counterpart without diabetes.

Major Diabetes Complications in USA

Hyperglycaemic Deaths

CVD Admissions

Source: Gregg et al, The Lancet Diabetes & Endocrinology 2016 4, 537-547
The Ticking Clock: ↑ CV Risk Before ↑ Glucose (Nurses’ Health Study)

20 yr F/U of 117,629 women: n=1,508 diabetes at B/L; n=5,894 developed diabetes; n=110,227 free from diabetes

Source: Hu et al, Diabetes Care 2002; 25: 1129-1134
Dysglycaemia and CV risk: Impact of glucose perturbations in patients who have experienced MIs

GAMI – long-term follow-up
First major event (death, MI, stroke, or severe HF)

DM, diabetes mellitus; GAMI, Glucose Tolerance in Patients with Acute Myocardial Infarction; HF, heart failure; IGT, impaired glucose tolerance; MI, myocardial infarction; NGT, normal glucose tolerance; Pat, patients

Log-rank overall: $p=0.0046$

Risk Factors for CVD in patients with T2DM

271,174 pts with T2DM matched to 1,355,870 controls
Median F/U = 5.7 years with 175,345 deaths

Death From Any Cause

Acute Myocardial Infarction

Stroke

Heart Failure

Healthy Lifestyle and CVD in T2DM

CVD Incidence

CVD Mortality

Source: Lui, G et al, JACC 2018;71(25):2867-76
Diabetes is a condition which causes CVD to Diabetes is a state of enhanced CV risk

Source: Goldner MG, JAMA 1971,218, 1400-10
Management should be targeted at reducing/delaying CV complications in patients with T2DM with and without clinical CVD and in those with pre-diabetes.

Most cardiologists have focused efforts on ‘traditional’ CVRFs and not on glucose lowering.

Source: Goldner MG, JAMA 1971,218, 1400-10
CARDS: Cumulative Hazard for MI and CV Death

Relative Risk -37% (95% CI: -52, -17) P=0.001

Cumulative Hazard (%)

Placebo
Atorvastatin

Years
0 1 2 3 4 4.75
Heart Protection Study: Impact of Diabetes on CV outcome

- **Placebo**
  - Diabetes + CHD: RRR 12%
  - No diabetes + CHD: RRR 23%
  - Diabetes + other CVD: RRR 22%
  - No diabetes + other CVD: RRR 19%
  - Diabetes + no CVD: RRR 31%

- **Simvastatin 40 mg**

Benefit of Different Interventions per 200 Diabetes Patients Treated for 5 years

Using traditional Glucose lowering treatments

- Per 4mm Hg lower SBP: -12.5
- Per 1mmol/L lower LDL-C: -8.2
- Per 0.9% lower HbA1c: -2.9

Diabetes and Cardiovascular Disease: The Perfect Storm

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Rosiglitazone Group</th>
<th>Control Group</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Small trials combined</td>
<td>44/10,285 (0.43%)</td>
<td>22/6106 (0.36%)</td>
<td>1.45 (0.88–2.39)</td>
<td>0.13</td>
</tr>
<tr>
<td>DREAM</td>
<td>15/2,635 (0.57%)</td>
<td>9/2634 (0.34%)</td>
<td>1.65 (0.74–3.68)</td>
<td>0.22</td>
</tr>
<tr>
<td>ADOPT</td>
<td>27/1,456 (1.85%)</td>
<td>41/2895 (1.42%)</td>
<td>1.33 (0.80–2.11)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td>1.43 (1.03–1.98)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Death from cardiovascular causes</strong></td>
<td></td>
<td></td>
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<tr>
<td>Small trials combined</td>
<td>25/6,845 (0.36%)</td>
<td>7/3980 (0.18%)</td>
<td>2.40 (1.17–4.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>DREAM</td>
<td>12/2,635 (0.46%)</td>
<td>10/2634 (0.38%)</td>
<td>1.20 (0.52–2.78)</td>
<td>0.67</td>
</tr>
<tr>
<td>ADOPT</td>
<td>2/1,456 (0.14%)</td>
<td>5/2895 (0.17%)</td>
<td>0.80 (0.17–3.86)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td>1.64 (0.98–2.74)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Diabetes Medications and Possible Increased CV Risk

FDA / EMA requirements:

- New diabetes drugs should demonstrate CV safety with meta-analysis and CV outcome trial
New Approaches To Reducing Blood Glucose

**Incretins (GIP, GLP-1)**
- Stimulate insulin release
- Inhibit glucagon release
- Reduce blood glucose

**DPP4 inhibitors ("gliptins")**
- Breakdown products
- Inhibit glucagon release
- Inhibit renal re-absorption (SGLT2 inhibitors)

**GLP-1 agonists/analogues**
- Inhibit gastrointestinal absorption (α-glucosidase inhib’ s)
- Reduce blood glucose
Empagliflozin, CV Outcomes and Mortality in T2DM

**Primary Outcome**

- **Death from Cardiovascular Causes**
  
  Hazard ratio, 0.86 (95% CI, 0.74–0.99)
  
  P = 0.04 for superiority

- **Death from Any Cause**
  
  Hazard ratio, 0.68 (95% CI, 0.57–0.82)
  
  P < 0.001

- **Hospitalization for Heart Failure**
  
  Hazard ratio, 0.65 (95% CI, 0.50–0.85)
  
  P = 0.002

**Source:** Zinman N Engl J Med 2015;373:2117-28
GLP1-RA: Liraglutide and CV Outcomes in T2DM - LEADER Trial

Primary Outcome

- HR 0.85, P=0.02

Death from Any Cause

- HR 0.87, P=0.01

New Diabetes Drugs and Patterns of CV Benefits in Patients With T2DM and CV Disease

- Atherogenesis
- Volume overload
- Myocardial fibrosis

Reduced stroke and MI risk

Possible lowered by GLP-1RA

Reduced – CV-death– Heart failure risk

? ↓ atherothrombosis ± avoidance of hypoglycaemia

? Hemodynamic/metabolic mechanisms

Lowered by SGLT2 inhibitors

Source: Sattar J Am Coll Cardiol 2017; 69: 2646–56
GLP-1 RA in combination with SGLT2-i better than monotherapy in diabetic patients (on HbA1c)

52 weeks results of the DURATION-8 study

Percentage of patients achieving their glycemic and weight targets

- HbA1c <7.0%
- HbA1c <=6.5%
- BW loss >=5%

Source: Jabbour et al, Diab Care July 2018, pub ahead of print, doi:10.2337/dc18-0680/-/DC1
In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently, empagliflozin and liraglutide), after considering drug-specific and patient factors (Table 8.1).

Novel ‘Diabetes’ Drugs: Unanswered Questions

? Are these drugs equally effective in patients without CVD or without DM (primary prevention)?

? Which patients benefit most from each drug? e.g. patients with HF or kidney disease

? Mechanisms by which drugs mediate CV benefit?

Heart failure

Diabetic nephropathy

Obesity

Future CVOTs
Impact of GLP1-RA on Obesity

New Era for CVD Management in DM: Some Thoughts

- In addition to BP and Cholesterol lowering, CVD and renal benefit with two new glucose lowering drug classes, SGLT2i and GLP1-RA
- Has already changed guidelines for DM care
- Novel multiple mechanisms, especially with lack of hypoglycaemia may broaden indications towards early treatment, prevention, even without DM