Sugar vs Fat: is treatment of dyslipidaemia relevant for diabetes?

Naveed Sattar

BHF Cardiovascular Research Centre
University of Glasgow
Is treatment of dyslipidaemia relevant for diabetes?

- YES
- VERY!
<table>
<thead>
<tr>
<th></th>
<th>Glucose-lowering</th>
<th>BP lowering</th>
<th>Statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD*</td>
<td>↓*</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Affordability</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Simplicity</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Ferguson & Sattar (2013) DOM
Diabetes doubles CVD risk on average

ERFC (2010) Lancet

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary heart disease</strong>*</td>
<td>26,505</td>
</tr>
<tr>
<td>Coronary death</td>
<td>11,556</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>14,741</td>
</tr>
</tbody>
</table>

**Stroke subtypes***

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic stroke</td>
<td>3,799</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1,183</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>4,973</td>
</tr>
<tr>
<td>Other vascular deaths</td>
<td>3,826</td>
</tr>
</tbody>
</table>

Hazard ratios for vascular outcomes DM vs. no DM
Diabetes and CVD risk: duration
Diagnosis and age of onset matter

Sattar (2013) Diabetologia  (several studies support concept)
Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study

Marcello Tonelli, Paul Muntner, Anita Lloyd, Braden J Manns, Scott Klarenbach, Neesh Pannu, Matthew T James, Brenda R Hemmelgarn, for the Alberta Kidney Disease Network

Figure 1: Unadjusted rates of clinical outcomes in each risk group
Unadjusted rates and 95% CIs of myocardial infarction (A) and all-cause mortality (B) per 1000 person-years. Chronic kidney disease is defined as estimated glomerular filtration rate lower than 60 mL/min per 1.73 m² with or without proteinuria. CKD=chronic kidney disease. *Includes participants with or without diabetes and chronic kidney disease.
29 RCTs diabetes: proteinuria as bad as CVD
Preiss, Sattar, McMurray (AHJ 2010)
Diabetes broad CVD effect

- **CVD risk double on average**
  - Decade of diabetes…..towards CHD risk equiv.
  - Or proteinuria / low eGFR

- **CHF, PAD commonest 1\textsuperscript{ST} CVD events in DM**

- **Statins lower HF risks**
  - Preiss et al (2015) EHJ
Questions

- What LLT to give?
- When to start?
- What target?
Diabetes is associated with characteristic dyslipidaemia

- LDL-c around same
- Trig $\uparrow$ (2-4mmol/l)
- HDL-c $\downarrow$ (0.7-1mmol/l)
- Insulin resistance pattern
- Fibrates?

Mr H, 53 diagnosed 4 months – FH?

- Cholesterol 11mmol/l
- Triglyceride 13mmol/l
- Poor sugar control?
  - HbA1c 93mmol/mol
  - 10.7%
STATINS WORK AS WELL IN DM AS IN NON-DM
Heart Protection Study (2002) Lancet

<table>
<thead>
<tr>
<th>Baseline feature</th>
<th>STATIN (10269)</th>
<th>PLACEBO (10267)</th>
<th>Risk ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous MI</td>
<td>1007</td>
<td>1255</td>
<td>STATIN better</td>
</tr>
<tr>
<td>Other CHD (not MI)</td>
<td>452</td>
<td>597</td>
<td>STATIN worse</td>
</tr>
<tr>
<td>No prior CHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>182</td>
<td>215</td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td>332</td>
<td>427</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>279</td>
<td>369</td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2042 (19.9%)</td>
<td>2606 (25.4%)</td>
<td>24% SE 2.6 reduction (2P&lt;0.00001)</td>
</tr>
</tbody>
</table>

CARDS (A10), CTT all consistent
Cholesterol has been falling in diabetes patients

- **Cholesterol**

- Preiss (2011) AHJ – average DM trials
  - 1990 ~ 5.4mmol/l

- UK 2006 – 4.5mmol/l
  - 2008 – 4.2mmol/l
HBA1c 7.7 to 7.3%       Smoking 20% to 15%       SBP 130.5 to 128.7
Mortality in DM declined last 3 decades

<table>
<thead>
<tr>
<th>Year of baseline survey</th>
<th>No. of deaths</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960-69</td>
<td>9751</td>
<td>1.67 (1.44, 1.94)</td>
</tr>
<tr>
<td>1970-79</td>
<td>45666</td>
<td>2.16 (1.87, 2.48)</td>
</tr>
<tr>
<td>1980-89</td>
<td>29299</td>
<td></td>
</tr>
<tr>
<td>1990-99</td>
<td>24619</td>
<td></td>
</tr>
<tr>
<td>2000-09</td>
<td>1002</td>
<td></td>
</tr>
</tbody>
</table>

ERFC (2011) NEJM
Estimated future years of life lost due to diabetes by sex, age and cause

Men

Women

- Vascular deaths
- Cancer deaths
- Non-cancer non-vascular deaths
- Unknown causes

ERFC (2011) NEJM
BP meds and STATINS trump DM lowering for CVD per 200 diabetes pts treated for 5 years.

-12.5
-8.2
-2.9
-20
-15
-10
-5
0
5
CV events

Per 4mmHg lower SBP
Per 1mmol/L lower LDL-C
Per 0.9% lower HbA1c

### Small differentials in HbA1c - negligible CVD effect in recent trials

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Baseline HbA1c</th>
<th>Treatment difference</th>
<th>Duration</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAVOR</strong></td>
<td>DPP-4</td>
<td>8.0%</td>
<td>~ 0.3%</td>
<td>2.1 years</td>
<td>Null</td>
</tr>
<tr>
<td><strong>ORIGIN</strong></td>
<td>Insulin</td>
<td>6.4%</td>
<td>~ 0.3%</td>
<td>6.2 years</td>
<td>Null</td>
</tr>
<tr>
<td><strong>Look AHEAD</strong></td>
<td>Lifestyle</td>
<td>7.3%</td>
<td>~0.27% average 4 years</td>
<td>9.6 years</td>
<td>Null</td>
</tr>
</tbody>
</table>
Fibrate trials (far) less convincing

- Cholesterol 4.2 mmol/l (160 mg/dl) TG 4.1 HDL-c 0.9? Add fibrate?

- ACCORD / FIELD –ve overall CVD but
  - Lower non-fatal MI
  - No change overall mortality
  - FDA: need additional trial

- Statins also lower Trigs /pancreatitis
Questions

- What LLT to give?
  - Statins first line......nearly always
    - If not at target despite max tolerated therapy?
    - Ezetimibe (Improve-It)
    - Fibrates (if persistent high TG?)

- When to start?

- What target?
Next big LLT? PCSK9 inhibitors lower LDL-c by up to 70%
Statin dose: moderate for most

- **Atorvastatin 20mg** (NICE guideline)

- **Who deserves more intensive statin?**
  - All? Why not?
  - A80 £2.50 vs. A20 £1.41

- **A80: Selected very high risk groups**
  - CVD and DM
  - or + Renal disease (low eGFR)
  - Or + Proteinuria
Effect of statins on LDL-C

Dose response

Mean percentage change in LDL-C from baseline

10mg  20mg  40mg  80mg

Simvastatin

-28%
-35%
-39%

Atorvastatin

-37%
-43%
-51%

Rosuvastatin

-46%
-52%
-55%

Statin Intolerance (exists, proportion?)

Atorvastatin / Simvastatin

- 1. Re-challenge at same dose
- 2. Cut dose
- 3. Rosuvastatin 5mg (intermittent /titrate) OR pravastatin 10mg /day
- 4. Ezetimibe
## When to Start Statin – Mixed Views

<table>
<thead>
<tr>
<th>NICE</th>
<th>JBS3, EU, USA</th>
</tr>
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<tbody>
<tr>
<td>• Restart risk scoring in Diabetes patients</td>
<td></td>
</tr>
<tr>
<td>• QRISK2 risk score</td>
<td></td>
</tr>
<tr>
<td>• 10% risk threshold</td>
<td></td>
</tr>
<tr>
<td>• All T2DM &gt;40</td>
<td></td>
</tr>
<tr>
<td>• (all T1DM &gt;40)</td>
<td></td>
</tr>
</tbody>
</table>
| • Younger if evidence of end-organ damage….
| • *PREFER* fire & forget…… |
|   – *DM at 40 years higher RR* |
Targets: approach varies

- **QOF – UK**
  - $<\text{TC} \ 5 \ \text{mmol/l}$ or $>1 \ \text{mmol/l}$ reduction

- **NICE – UK**
  - $>40\%$ reduction in non-HDL-c
  - $\text{TC} \ - \ \text{HDL-c}$

- **NO NEED TO FAST for lipid determinations**

- **USA**
  - Moderate dose statins
  - No target

- **EU guidelines**
  - Under development
  - $\text{LDL-c} < 2.5 \ \text{mmol/l}$?
  - non-$\text{HDL-c} < 3.2 \ \text{mmol/l}$
  - $\sim \text{TC} < 4.5 \ \text{mmol/l}$?
## Lowering risk in DM by key modalities

Ferguson & Sattar (2013) DOM

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<td>↓</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Renal disease</td>
<td>↓/↓↓↓*</td>
<td>↓↓↓ (ACE/ARB)</td>
<td>↓</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
<td>→ (fibrate: 37%↓↓? Need new trial)</td>
</tr>
</tbody>
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Lipid-lowering key in Diabetes risk reduction

- Most need statins: CVD gains clear cut
- Most guidelines: >40 yrs T2DM (+T1DM): More guidance at younger ages
- Targets variable: non-HDL-c targets appearing
  - Atorvastatin 20mg good reduction
  - More intensive when DM+CVD, renal disease
  - Vast majority can take some statin
- Newer drugs have a role in some