Glucose Control and Prevention of Cardiovascular Disease

Dr Peter A Senior
BMedSci MBBS PhD FRCP(E)
Associate Professor, Director
Division of Endocrinology, University of Alberta

Diabetes Update+, March 2014
Disclosures

• Grants/Research Support: Boehringer-Ingelheim, BMS, GSK, ISIS, Lilly, Novo

• Speakers Bureau/Honoraria: Animas, Astra Zeneca, BD, Bayer, BMS, Lilly, Merck, Novo Nordisk, Sanofi-Aventis, Servier

• Consulting Fees: Abbott, Astra Zeneca, Bayer, GSK, Janssen, Lilly, Medtronic, Novo Nordisk, Sanofi

• Other: Associate Professor at University of Alberta
What is the Role of Oral Hygiene to Prevent Dental Caries?

• in a toddler?

• in an adolescent who drinks pop?

• in an adult with sensitivity?

• in an adult with dental abscess?
True or False

• Hyperglycemia is a key risk factor for coronary heart disease
A1c predicts CHD & Death

Age Adjusted Relative Risk

EPIC-Norfolk

Ann Intern Med 2004; 141:413–20
Intensive glycemic control in people with diabetes is effective to prevent cardiovascular disease in

- Type 1 diabetes
- Newly diagnosed type 2 diabetes
- Longstanding type 2 diabetes
- A and B
- A and B and C
A Conundrum

- Obesity
- Dyslipidemia
- Insulin Resistance
- Hyperglycemia
- HTN

- CVD

- DM Rx
  - toxicity
  - hypoglycemia
  - AGEs
  - inflammation
  - etc
T1DM - DCCT & EDIC

DCCT

Intensive n=700

Conventional n=700

6.5 years

EDIC

“Intensive”

8 years

What happens next?
EDIC – $A_{1c}$ converges

Figure 1. Distribution of HbA$_{1c}$ Concentration by Randomized Treatment Group at the End of the DCCT and in Each Year of the EDIC Study.
Reduced Risk of Nonfatal MI, Stroke or CVD Death

57% risk reduction
\((P=0.02; 95\% \text{ CI: } 12–79\%)\)

Achieved A1C
- Intensive: 7.4%
- Conventional: 9.1%

DCCT Clinical Trial
EDIC Follow-up

Conventional treatment
Intensive treatment
Relationship Between A1C and Micro- and Macrovascular Disease

![Graph showing the relationship between mean HbA1c levels and incidence of microvascular and myocardial infarction.](image)

CHD in UKPDS

Myocardial Infarct

p = 0.052

UKPDS Lancet 1998
UKPDS+10 - glycemia
UKPDS+10 – glycemia

Death from Any Cause

Proportion with Event

P=0.006

Years since Randomization

No. at Risk

Conventional therapy

Sulfonylurea–insulin

Effects of More vs. Less Intensive Glycemic Control on CV Events

<table>
<thead>
<tr>
<th>Trials</th>
<th>Annual event rate (%)</th>
<th>ΔHbA₁c (%)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More intensive</td>
<td>Less intensive</td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>352 (2.11)</td>
<td>371 (2.29)</td>
<td>-1.01</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>557 (2.15)</td>
<td>590 (2.28)</td>
<td>-0.72</td>
</tr>
<tr>
<td>UKPDS</td>
<td>169 (1.30)</td>
<td>87 (1.60)</td>
<td>-0.66</td>
</tr>
<tr>
<td>VADT</td>
<td>116 (2.68)</td>
<td>128 (2.98)</td>
<td>-1.16</td>
</tr>
<tr>
<td>Overall</td>
<td>1194</td>
<td>1176</td>
<td>-0.88</td>
</tr>
</tbody>
</table>
Effects of More vs. Less Intensive Glycemic Control on MI

### Myocardial infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall Events</th>
<th>Overall Follow-up</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>198 (1.18)</td>
<td>245 (1.51)</td>
<td>-1.01</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>310 (1.18)</td>
<td>337 (1.28)</td>
<td>-0.72</td>
</tr>
<tr>
<td>UKPDS</td>
<td>150 (1.20)</td>
<td>76 (1.40)</td>
<td>-0.66</td>
</tr>
<tr>
<td>VADT</td>
<td>72 (1.65)</td>
<td>87 (1.99)</td>
<td>-1.16</td>
</tr>
</tbody>
</table>

| Overall | 730            | 745               | **0.85 (0.76 – 0.94)** |

(Q = 2.25, p = 0.52, I² = 0.0%)

HbA$_1$c
ACCORD
Total Mortality

5% v 4%, ↑
1.422% 1.1 %/year

p=0.04

NEJM 2008 vol. 358 (24) pp. 2545-59
MI, CVA & CV death

p=ns

NEJM 2008 vol. 358 (24) pp. 2545–59
## ACCORD

### Figure 3. Hazard Ratios for the Primary Outcome and Death from Any Cause in Prespecified Subgroups.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10,251</td>
<td>460</td>
<td></td>
</tr>
<tr>
<td>Previous cardiovascular event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6,643</td>
<td>220</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3,608</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3,952</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6,299</td>
<td>328</td>
<td></td>
</tr>
<tr>
<td>Age at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>6,779</td>
<td>212</td>
<td></td>
</tr>
<tr>
<td>≥65 yr</td>
<td>3,472</td>
<td>248</td>
<td></td>
</tr>
<tr>
<td>Glycated hemoglobin at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤8.0%</td>
<td>4,868</td>
<td>204</td>
<td></td>
</tr>
<tr>
<td>&gt;8.0%</td>
<td>5,360</td>
<td>256</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td>3,647</td>
<td>131</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>6,604</td>
<td>329</td>
<td></td>
</tr>
</tbody>
</table>

NEJM, June 2008
Which are true?

A. Diabetes is bad for the cardiovascular system

B. Good glycemic control is good for the CVS

C. Tight glycemic control by any means is good for the CVS

D. A and B

E. A and B and C
VA–DT

- No reduction in CV events
  - 25.9 v 29.3% [HR=0.87, p=0.12]
- Predictors of mortality
  - prev CHD [HR 3.6]
  - recent hypoglycemia [HR 2.06]

presented at ADA, Chicago. June 2008
Mechanisms for Hypoglycemia causing CV Events

- Neutrophil activation
- Platelet activation
- Factor VII

Blood coagulation abnormalities

Inflammation
- CRP
- VEGF
- IL-6

Endothelial dysfunction
- Vasodilation

Sympathoadrenal response

Rhythm abnormalities
- Heart rate variability

Hemodynamic changes
- Adrenaline
- Oxygen consumption
- Contractility
- Heart workload

PROACTIVE: Pioglitazone in High CVD Risk

5128 T2 DM patients
With macrovascular disease
Pioglitazone 15-45mg or placebo
With usual medications

Heart failure admissions 6 vs 4%
P=0.007  NNH 50

Primary endpoint
(CVD, MI, CVA, Revascularisation)

Secondary endpoint
(CVD, MI, CVA)

Pro-ACTIVE
ORIGIN: No Harm or Benefit from Basal Insulin in Patients with Dysglycemia and High CVD Risk

12,537 subjects with high CV risk
T2 diabetes (on 1 or 2 oral agents) or Dysglycemia (IFG or IGT)
Basal insulin glargine
(titrated to FBG ≤5.3 mmol/l or Standard glycemic control)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First coprimary outcome (CV Death, MI, CVA)</td>
<td>1.02</td>
<td>0.94-1.11</td>
<td>.63</td>
</tr>
<tr>
<td>Second coprimary outcome (CV Death, MI, CVA, Revascularisation, Heart failure)</td>
<td>1.04</td>
<td>0.97-1.11</td>
<td>.27</td>
</tr>
<tr>
<td>Total mortality</td>
<td>0.98</td>
<td>0.90-1.08</td>
<td>.70</td>
</tr>
</tbody>
</table>

SU Monotherapy in T2D on Mortality
(Cochrane Database Review of 72 RCTS)

First generation SU vs placebo
2 trials; 553 participants; high risk of bias (HRB)

First generation SU vs insulin
2 trials; 1944 participants; HRB

Second-generation sulphonylureas (SGS) vs metformin
6 trials; 3528 participants; HRB

SGS vs TZDs
7 trials; 4955 participants; HRB

SGS vs Insulin
4 trials; 1642 participants; HRB

SGS vs meglitinides
7 trials; 2038 participants; HRB

SGS vs incretin-based therapies
2 trials; 1503 participants; HRB

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>RR</th>
<th>CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First generation SU vs placebo</td>
<td>1.46</td>
<td>0.87-2.45</td>
<td>0.15</td>
</tr>
<tr>
<td>First generation SU vs insulin</td>
<td>1.18</td>
<td>0.88-1.59</td>
<td>0.26</td>
</tr>
<tr>
<td>Second-generation sulphonylureas (SGS) vs metformin</td>
<td>0.98</td>
<td>0.61-1.58</td>
<td>0.68</td>
</tr>
<tr>
<td>SGS vs TZDs</td>
<td>0.92</td>
<td>0.60-1.41</td>
<td>0.70</td>
</tr>
<tr>
<td>SGS vs Insulin</td>
<td>0.96</td>
<td>0.79-1.18</td>
<td>0.72</td>
</tr>
<tr>
<td>SGS vs meglitinides</td>
<td>1.44</td>
<td>0.47-4.42</td>
<td>0.52</td>
</tr>
<tr>
<td>SGS vs incretin-based therapies</td>
<td>1.39</td>
<td>0.52-3.68</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Hemmingsen B et al. Cochrane Database of Systematic Reviews 2013 Apr 30;4
Certain Sulfonylureas May Increase Mortality

Denmark n=107,806 monotherapy with sulphonylureas or metformin

Schramm TK et al. Eur Heart J 2011; 32:1900-1908
RCT Metformin v Glipizide in T2DM with CAD

Hong et al Diabetes Care 2013

p=0.026

Glipizide (n=148)
Metformin (n=156)

Primary End Point

Death
MI
Stroke
Revasc
ADVANCE

No reduction in Macrovascular Disease
No increase in Mortality

NEJM, June 2008
VA–DT

- Post-hoc analysis
  - Intensive helpful in short duration but harmful in longer diabetes duration
- Sub-group analysis
  - intensive control beneficial in those with low coronary artery calcification score but harmful in those with high CAC score

presented at ADA, Chicago. June 2008
Consider

• Observation: rain and salt are important causes of corrosion on motor vehicles

• Hypothesis: regular car wash and application of wax will prevent corrosion on motor vehicles

True or False?
For which car will regular hand wash and waxing be most effective?

A

B
Summary

- Hyperglycemia is an important CV risk factor
- Recent “negative” trials (ACCORD, ADVANCE, VA-DT)
  - event rates very low
  - long DM duration
  - short follow-up
- to Prevent CVD by improved glycemic control ...
  - start early
  - a long term investment