Update on Cardiovascular Outcome Trials in Diabetes

Rury R. Holman, FMedSci
NIHR Senior Investigator
11th February 2013
Analyses based on 530,083 participants from 102 prospective studies. HRs adjusted for age, smoking status, body-mass index and systolic blood pressure, and, where appropriate, stratified by sex and trial arm.

## Impact of Glycaemic Lowering

### ACCORD, ADVANCE, UKPDS & VADT meta-analysis of fatal and non-fatal myocardial infarction

<table>
<thead>
<tr>
<th>Trials</th>
<th>Number of events (annual event rate, %)</th>
<th>$\Delta$HbA$_{1c}$ (%)</th>
<th>Favours more intensive</th>
<th>Favours less intensive</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More intensive</td>
<td>Less intensive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>198 (1.18)</td>
<td>245 (1.51)</td>
<td>−1.01</td>
<td></td>
<td>0.77 (0.64–0.93)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>310 (1.18)</td>
<td>337 (1.28)</td>
<td>−0.72</td>
<td></td>
<td>0.92 (0.79–1.07)</td>
</tr>
<tr>
<td>* UKPDS</td>
<td>150 (1.20)</td>
<td>76 (1.40)</td>
<td>−0.66</td>
<td></td>
<td>0.81 (0.62–1.07)</td>
</tr>
<tr>
<td>VADT</td>
<td>72 (1.65)</td>
<td>87 (1.99)</td>
<td>−1.16</td>
<td></td>
<td>0.83 (0.61–1.13)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>730</td>
<td>745</td>
<td>−0.88</td>
<td></td>
<td>0.85 (0.76–0.94)</td>
</tr>
</tbody>
</table>

* Only first five years of UKPDS data included

* CONTROL Group. Diabetologia 2009;52:2288-2298
<table>
<thead>
<tr>
<th>TRIAL</th>
<th>YEAR</th>
<th>DRUG</th>
<th>ISSUE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGDP</td>
<td>1969</td>
<td>Tolbutamide</td>
<td>MI</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>UGDP</td>
<td>1971</td>
<td>Phenformin</td>
<td>MI</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lilly</td>
<td>1988</td>
<td>Proinsulin</td>
<td>MI</td>
<td>n.s.</td>
</tr>
<tr>
<td>VA Study</td>
<td>1994</td>
<td>Intensive insulin</td>
<td>MI</td>
<td>n.s.</td>
</tr>
<tr>
<td>DPP</td>
<td>2000</td>
<td>Troglitazone</td>
<td>Liver</td>
<td>n.s.</td>
</tr>
<tr>
<td>Meta analysis</td>
<td>2005</td>
<td>Muriglitazar†</td>
<td>CVD</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>ADOPT</td>
<td>2006</td>
<td>Rosiglitazone</td>
<td>Fractures</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Meta analysis</td>
<td>2007</td>
<td>Rosiglitazone*</td>
<td>CVD</td>
<td>&lt;0.043</td>
</tr>
<tr>
<td>ACCORD</td>
<td>2008</td>
<td>Intensive glucose control</td>
<td>Death</td>
<td>&lt;0.04</td>
</tr>
</tbody>
</table>

† Nissen & Wolski, JAMA 2005;294:2581–6
* Nissen & Wolski, NEJM 2007;356:2457-7
Before approval, a randomized cardiovascular event driven trial is required to rule out an unacceptable harm.
<table>
<thead>
<tr>
<th>Pre 2000 (5)</th>
<th>2009 to date (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT</td>
<td>ORIGIN</td>
</tr>
<tr>
<td>Kumamoto</td>
<td>ACE</td>
</tr>
<tr>
<td>UGDP</td>
<td>ALECARDIO</td>
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<tr>
<td>UKPDS</td>
<td>CANVAS</td>
</tr>
<tr>
<td></td>
<td>CAROLINA</td>
</tr>
<tr>
<td>2000-2008 (8)</td>
<td>ELIXA</td>
</tr>
<tr>
<td>ACCORD</td>
<td>EXAMINE</td>
</tr>
<tr>
<td>Advance</td>
<td>EXSCEL</td>
</tr>
<tr>
<td>Bari 2D</td>
<td>GLINT</td>
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<tr>
<td>Heart 2D</td>
<td>LEADER</td>
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<tr>
<td>NAVIGATOR</td>
<td>LOOK AHEAD</td>
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<tr>
<td>ProACTIVE</td>
<td>REWIND</td>
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<tr>
<td>RECORD</td>
<td>SAVOR-TIMI53</td>
</tr>
<tr>
<td>VADT</td>
<td>TECOS</td>
</tr>
<tr>
<td></td>
<td>TIDE</td>
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</tbody>
</table>
CV Outcome Trials in T2DM
Alphaglucosidase Inhibitors

• Accumulating evidence suggests there is a close association between “prediabetes” and cardiovascular disease

• Post prandial hyperglycaemia may explain the excess risk seen in diabetes and “prediabetes”

• Alphaglucosidase inhibitors delay breakdown of polysaccharides to monosaccharides, delaying their absorption to lower in the bowel and enhancing GLP-1 secretion
STOP-NIDDM – 2° CV Outcome

Acarbose 100 mg TID

Any Cardiovascular Event

HR 0.51, 95% CI 0.28, 0.95

P = 0.03 (15 vs. 32 events)

49% RRR

Chiasson et al. JAMA 2003;290:486-94.
NAVIGATOR Cardiovascular Outcomes

Placebo 707 events (15.2%)
Nateglinide 658 events (14.2%)
7% RRR

Nateglinide 60 mg TID

Placebo 387 events (8.3%)
Nateglinide 365 events (7.9%)
6% RRR

Secondary CVD prevention trial in 7,500 patients with CVD & IGT
150 hospitals in PRC and HK
ISRCTN number: 91899513
www.ace-study.org

Chair: Rury Holman, University of Oxford, UK
Co-Chairs: Hu Dayi, University of Peking People’s Hospital, Beijing, China
Pan Changyu, Chinese PLA General Hospital, Beijing, China
Sponsor: University of Oxford
Funding: Bayer HealthCare
ACE Trial Design

- Secondary prevention trial in 7,500 Chinese patients with cardiovascular disease and impaired glucose tolerance
- Conducted in 150 Hospitals in the People’s Republic of China and Hong Kong
- Evaluating the double-blind addition of acarbose (50 mg) or matching placebo three times a day to fully optimised usual cardiovascular disease care
- Primary endpoint is the time to the first occurrence of:
  - Cardiovascular death
  - Non-fatal myocardial infarction
  - Non-fatal stroke
- Academically led, analysed and reported with an independent Data Safety Monitoring Board
- Results expected 2018

CV Outcome Trials in T2DM

*DPP-4 Inhibitors*

• Improve glycaemic control by inhibiting the metabolism and inactivation of the incretin hormones GLP-1 and GIP
DPP-4 inhibitors – A CVD Meta-analysis

18 RCTs. 4,998 randomized to DPP-4 inhibitors and 3,546 to a comparator. Median duration of therapy 46.4 weeks

RR of any CV event 0.48 (0.31 to 0.75, p=0.001)

RR for nonfatal myocardial infarction or acute coronary syndrome 0.40 (0.18 to 0.88, p=0.02)
## CV Outcome Trials in T2DM

### DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Inclusion criteria</th>
<th>Primary endpoint</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXAMINE</td>
<td>Placebo</td>
<td>T2DM HbA1c 6.5 – 11.0% ≥ 18 years ACS</td>
<td>CV death, MI, stroke</td>
<td>5400</td>
</tr>
<tr>
<td></td>
<td>Alogliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TECOS</td>
<td>Placebo</td>
<td>T2DM HbA1c 6.5 – 8.0% ≥ 50 years CVD</td>
<td>CV death, MI, stroke or UA</td>
<td>14500</td>
</tr>
<tr>
<td></td>
<td>Sitagliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVOR (TIMI-53)</td>
<td>Placebo</td>
<td>T2DM HbA1c ≥ 6.5% ≥ 40 years CVD/CV risk factors</td>
<td>CV death, MI, stroke</td>
<td>16500</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAROLINA</td>
<td>Glimepiride</td>
<td>T2DM HbA1c 6.5-8.5% 40-85 years CVD/CV risk factors/diabetes end organ damage</td>
<td>CV death, MI, stroke or UA</td>
<td>6000</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CVD outcome trial in 14,500 patients with CVD and T2DM
>600 sites in 40 countries
ClinTrials.gov: NCT00790205
www.tecos-study.org

Joint-Chairs: Rury Holman, University of Oxford, UK
Rob Califf, Duke Clinical Research Institute, North Carolina, US

Sponsor: Merck
Funding: Merck
TECOS Trial

- Multinational, randomised, placebo-controlled, double-blind, pragmatic, secondary cardiovascular prevention trial in patients with pre-existing cardiovascular disease and type 2 diabetes under conditions of glycaemic equipoise
- Sitagliptin (100 mg) or matching placebo once daily, given in addition to usual care
- Academic led, analysed and reported
- Event driven (1300 adjudicated primary events)
- Primary Endpoint is the time to the first occurrence of:
  - Cardiovascular death
  - Nonfatal myocardial infarction or nonfatal stroke
  - Hospitalization for unstable angina
- Results expected 2015
CV Outcome Trials in T2DM
*GLP-1 Receptor Agonists*

Shown in randomized clinical trials to:

- Augment endogenous insulin secretion and reduce glucagon secretion in a glucose dependent manner
- Slow gastric emptying
- Improve glycaemic control
- Reduce blood pressure
- Promote weight loss
39,275 T2DM patients treated with exenatide twice daily versus 381,218 patients were treated with other glucose-lowering therapies.

Error bars represent 95% CIs. Propensity Score-Stratified = propensity score, stratified by decile

Best JH et al. Diabetes Care January 2011 34:90-95
## CV Outcome Trials in T2DM
### GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Inclusion criteria</th>
<th>Primary endpoint</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA</td>
<td>Placebo Lixisenatide</td>
<td>T2DM HbA1c 6.0% - 10.0% ACS</td>
<td>CV death, MI, stroke or UA</td>
<td>6000</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>Placebo Exenatide</td>
<td>T2DM HbA1c 7.0% - 10.0% CVD in 60%</td>
<td>CV death, MI or stroke</td>
<td>9500</td>
</tr>
<tr>
<td>LEADER</td>
<td>Placebo Liraglutide</td>
<td>T2DM HbA1c ≥ 7.0% ≥50 years + CVD ≥60 years + CV risk factors</td>
<td>CV death, MI or stroke</td>
<td>8754</td>
</tr>
<tr>
<td>REWIND</td>
<td>Placebo Dulaglutide</td>
<td>T2DM, HbA1c &lt; 9.5% ≥50 yrs + CVD ≥55 yrs + subclinical CV ≥60 yrs + ≥2 CV risk factors</td>
<td>CV death, MI or stroke</td>
<td>9600</td>
</tr>
</tbody>
</table>
CVD outcome trial in 9,500 pts with/without CVD and T2DM
>500 sites in 36 countries
ClinTrials.gov: NCT01144338
www.exscel-study.org

Joint-Chairs: Rury Holman, University of Oxford, UK
Rob Califf, Duke Clinical Research Institute, North Carolina, US

Sponsor: Amylin
Funding: Amylin

...in an academic collaboration with
Exenatide Once Weekly (Bydureon)

Biodegradable polymeric microspheres for extended release

Exenatide once weekly received EMA and FDA approval in June 2011 and January 2012, respectively
EXSCEL Trial

- Exenatide QW (2 mg) or matching placebo once weekly, given in addition to usual care

- Primary Endpoint
  - time to the first occurrence of:
    - Cardiovascular death
    - Nonfatal myocardial infarction
    - Nonfatal stroke

- Event driven
  - requires 1591 confirmed primary endpoint events
  - 90% power to detect a 15% relative risk decrease

- Results expected 2018
## CV Outcome Trials in T2DM

**SGLT2 Inhibitors**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Inclusion criteria</th>
<th>Primary endpoint</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS</td>
<td>Placebo</td>
<td>T2DM, HbA$_{1c}$ 7.0-10.0%</td>
<td>CV death, MI or stroke</td>
<td>6-7000</td>
</tr>
<tr>
<td></td>
<td>Canagliflozin</td>
<td>High CV risk, ≥30 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## CV Outcome Trials in T2DM

**Dual PPAR Agonists**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Inclusion criteria</th>
<th>Primary endpoint</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALECARDIO</td>
<td>Placebo</td>
<td>T2DM and hospitalization for acute coronary syndrome within the previous 2–6 weeks</td>
<td>CV death, MI or stroke</td>
<td>6-7000</td>
</tr>
<tr>
<td>ALECARDIO</td>
<td>Aleglitazar</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Look AHEAD: Study Design
Action for HEA1th in Diabetes

- Investigation of long-term health effects of intentional weight loss with lifestyle modification
- > 5000 overweight or obese adults with type 2 diabetes; up to 11.5 years of followup
- Standard medical care vs standard medical care with intensive lifestyle intervention for 4 years
  - Goal of lifestyle intervention
    - Weight reduction of ≥7% in the first year
    - Maintain ≥175 minutes per week of moderate intensity physical activity at the end of 6 months
- Outcome measures: time to first occurrence of
  - Primary – CV death, nonfatal myocardial infarction, or nonfatal stroke
  - Secondary – all-cause mortality, coronary artery bypass grafting and/or percutaneous coronary angioplasty, hospitalization for CHF, carotid endarterectomy, or peripheral vascular procedures

Weight loss does not lower heart disease risk from type 2 diabetes

*Intervention stopped early in NIH-funded study of weight loss in overweight and obese adults with type 2 diabetes after finding no harm, but no cardiovascular benefits*
CV Outcome Trials in T2DM

*Metformin*

Shown in UKPDS to:

- Reduce risk of MI by 39%, p=0.010
- Reduce risk of death by 36%, p=0.011

With a legacy effect 10 years later of:

- Reduced risk of MI by 33%, p=0.005
- Reduced risk of death by 27%, p=0.002
Glucose Lowering In Non-diabetic hyperglycaemia Trial

Rury Holman (Joint-Chair)
Nick Wareham (Joint-Chair)

Angie Bethel (Joint Clinical Lead)
Simon Griffin (Joint Clinical Lead)

Sponsor: University of Cambridge
Funding: NIHR Health Technology Assessment Programme

- Primary CVD prevention
- 11,834 patients with non-diabetic hyperglycaemia & without CVD
- UK Multicentre Trial
GLINT Trial

- Men and women aged ≥40 years with a 10-year CVD risk ≥20%, with an HbA1c ≥5.5% and <6.5%, and no prior history of diabetes / CVD in general practices in England

- Metformin SR (500 mg) or matching placebo TID

- Primary Endpoint
  - Cardiovascular death
  - Nonfatal myocardial infarction
  - Nonfatal stroke

- Secondary endpoints include cancer

- Pilot phase 2013-2015

- Main trial 2015-17 with follow-up to 2022

- Results expected 2023
But we need ‘Smart’ Trials

- Trials are moving into a new era
- We should be testing multiple interventions in factorial or head to head designs to be more efficient and more informative
- When testing drugs within the same class, data from similar trials should be utilised to inform design and sample size requirements
- Trials will likely still be powered on the time to the first primary endpoint but subsequent events also need to be evaluated to capture the full impact of treatments, for both benefits and risks