Contribution to clinicians of the last revision of the UKPDS study

Prof. David R. Matthews

Salamanca 29th January 2010. IV congress on Diabetes and obesity

The Oxford Centre for Diabetes, Endocrinology and Metabolism
• Title: Contribution to clinicians of the last revision of the UKPDS study Given where: Salamanca, Spain
• Based on: Florence, Teneriffe
• Keywords: Glycaemia, trials, Advance, Record, Adopt, UKPDS, Proactive

• Date: 29/01/2010
• Occasion: IV congress on Diabetes and Obesity
• Sponsor:
• Contact: academic
• Feedback:
• Duration: 45mins
• Timing:
• Notes:
• Discussion:
• Thoughts:
• Revisions necessary
Risks of complications in type 2 diabetes

- Glycaemia *
- Hypertension *
- Dyslipidaemia
- Smoking
- Obesity

- Age
- Sex
- Race
- Genes (within race)
- Competing risks
The problem

• We utilise glucose as our main metabolic fuel
• Glucose can be stored and mobilised in seconds
• A fit person can run on glucose energy for about 15 miles

BUT
Glucose is very osmotically active
Even 8 mmol/l will damage vessels
If we could survive with glucose at just 12 mmol/l most diabetes would be irrelevant
How do we know that high glucose is dangerous?

- Rats and mice run a higher blood glucose than man – typically 8mmol/l
  - Evolutionary pressure is not about 70-year survival but 3 year survival
  - Fuel more important than glucose risk
- *In man we have trial evidence of the risk*
Trials relating to glycaemia and outcomes

- UGDP
- UKPDS
- PROactive
- (ADOPT)
- (Nissen et al meta-analysis)
- RECORD
- ACCORD
- ADVANCE
- UKDPS PTM
- VADT
Glycaemic outcome trials

- UGDP
- UKPDS
- ADVANCE
- ACCORD
- VADT
- RECORD
- PROACTIVE
Glycaemic outcome trials

Each of these trials was controversial in some respects

- UGDP
- UKPDS
- ADVANCE
- Accord
- VADT
- RECORD
- ProActive

The Oxford Centre
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Randomised controlled trials

- Define the population
- How long?
- Is it safe?
- Treatment A vs. Treatment B
- What difference is going to be measured?
- How many? = power
- What complexity?
Problems in trials

Define the population

How long?

Is it safe?

What difference is going to be measured?

Treatment A

Treatment B

What complexity?

How many? = power

UGDP

VADT

ADVANCE

ACCORD

ProActive

RECORD

UKPDS

UGDP
UGDP – perhaps tolbutamide was dangerous?

More people died in the tolbutamide group

UGDP

Define the population

there were 30% more baseline ECG abnormalities in the tolbutamide group

there was 40% more angina in the tolbutamide group

Tolbutamide group

More deaths

Comparator groups

Randomise
UKPDS

• Primary intervention randomised controlled outcome trial
• Used sulphonylureas
  — mainly glibenclamide and chlorpropamidine
  — small number of patients used gliclazide and acarbose (not formally part of the trial)
• Used metformin in the overweight (120% Ideal body weight)
• Used insulin as primary intervention
• Recruited patients with fasting glucose greater than 6mmol/l
UKPDS assessment design (end-point counting)

Randomised trial

Numbers in the study

Deaths

1997: end

1998: publish

†

20 years

5012
UKPDS design

Randomised trial

Post-study monitoring (non-randomised)

5012

Deaths

1997: end
1998: publish

50% mortality
~30 years

20 years

Numbers in the study
Mortality in the UKPDS (1997)

- Cardiac: 41%
- Cancer: 25%
- Stroke: 9%
- Unknown: 2%
- Sudden: 6%
- Other: 15%
- Accident: 2%
- Other: 15%

End of the trial (1997): 1/7 of all the patients had died (20y)
By 2000: 1/4 of all the patients had died
End of Post Study Monitoring: 1/2 of all the patients had died (30y)
HbA<sub>1c</sub>

cohort, median data

Years from randomisation

HbA1c

%
UKPDS: Any Diabetes Related endpoints

...but myocardial infarction reduction in the main trial was not significantly (p=0.052) reduced

Glucose control trial

Blood pressure control trial
Epidemiology vs trial

- Trials randomise patients and examine the outcome on the basis of the randomised intervention.
- Epidemiological analyses examine a surrogate marker within the trial (e.g. the glucose or the blood pressure) and examine the outcome based on what was achieved rather than what was administered.
Microvascular disease

37% decrease per 1% decrement in HbA1c

p<0.0001
Myocardial infarction

14% decrease per 1% decrement in HbA1c

p<0.0001
Diabetes related deaths

21% decrease per 1% decrement in HbA1c

p<0.0001

updated mean HbA1c

hazard ratio
Any Diabetes Related endpoints

- HbA₁c (%)
  - >8
  - 7-8
  - 6-7
  - <6
  - <130
  - 130-140
  - 140-150
  - >150

- Systolic blood pressure
  - <130
  - 130-140
  - 140-150
  - >150

Hazard ratio

- 0
- 1
- 2
- 3
- 4
- 5
Microvascular endpoints

HbA$_1^c$ (%)

7-8
6-7
<6
<13
130-140
140-150
>15

systolic blood pressure

hazard ratio

<8
7-8
6-7
<6
<13
130-150
>15

0
5
10
15
20
25

The Oxford Centre
for Diabetes, Endocrinology and Metabolism
PROactive
PROactive

- Pioglitazone
- Secondary prevention in type 2 diabetes and macrovascular disease
- \(N=5238\)  Duration 34.5 months
- Primary outcome: composite of all-cause mortality, non-fatal MI (including silent MI), non-fatal stroke, major leg amputation, ACS, cardiac intervention (bypass graft or percutaneous coronary intervention), and leg revascularization
Proactive composite outcome

Primary composite event rate

Placebo 572 events

Pio 514 events

P=0.095

ProActive

What difference is going to be measured?

Pioglitazone

Comparator
Pioglitazone meta-analyses

Rosiglitazone Meta-analysis

42 trials
study duration of more than 24 weeks
mean age 56 years; baseline HbA1c 8.2%

odds ratios:

1.43 (95% CI, 1.03 to 1.98; P=0.03)
1.64 (95% CI, 0.98 to 2.74; P=0.06).

comparisons were randomized control groups not receiving rosiglitazone

EDIC
(DCCT post trial monitoring)
Distribution of HbA1c Concentration by Randomized Treatment Group at the End of the DCCT and in Each Year of the EDIC Study

JAMA 2003;290:2159-2167.
Prevalence and Cumulative Incidence of Microalbuminuria
RECORD
An outcome trial of Rosiglitazone: interim results

- The interim results for the primary end point were inconclusive
- A hazard ratio of 1.08 (95% CI, 0.89 to 1.31) on the basis of events adjudicated by the committee reviewing clinical end points.
- In any interim trial report, there are inevitably some potential primary events pending adjudication. Adding in these pending events increased the hazard ratio to 1.11 (95% CI, 0.93 to 1.32).
Figure 2: Kaplan-Meier plots of time to the primary endpoint (cardiovascular death or cardiovascular hospitalisation)
HR=hazard ratio.
RECORD

How long?

Rosiglitazone

Is it safe?

What difference is going to be measured?

Comparator

How many? = power
ACCORD (Action to Control Cardiovascular Risk in Diabetes) Design

to determine whether intensively lowering blood sugar would reduce the risk of cardiovascular events such as heart attack, stroke, or death from cardiovascular disease, specifically in people with type 2 diabetes who are at particularly high risk for a cardiovascular event
Accord Study design

• 77 sites USA and Canada,
• includes adults
• ages of 40 – 82y at enrolment
• type 2 diabetes,
• PLUS:
  - two or more other risk factors for heart disease
  - or had been diagnosed with heart disease before entering the study.
Enrolment

• average diabetes duration of 10 years at enrolment,
• randomly assigned to either standard (n=5,123 participants) or intensive (n=5,128) blood sugar treatment goals.
• also enrolled in one of two other ACCORD randomized clinical trials examining effects of treatments for blood pressure or blood lipids.
**ACCORD: Patient Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive Therapy (N=5128)</th>
<th>Standard Therapy (N=5123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62.2±6.8</td>
<td>62.2±6.8</td>
</tr>
<tr>
<td>Median duration of diabetes (yr)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Previous cardiovascular event (%)</td>
<td>35.6</td>
<td>34.8</td>
</tr>
<tr>
<td>Previous congestive heart failure (%)</td>
<td>4.9</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*Table 1. Characteristics of the Patients at Baseline.*
Glucose control in ACCORD

Treatments in intensive control group

- Insulin 77%
- TZD 92%
- SU 78%
- Metformin 95%

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Standard therapy</th>
<th>Intensive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5109</td>
<td>5119</td>
</tr>
<tr>
<td>1 year</td>
<td>4774</td>
<td>4768</td>
</tr>
<tr>
<td>2 years</td>
<td>4588</td>
<td>4585</td>
</tr>
<tr>
<td>3 years</td>
<td>3186</td>
<td>3165</td>
</tr>
<tr>
<td>4 years</td>
<td>1744</td>
<td>1706</td>
</tr>
<tr>
<td>5 years</td>
<td>455</td>
<td>476</td>
</tr>
<tr>
<td>6 years</td>
<td>436</td>
<td>471</td>
</tr>
</tbody>
</table>

UKPDS and ACCORD

cohort, median data

HbA1c

Years from randomisation

0 2 4 6 8 10
ACCORD
Primary outcome

The first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes.

The latter included death from myocardial infarction, heart failure, arrhythmia, invasive cardiovascular interventions, cardiovascular causes after noncardiovascular surgery, stroke, unexpected death presumed to be from ischaemic cardiovascular disease occurring within 24 hours after the onset of symptoms, and death from other vascular diseases.
A Primary Outcome

ACCORD

No. at Risk

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No. at Risk</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive therapy</td>
<td>5128</td>
<td>4843</td>
<td>4390</td>
<td>2839</td>
<td>1337</td>
<td>475</td>
<td>448</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>5123</td>
<td>4827</td>
<td>4262</td>
<td>2702</td>
<td>1186</td>
<td>440</td>
<td>395</td>
<td></td>
</tr>
</tbody>
</table>
Discontinued 2008 on advice from Data Monitoring and Ethics Group

54 excess deaths in the intensive group

257 deaths

203 deaths

Figure 2. Kaplan–Meier Curves for the Primary Outcome and Death from Any Cause.
Risk profile high

Participants were included in the ACCORD trial because they were at especially high risk—more risk than is associated with diabetes alone—for having a heart attack, stroke, or of dying from cardiovascular disease.
HbA1c

- intensive treatment group participants achieved, on average, A1C values lower than standard treatment group participants.
- half of the participants in the intensive treatment group achieved an A1C of less than 6.4 percent.
- half of the participants in the standard treatment group achieved an A1C of less than 7.5 percent.
- The average blood sugar levels for both groups were lower than when they entered the study.
### ACCORD Primary Outcome

#### A. Primary Outcome

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10,251</td>
<td>723</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous cardiovascular event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6,643</td>
<td>330</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Yes</td>
<td>3,608</td>
<td>393</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>Female</td>
<td>3,952</td>
<td>212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6,299</td>
<td>511</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>6,779</td>
<td>383</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 yr</td>
<td>3,472</td>
<td>340</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycated hemoglobin at baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>≤8.0%</td>
<td>4,868</td>
<td>284</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;8.0%</td>
<td>5,360</td>
<td>438</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>3,647</td>
<td>222</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>6,604</td>
<td>501</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- **Intensive Therapy Better:** Data point is to the left of the dotted line, indicating a lower risk with intensive therapy.
- **Standard Therapy Better:** Data point is to the right of the dotted line, indicating a lower risk with standard therapy.
**ACCORD death from any cause**

### Death from Any Cause

<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>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>6,779</td>
<td>212</td>
<td></td>
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<td>248</td>
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</tr>
<tr>
<td>Glycated hemoglobin at baseline</td>
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<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>

Circle highlighting:
- Younger
- Higher
- A1c
Table 3. Adverse Events, Clinical Measures, Tobacco Use, and Use of Nonglycemic Medication after Randomization.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive Therapy (N=5128)</th>
<th>Standard Therapy (N=5123)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Requiring medical assistance</td>
<td>538 (10.5)</td>
<td>179 (3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Requiring any assistance</td>
<td>830 (16.2)</td>
<td>261 (5.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
The problem

• enrolled 10,251 participants.
• Of these, 257 in the intensive treatment group died, compared with 203 within the standard treatment group.
• This is a difference of 54 deaths, or 3 per 1,000 participants each year, over an average of almost four years of treatment.
• Participants had been followed for 2 years to 7 years at the time the intensive blood sugar control treatment was stopped.
• The death rates in both groups were lower than seen in similar populations in other studies.

(14 deaths per 1000 patients per year versus 11 per 1000 patients per year in the standard treatment program; a difference of 0.3 deaths per 100 patients per year).
ACCORD

Define the population

Is it safe?

Aggressive

Non-aggressive
ADVANCE
ADVANCE Inclusion criteria

- Type 2 diabetes mellitus
- Age 55 years or older
- Additional risk of vascular event
  - Age $\geq 65$ years
  - History of major macrovascular disease
  - History of major microvascular disease
  - First diagnosis of diabetes $>10$ years prior to entry
  - Other major risk factor
- Any level of blood pressure
- Any level of glucose control but no definite indication for long-term insulin
## ADVANCE: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Randomised treatment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active (n=5569)</td>
<td>Placebo (n=5571)</td>
<td></td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>66 (6)</td>
<td>66 (7)</td>
<td>8 Years</td>
</tr>
<tr>
<td>Age when diabetes first diagnosed (years), mean (SD)</td>
<td>58 (9)</td>
<td>58 (9)</td>
<td></td>
</tr>
<tr>
<td>Previous vascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of major macrovascular disease, n (%)</td>
<td>1798 (32%)</td>
<td>1792 (32%)</td>
<td></td>
</tr>
<tr>
<td>History of myocardial infarction, n (%)</td>
<td>678 (12%)</td>
<td>656 (12%)</td>
<td></td>
</tr>
<tr>
<td>History of stroke, n (%)</td>
<td>502 (9%)</td>
<td>520 (9%)</td>
<td></td>
</tr>
<tr>
<td>History of major microvascular disease, n (%)</td>
<td>568 (10%)</td>
<td>584 (10%)</td>
<td></td>
</tr>
<tr>
<td>History of macroalbuminuria†, n (%)</td>
<td>197 (4%)</td>
<td>204 (4%)</td>
<td></td>
</tr>
<tr>
<td>History of microvascular eye disease‡, n (%)</td>
<td>389 (7%)</td>
<td>404 (7%)</td>
<td></td>
</tr>
<tr>
<td>Blood pressure control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg), mean (SD)</td>
<td>145 (22)</td>
<td>145 (21)</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg), mean (SD)</td>
<td>81 (11)</td>
<td>81 (11)</td>
<td></td>
</tr>
<tr>
<td>History of currently treated hypertension, n (%)</td>
<td>3802 (68%)</td>
<td>3853 (69%)</td>
<td></td>
</tr>
</tbody>
</table>
ADVANCE
Intensive glucose control strategy

- More frequent visits
- Emphasis on lifestyle management
- Drug titration at physician’s discretion based on HbA$_{1c}$ and FBG levels:
  - Maximize gliclazide MR dose
  - Add other oral agents
  - Add long-acting insulin
  - Use multiple insulin injection therapy
ADVANCE Hemoglobin $A_{1c}$

$\Delta$ 0.67% (95% CI 0.64 - 0.70); p<0.001

Mean HbA$_{1c}$ (%)

Follow-up (Months)

Mean HbA$_{1c}$ at final visit

7.3 %

6.5%
ADVANCE
Major macrovascular events

Relative risk reduction
6%: 95% CI: -6 to 16%
p=0.32
ADVANCE
Major microvascular events

Relative risk reduction 14%: 95% CI: 3 to 23%  
\( p = 0.015 \)
## ADVANCE

### Major microvascular events

<table>
<thead>
<tr>
<th>Number of patients with event</th>
<th>Intensive (n=5,571)</th>
<th>Standard (n=5,569)</th>
<th>Favors Intensive</th>
<th>Favors Standard</th>
<th>Relative risk reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microvascular</td>
<td>526</td>
<td>605</td>
<td></td>
<td></td>
<td>14% (3 to 23) †</td>
</tr>
<tr>
<td>New or worsening retinopathy</td>
<td>332</td>
<td>349</td>
<td></td>
<td></td>
<td>5% (-10 to 18)</td>
</tr>
<tr>
<td>New or worsening nephropathy</td>
<td>230</td>
<td>292</td>
<td></td>
<td></td>
<td>21% (7 to 34) ‡</td>
</tr>
</tbody>
</table>

†P=0.01
‡P=0.006
ADVANCE

How long?

Sulphonylurea

Comparators

What difference is going to be measured?
VADT
VADT

- 20 centres
- 1791 patients
- Major CVD events
- 97% male
- Duration 7.5 years
- median f-up 6 years
- Median 7% vs 8.4% HbA1c in groups
- No difference in cardiovascular outcome

Underpowered trial
At the end of a trial all subjects are treated with the best option.

Did being in Group A or B years ago make a difference to what is happening now?
UKPDS Post Trial Monitoring
UK Prospective Diabetes Study

20-year Interventional Trial from 1977 to 1997
- 5,102 patients with newly-diagnosed type 2 diabetes recruited between 1977 and 1991
- Median follow-up 10.0 years, range 6 to 20 years
- Results presented at the 1998 EASD Barcelona meeting

10-year Post-Trial Monitoring from 1997 to 2007
- Annual follow-up of the survivor cohort
- Clinic-based for first five years
- Questionnaire-based for last five years

Median overall follow-up 17.0 years, range 16 to 30 years
Post-Trial Monitoring: Aims

- To observe HbA$_{1c}$ levels after cessation of the intervention trial
- To observe glucose therapy regimens after cessation of the intervention trial
- To determine the longer-term impact of earlier improved glucose control on microvascular and on macrovascular outcomes
- To evaluate the health economic implications with a projected 50% mortality at ten years post trial
Glucose Interventional Trial

Dietary Run-in

- **744** Diet failure
  - FPG >15 mmol/l

- **5,102** Newly-diagnosed type 2 diabetes

- **149** Diet satisfactory
  - FPG <6 mmol/l

Mean age 54 years (IQR 48–60)

Randomisation 1977-1991

- **2,729** Intensive
  - with sulfonylurea/insulin

- **1,138** (411 overweight)
  - Conventional
  - with diet

- **342** (all overweight)
  - Intensive
  - with metformin

Trial end 1997

- Intensive
- Conventional
- Intensive

*UKPDS 8. Diabetologia 1991; 34: 877-89*
**Post-Trial Monitoring: Patients**

**1997**

<table>
<thead>
<tr>
<th># in survivor cohort</th>
<th>Clinical</th>
<th>Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2,118</strong> Sulfonylurea/Insulin</td>
<td>Clinic</td>
<td>Questionnaire</td>
</tr>
<tr>
<td><strong>880</strong> Conventional</td>
<td>Clinic</td>
<td>Questionnaire</td>
</tr>
<tr>
<td><strong>279</strong> Metformin</td>
<td>Clinic</td>
<td>Questionnaire</td>
</tr>
</tbody>
</table>

**2002**

<table>
<thead>
<tr>
<th># with final year data</th>
<th>Clinical</th>
<th>Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1,010</strong> Sulfonylurea/Insulin</td>
<td>Questionnaire</td>
<td></td>
</tr>
<tr>
<td><strong>379</strong> Conventional</td>
<td>Questionnaire</td>
<td></td>
</tr>
<tr>
<td><strong>136</strong> Metformin</td>
<td>Questionnaire</td>
<td></td>
</tr>
</tbody>
</table>

**2007**

<table>
<thead>
<tr>
<th># with final year data</th>
<th>Clinical</th>
<th>Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1,010</strong> Sulfonylurea/Insulin</td>
<td>Questionnaire</td>
<td></td>
</tr>
<tr>
<td><strong>379</strong> Conventional</td>
<td>Questionnaire</td>
<td></td>
</tr>
<tr>
<td><strong>136</strong> Metformin</td>
<td>Questionnaire</td>
<td></td>
</tr>
</tbody>
</table>

*Mean age 62±8 years*

**Mortality 44% (1,852)**

**Lost-to-follow-up 3.5% (146)**
Therapy for Glycaemia at 5 Years

Original randomisation

Proportion of patients

Conventional

Intensive

Diet alone
Oral monotherapy
Combined oral
Oral + insulin
Basal insulin
Basal + soluble

0%
20%
40%
60%
80%
100%

77%
Post-Trial Changes in HbA$_{1c}$

Sulfonylurea/Insulin vs. Conventional

UKPDS results presented

Mean (95%CI)

Glycated haemoglobin (%)

p=0.008

Any Diabetes-related Endpoint

A “legacy effect” of prior improved glucose control

RR=0.88 (0.79-0.99)
P=0.029
Any Diabetes Related Endpoint Hazard Ratio

Intensive (SU/Ins) vs. Conventional glucose control

Any diabetes related endpoint
HR = 0.88
p = 0.029

1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Hazard ratio

Number of events
Con: 438
Int: 963

HR (95% CI)
Microvascular Disease Hazard Ratio

(photocoagulation, vitreous haemorrhage, renal failure)

Intensive (SU/Ins) vs. Conventional glucose control

Microvascular disease
HR=0.75
p=0.0099

HR=0.76
p=0.001

Hazard ratio

Number of events
Con: 213 267 330 400 460 537
Int: 489 610 737 868 1028 1162

1997 1999 2001 2003 2005 2007

HR (95%CI)
Myocardial Infarction Hazard Ratio
(fatal or non-fatal myocardial infarction or sudden death)

Intensive (SU/Ins) vs. Conventional glucose control

<table>
<thead>
<tr>
<th>Year</th>
<th>Con: Events</th>
<th>Int: Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>186</td>
<td>387</td>
</tr>
<tr>
<td>1999</td>
<td>212</td>
<td>450</td>
</tr>
<tr>
<td>2001</td>
<td>239</td>
<td>513</td>
</tr>
<tr>
<td>2003</td>
<td>271</td>
<td>573</td>
</tr>
<tr>
<td>2005</td>
<td>296</td>
<td>636</td>
</tr>
<tr>
<td>2007</td>
<td>319</td>
<td>678</td>
</tr>
</tbody>
</table>

Myocardial infarction
HR = 0.84
p = 0.052

Conventional glucose control
HR = 0.85
p = 0.014

HR (95% CI)
Post-Trial Monitoring: Protocol

- At trial end, patients were returned to usual physician care for their diabetes management
- No attempt was made to maintain them in randomised groups, or to influence their therapy
- All endpoints were adjudicated in an identical manner by the same Adjudication Committee as during the trial

From 1997 to 2002:
- Patients were seen annually in UKPDS clinics for standardised collection of clinical and biochemical data

From 2002 to 2007:
- Clinical outcomes were ascertained remotely by questionnaires sent to patients and GPs
All-cause Mortality Hazard Ratio

Intensive (SU/Ins) vs. Conventional glucose control

All-cause mortality
HR = 0.94
p = 0.44

HR = 0.87
p = 0.006

Hazard ratio

Number of events
Con: 213 267 330 400 460 537
Int: 489 610 737 868 1028 1163

1997 1999 2001 2003 2005 2007

HR (95%CI)
Post-Trial Changes in HbA$_1c$

Metformin vs. Conventional

UKPDS results presented

Mean (95%CI)
Any Diabetes Related Endpoint Hazard Ratio

Intensive (metformin) vs. Conventional glucose control

Any diabetes related endpoint
HR = 0.68
p = 0.0023

HR = 0.79
p = 0.012

Hazard ratio

Number of events
Con: 160 190 220 240 252 262
Met: 98 126 152 175 189 209

1997 1999 2001 2003 2005 2007
Microvascular Disease Hazard Ratio

*(photocoagulation, vitreous haemorrhage, renal failure)*

Intensive (metformin) vs. Conventional glucose control

<table>
<thead>
<tr>
<th>Year</th>
<th>Con</th>
<th>Met</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>38</td>
<td>24</td>
<td>1.0, 1.0</td>
</tr>
<tr>
<td>1999</td>
<td>58</td>
<td>37</td>
<td>0.84 (0.63, 1.14)</td>
</tr>
<tr>
<td>2001</td>
<td>70</td>
<td>44</td>
<td>0.97 (0.76, 1.25)</td>
</tr>
<tr>
<td>2003</td>
<td>73</td>
<td>52</td>
<td>0.95 (0.74, 1.22)</td>
</tr>
<tr>
<td>2005</td>
<td>74</td>
<td>58</td>
<td>0.92 (0.71, 1.19)</td>
</tr>
<tr>
<td>2007</td>
<td>78</td>
<td>66</td>
<td>0.90 (0.70, 1.17)</td>
</tr>
</tbody>
</table>

HR = 0.71, p = 0.19

HR = 0.84, p = 0.30
Myocardial Infarction Hazard Ratio

(fatal or non-fatal myocardial infarction or sudden death)

Intensive (metformin) vs. Conventional glucose control

HR (95%CI)

Myocardial infarction
HR=0.61
p=0.010

HR=0.67
p=0.005

Number of events
Con: 73 83 92 106 118 126
Met: 39 45 55 64 68 81

1997 1999 2001 2003 2005 2007
All-cause Mortality Hazard Ratio

Intensive (metformin) vs. Conventional glucose control

All-cause mortality

HR = 0.64
p = 0.011

HR = 0.73
p = 0.002

Hazard ratio

Con: 89 113 136 160 183 217
Met: 50 70 86 110 123 152

Number of events

1997 1999 2001 2003 2005 2007

HR (95%CI)
Are there Blood Pressure Therapy Legacy Effects?
Hypertension in Diabetes Study (HDS)

10-year Intervention Trial 1987-1997
- 1,148 patients with blood pressure $\geq 160/90$ mm Hg, or $\geq 150/85$ mm Hg if receiving antihypertensive treatment, enrolled over four years from 1987
- Median follow-up 8.4 years, range 6 to 10 years
- Results presented at the 1998 EASD Barcelona meeting

10-year Post-trial Monitoring 1997-2007
- Annual follow-up of the survivor cohort
- Clinic-based for first five years
- Questionnaire-based for last five years

*Median overall follow-up 14.6 years, range 16 to 20 years*
Blood Pressure Interventional Trial

5,102
UKPDS patients

1,148
BP >160/90 mm Hg
or >150/80 on Rx

Mean age
56±8 years

Randomisation
1987-1991

759
Tight control
ACEI or β-blocker

390
Less-tight control
No ACEI or β-blocker

Trial end
1997

1997

P

Post-Trial Monitoring: Patients

1997
# in survivor cohort

592
Tight control

292
Less-tight control

2002

Clinic

Questionnaire

2007
# with final year data

250
Tight control

126
Less-tight control

Mean age
63±8 years

Mortality 51% (584)
Lost-to-follow-up 2.0% (23)
Antihypertensive Therapy at 5 years

Proportion of patients

Less Tight

Tight

Number of agents

Original randomisation

0

74%
Post-Trials Changes in Blood Pressure

UKPDS results presented

Less-tight vs. Tight

Mean (95%CI)

Blood pressure (mm Hg)

- 1997: Mean ± SD
  - Less-tight: 160 ± 10
  - Tight: 150 ± 10
  - P = 0.042

- 2002: Mean ± SD
  - Less-tight: 80 ± 5
  - Tight: 85 ± 5
  - P = 0.20


ukpds~ptm
Any Diabetes Related Endpoint Hazard Ratio

Less-tight vs. Tight blood pressure control

Any diabetes related endpoint
HR=0.76
p=0.0046

HR=0.93
p=0.35

Hazard ratio

Number of events
LT: 170 195 211 227 237 248
T: 259 323 371 410 441 466

1997 1999 2001 2003 2005 2007
Microvascular Disease Hazard Ratio

(photocoagulation, vitreous haemorrhage, renal failure)

Less-tight vs. Tight blood pressure control

Microvascular disease
HR = 0.63
p = 0.0092

HR = 0.84
p = 0.20

Hazard ratio

Number of events

LT: 54 66 72 75 79 82
T: 68 88 108 124 133 141

1997 1999 2001 2003 2005 2007
Myocardial Infarction Hazard Ratios

(fatal or non-fatal myocardial infarction or sudden death)

Less-tight vs. Tight blood pressure control

Myocardial infarction

HR = 0.79
p = 0.13

HR = 0.90
p = 0.35

Hazard ratio

Number of events

LT: 69 77 87 99 105 115
T: 107 130 148 169 189 205

1997 1999 2001 2003 2005 2007
All-cause Mortality Hazard Ratios

Less-tight vs. Tight blood pressure control

All-cause mortality
HR=0.82
p=0.17

HR=0.89
p=0.18

Hazard ratio

Number of events
LT:  83  111  136  159  180  211
T:  134  177  224  267  322  373

1997  1999  2001  2003  2005  2007

ukpds~ptm
Legacy Effect of Earlier Glucose Control

After median 8.5 years post-trial follow-up

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>RRR: 12%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P: 0.029</td>
<td></td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 25%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P: 0.0099</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 16%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P: 0.052</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P: 0.44</td>
<td></td>
</tr>
</tbody>
</table>

RRR = Relative Risk Reduction, P = Log Rank
### Legacy Effect of Earlier Metformin Therapy

*After median 8.8 years post-trial follow-up*

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RRR:</strong></td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td><strong>P:</strong></td>
<td>0.0023</td>
<td></td>
</tr>
<tr>
<td>Microvascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RRR:</strong></td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td><strong>P:</strong></td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RRR:</strong></td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td><strong>P:</strong></td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RRR:</strong></td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td><strong>P:</strong></td>
<td>0.011</td>
<td></td>
</tr>
</tbody>
</table>

*RRR = Relative Risk Reduction, P = Log Rank*
The Benefits of Early Tight Control- UKPDS 10 year Post-Trial Follow-Up

# No Legacy Effect of Earlier BP Control

After median 8.0 years post-trial follow-up

## Aggregate Endpoint

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>1997</th>
<th>2007</th>
<th>RRR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td></td>
<td></td>
<td>24%</td>
<td>0.0046</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td></td>
<td></td>
<td>37%</td>
<td>0.0092</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td>21%</td>
<td>0.13</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td>18%</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*RRR = Relative Risk Reduction, P = Log Rank*
Legacy effects

• Legacy: “something handed on by or left unfinished by a predecessor or previous owner”*
• More likely to be gradually developing pathology than “metabolic memory”

*Chambers Dictionary 10th edition
The performance of this machine may depend on its previous history as well as standards of care today.
Accidents likely to happen

The rust on this machine today is the result of what has happened in the distant past.

The air pressure in the tyres of this machine is the result of what has happened in the recent past.

Glycaemic control in the distant past reduces the risks of events today.

Blood pressure control in the recent past reduces the risks of events today.
What do we change in clinical practice?

- Evidence is strongly in favour of intensive treatment for glycaemia **early** in T2DM
- Evidence suggests that in those with established CVD that a rapid lowering of glycaemia to aggressive targets may cause excess mortality.
- Rosiglitazone needs further evidence for its safety in established T2DM
- Sulphonylureas may be appropriate for preventing microvascular disease (nephropathy)
With thanks to...

Aberdeen  John Stowers, Lilian
Belfast City  Randal Hayes
Belfast Royal  David Hadden
Birmingham  David Wright
Carshalton  Steve Hyer, Memo S
Derby  Ian Peacock
Dundee  Ray Newton, Roland
Exeter  Kenneth McLeod, Jo
Hammersmith  Anne Dornhorst, Eva
Ipswich  John Day
Leicester  Felix Burden
Manchester  Andrew Boulton
Northampton  Charles Fox
Norwich  Richard Greenwood
Oxford  Robert Turner, Rury
Peterborough  Jonathan Roland
Salford  Tim Dornan, Martin C
Scarborough  Phil Brown
St George’s  Nigel Oakley, Arshia
Stevenage  Les Borthwick
Stoke on Trent  John Scarpell, Lionel
Torbay  Richard Paisey
Whittington  John Yudkin

…Robert Turner died August 1999
…Carole Cull died June 2007

1998 EASD Investigator Meeting in Barcelona
## Funding

<table>
<thead>
<tr>
<th>1997 to 2002</th>
<th>2002 to 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UK Medical Research Council</strong></td>
<td><strong>Bristol-Myers Squibb</strong></td>
</tr>
<tr>
<td><strong>UK Department of Health</strong></td>
<td><strong>GlaxoSmithKline</strong></td>
</tr>
<tr>
<td><strong>Diabetes UK</strong></td>
<td><strong>Merck Serono</strong></td>
</tr>
<tr>
<td><strong>British Heart Foundation</strong></td>
<td><strong>Novartis</strong></td>
</tr>
<tr>
<td><strong>National Institutes for Health (NEI, NIDDK)</strong></td>
<td><strong>Novo Nordisk</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Pfizer</strong></td>
</tr>
</tbody>
</table>
MEGA-trials

(No cardiovascular outcomes assessable in diabetes without mega-trials)

Defined (by me) as a randomised interventive trial with outcomes where greater than about 5,000,000 patient days are reported
(e.g. 1,000 patients for 3 years…or greater)

AND they need to last longer than 5 years
AND the glycaemic difference needs to be >0.5% Hba1c.
What do we change in clinical practice (1)?

- Evidence is strongly in favour of intensive treatment for glycaemia early in T2DM
- Evidence suggests that in those with established CVD that a rapid lowering of glycaemia to aggressive targets may cause excess mortality.
- Rosiglitazone needs further evidence for its safety in established T2DM
- Gliclazide MR use may be appropriate for preventing microvascular disease (nephropathy)
What do we change in clinical practice (2)?

• Evidence suggests that recent blood pressure control is protective, while a past history of good control is less significant.

• Evidence suggests that MULTIPLE risk-factor intervention is important.
  — (Steno studies – not reviewed today, but suggest that a well-delivered package of intervention has beneficial outcome)
“You might as well fall flat on your face, as lean over too far backwards”

James Thurber.
Fl. 1945
The roller-coaster: trials relating to glycaemia
The roller-coaster: trials relating to glycaemia

Enthusiasm

Time

UGDP

UKPDS

ADOPT

RECORD

ACCORD

ADVANCE

Æ

VADT?
The roller-coaster: trials relating to glycaemia

Enthusiasm

UGDP

UKPDS

PROactive (EASD)

Time
The roller-coaster: trials relating to glycaemia

Enthusiasm

Time

UGDP

UKPDS

PROactive (on reflection)

PROactive (EASD)

ADOPT

RECORD

ACCORD

ADVANCE

Æ

VADT?
The roller-coaster: trials relating to glycaemia

Enthusiasm

Time

UGDP
PROactive (EASD)
PROactive (on reflection)
(Ennis
Meta analysis)

The Oxford Centre for Diabetes, Endocrinology and Metabolism
The roller-coaster: trials relating to glycaemia

Enthusiasm

UGDP

PROactive (EASD) (Nissen Meta analysis)

UKPDS

PROactive (on reflection)

ADOPT

Time
The roller-coaster: trials relating to glycaemia

- UGDP
- PROactive (EASD)
- PROactive (Nissen Meta analysis)
- UKPDS
- ADOPT
- RECORD
- PROactive (on reflection)
- (EASD)
The roller-coaster: trials relating to glycaemia

Enthusiasm

UKPDS
PROactive (on reflection)
ADOPT
RECORD
PROactive (EASD)
UGDP (Nissen Meta analysis)
ACCORD

Time
The roller-coaster: trials relating to glycaemia

Enthusiasm

Time

- UKPDS
- PROactive (on reflection)
- ADOPT
- VADT?
- RECORD
- PROactive (EASD) (Nissen Meta analysis)
- UGDP
- ACCORD

The Oxford Centre
for Diabetes, Endocrinology and Metabolism
The roller-coaster: trials relating to glycaemia

Enthusiasm

Time

UGDP

PROactive (EASD)

PROactive (on reflection)

ADOPT

VADT?

RECORD

ADVANCE

ACCORD

(Nissen Meta analysis)
The roller-coaster: trials relating to glycaemia

- UGDP
- PROactive (EASD)
- PROactive (on reflection) (Nissen Meta analysis)
- ADOPT
- VADT?
- RECORD
- ADVANCE
- ACCORD
- VADT?
- UKPDS PTM

Enthusiasm

Time
Some cautions

• There will be those who say that glucose lowering is not cost effective

• There will be those who say that the target of 7.5% is adequate, without saying for whom

• There will be those who say that we should just lower cholesterol and blood pressure

• There will be those who will become famous for saying almost anything, but loudly
Good evidence that glycaemic control is beneficial – UKPDS and UKPDS-PTM

Fair evidence that aggressive late glycaemic control is harmful – ACCORD

Fair evidence that slow late glycaemic control is beneficial – ADVANCE

• Good evidence for metformin (UKPDS)
• Fair evidence for gliclazide and pioglitazone (ADVANCE and ProACTIVE)
• Poor evidence for rosiglitazone (ACCORD and RECORD)
If you have been...

...thank you for listening