Landmark Clinical Trials

Kim L Kelly, PharmD, BCPS, FCCP, CDTC, CPC, CEC
Polling Question

Which of the following is not considered a landmark trial in diabetes?

A. DPP-DPPOS
B. DCCT-EDIC
C. DMIT-35
D. UKPDS
What’s a Landmark Clinical Trial?

**landmark**

/ˈlan(d)ˌmärk/

n.

1. a prominent or well-known object in or feature of a particular landscape

2. an important or unique decision, event, fact, discovery, etc.
Some Landmark Trials …

• United Kingdom Prospective Diabetes Study (UKPDS) => UKPDS-PTM

• Diabetes Control and Complications Trial (DCCT) => EDIC

• Diabetes Prevention Program (DPP) => DPPOS

• Action to Control Cardiovascular Risk in Diabetes (ACCORD) => ACCORDION

• Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) => ADVANCE-ON

• Veterans Affairs Diabetes Trial (VADT)
United Kingdom Prospective Diabetes Study
(UKPDS) => UKPDS-PTM
Does an intensive glucose control policy reduce the risk of complications of diabetes?
Randomisation of Treatment Policies

Main Randomisation
n=4209 (82%)

342 allocated to metformin

3867

Conventional Policy
30% (n=1138)

Intensive Policy
70% (n=2729)

Sulphonylurea
n=1573

Insulin
n=1156
HbA1c

cross-sectional, median values

Conventional

Intensive

6.2% upper limit of normal range

Years from randomisation

HbA1c (%)
Hypoglycaemic episodes per annum

Actual Therapy Analysis

any episode

major episodes

Hypoglycaemia (%)

Years from randomisation
Glucose Control Study Summary

The intensive glucose control policy maintained a lower HbA1c by mean 0.9 % over a median follow up of 10 years from diagnosis of type 2 diabetes with reduction in risk of:

- 12% for any diabetes related endpoint
- 25% for microvascular endpoints
- 16% for myocardial infarction
- 24% for cataract extraction
- 21% for retinopathy at twelve years
- 33% for albuminuria at twelve years

All results are statistically significantly different from results seen in the ‘conventional’ policy patients
Blood Pressure Control Study Summary

The ‘tight’ blood pressure control arm resulted in a mean BP of 144/82 (use of ACEI or β-blocker) compared with the ‘less tight’ control BP of 154/87

24% for any diabetes related endpoint
32% for deaths related to diabetes
18% for all cause mortality
21% for myocardial infarction
44% for stroke
49% for peripheral vascular disease
37% for microvascular endpoints

All results are statistically significantly different from results seen in the ‘conventional’ policy patients
## 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>9%</td>
</tr>
<tr>
<td></td>
<td>P: 0.029</td>
<td>0.040</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 25%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>P: 0.0099</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 16%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>P: 0.052</td>
<td>0.014</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 6%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>P: 0.44</td>
<td>0.007</td>
</tr>
</tbody>
</table>

RRR = Relative Risk Reduction, P = Log Rank

![UKPDS Logo](https://example.com/logo.png)
# Legacy Effect of Earlier Metformin Therapy

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: 32%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>P: 0.0023</td>
<td>0.013</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 29%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>P: 0.19</td>
<td>0.31</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 39%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>P: 0.010</td>
<td>0.005</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 36%</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>P: 0.011</td>
<td>0.002</td>
</tr>
</tbody>
</table>

RRR = Relative Risk Reduction, P = Log Rank

[UKPDS Logo]
Diabetes Control and Complications Trial (DCCT) => EDIC
DCCT: intensive control reduces complications in type 1 diabetes

Conventional versus intensive insulin therapy (n = 1,441)

Conventional treatment (n = 730)

Intensive treatment (n = 711)

$P < 0.001$

*Subdivided to primary and secondary prevention of retinopathy. Age 27 years, HbA1c 8.8%. Insulin dose (U/kg/d) 0.62 (primary), 0.71 (secondary).

DCCT/EDIC: long-term follow-up and legacy effect

Glucose similar BUT CV events still higher

57% risk reduction in non-fatal MI, stroke or CVD death*

*Intensive vs conventional treatment.
Cumulative incidence of retinopathy over 10 years in EDIC following DCCT: the ‘legacy effect’

- 53% risk reduction with intensive therapy, 95% CI, 43%–61%; *P* < .001

Cumulative incidence, %

HbA1c (%)

DCCT closeout

EDIC study year

Error bars are 95% CI. *N* = 1211

Diabetes Prevention Program (DPP) => DPPOS
Polling Question

When intervening to prevent diabetes in a person with pre-diabetes, which of the following is the best indicator of long term success?

A. Insulin doses under 0.5U/kg
B. Stable dose of sulfonylurea agents
C. Weight gain of less than 5 kg
D. Return to normal glucose tolerance at least once
US DPP: Incidence of Type 2 Diabetes With Different Interventions

Cumulative incidence of diabetes (%)

Placebo
Metformin
Lifestyle

Years

P<0.001 for each comparison.

DPPOS Maintenance: Years 5-10

88% of DPP participants joined DPPOS

- Lifestyle (n=910)
- Metformin (n=924)
- Placebo (n=932)

- Interventions for participants who developed diabetes
  - Glucose testing within 6 wks to confirm diagnosis
  - Received 1 hr of individual counseling
  - Encouraged to monitor glucose levels once daily
  - Maintained in original treatment groups

DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program Outcomes Study
DPPOS Substudy: Effect of Regression from Prediabetes to NGR on Diabetes Risk

72% (n=1,990 of total 2,671) of subjects in DPPOS included in analysis

Lifestyle (n=736)  Metformin (n=647)  Placebo (n=607)

- Objective: quantify and predict diabetes risk reduction during DPPOS
- Examined participants who regressed to NGR* at least once on yearly OGTT during the DPP and never met criteria for diabetes diagnosis
- Those who regressed to NGR were compared with those who maintained prediabetes state† with and without stratification by previous DPP treatment group
- Included subjects had persistent prediabetes or restoration of NGR over 5.7 years of follow-up in DPPOS; any patient who progressed to diabetes during DPPOS was excluded

NGR=normal glucose regulation
*Defined as FPG <5.6 mmol/L and 2-hr glucose <7.8 mmol/L
†Defined as FPG 5.6-6.9 mmol/L and 2-hr glucose 7.8-11.0 mmol/L, or both, on yearly OGTT during DPP; never met criteria for diabetes diagnosis
DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program Outcomes Study
DPPOS Substudy: Additional Outcomes

Effects on diabetes risk in DPPOS

**Adverse**
- Increased weight loss during DPP (HR, 1.26; 95% CI, 1.15-1.39; \( P < 0.0001 \))
- Increased BMI at beginning of DPPOS (HR, 1.14; 95% CI, 1.05-1.25; \( P = 0.0021 \))

**Protective**
- Higher beta-cell function (HR, 0.80; 95% CI, 0.71-0.89; \( P < 0.0001 \))
- Insulin sensitivity (HR, 0.83; 95% CI, 0.74-0.94; \( P = 0.0001 \))

- Previous DPP treatment group assignment did not have an effect on risk reduction in DPPOS among those who attained NGR
- Participants who consistently stayed in a prediabetes state during DPP had increased diabetes risk despite intensive lifestyle intervention (HR, 1.31; 95% CI, 1.03-1.68; \( P = 0.0304 \)) and a lower chance of achieving NGR (OR, 0.59; 95% CI, 0.42-0.82; \( P = 0.0014 \)) vs placebo in DPPOS

NGR=normal glucose regulation
DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program Outcomes Study
DPPOS and weight loss

Figure 3: Diabetes cumulative incidence rates during DPPOS in participants who attained normal glucose regulation at least once during DPP compared with those who consistently had prediabetes, stratified by treatment group in DPP. DPP—Diabetes Prevention Program. DPPOS—Diabetes Prevention Program Outcomes Study. NGR—normal glucose regulation.

DPPOS and weight loss

(ACCORD) => ACCORDION
(ADVANCE) => ADVANCE-ON
(VADT)
Polling Question

Which of the following were associated with increased mortality in the ACCORD trial?

A. older age, male sex, longer diabetes duration

B. history of cardiovascular disease, heart failure, higher HbA1c

C. serum creatinine and urine albumin/creatinine ratio

D. all the above
Macrovascular Trials in Type 2 Diabetes (ACCORD, ADVANCE, VADT)

Table 1  Key characteristics of trials and length of follow-up

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Trial acronym</th>
<th>Year reported</th>
<th>Number</th>
<th>Design</th>
<th>Glycaemic control comparison</th>
<th>Entry criteria</th>
<th>Median follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Action to Control Cardiovascular Risk in Diabetes Study</td>
<td>ACCORD</td>
<td>2008</td>
<td>10,251</td>
<td>Randomised, double $2 \times 2$ factorial</td>
<td>Intensive (target HbA$<em>{1c}$ &lt;6%) vs standard (target HbA$</em>{1c}$ 7–7.9%)</td>
<td>Type 2 diabetes, HbA$_{1c}$ $\geq$7.5%, 40–79 years or 55–79 years$^a$</td>
<td>3.4$^b$</td>
</tr>
<tr>
<td>Action in Diabetes and Vascular Disease: Preterax® + Diamicron Modified Release Controlled Evaluation</td>
<td>ADVANCE</td>
<td>2008</td>
<td>11,140</td>
<td>Randomised, $2 \times 2$ factorial</td>
<td>Intensive (target HbA$<em>{1c}$ $\leq$6.5%) vs standard (target HbA$</em>{1c}$ $&gt;$6.5%)</td>
<td>Diagnosis of type 2 diabetes at $\geq$30 years, $\geq$55 years$^c$</td>
<td>4.9</td>
</tr>
<tr>
<td>UK Prospective Diabetes Study</td>
<td>UKPDS</td>
<td>1998</td>
<td>3,867</td>
<td>Randomised</td>
<td>Intensive (target FPG &lt;6 mmol/l) vs conventional (best achievable FPG with diet alone)</td>
<td>Newly diagnosed type 2 diabetes, 25–65 years old$^d$</td>
<td>5.0$^e$</td>
</tr>
<tr>
<td>Veterans Affairs Diabetes Trial</td>
<td>VADT</td>
<td>2008</td>
<td>1,791</td>
<td>Randomised</td>
<td>Intensive (target absolute reduction 1.5%) vs standard</td>
<td>Poorly controlled type 2 diabetes, military veterans$^f$</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Turnbull FM, et al.. Diabetologia 2009;52:2288–2298
Macrovascular Trial Outcomes

<table>
<thead>
<tr>
<th>Trials</th>
<th>Number of events (annual event rate, %)</th>
<th>( \Delta \text{HbA1c} ) (%</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>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>257 (1.41)</td>
<td>203 (1.14)</td>
<td>-1.01</td>
<td></td>
<td>1.22 (1.01–1.46)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>498 (1.86)</td>
<td>533 (1.99)</td>
<td>-0.72</td>
<td></td>
<td>0.93 (0.83–1.06)</td>
</tr>
<tr>
<td>UKPDS</td>
<td>123 (0.13)</td>
<td>53 (0.25)</td>
<td>-0.66</td>
<td></td>
<td>0.96 (0.70–1.33)</td>
</tr>
<tr>
<td>VADT</td>
<td>102 (2.22)</td>
<td>95 (2.06)</td>
<td>-1.16</td>
<td></td>
<td>1.07 (0.81–1.42)</td>
</tr>
<tr>
<td>Overall</td>
<td>980</td>
<td>884</td>
<td>-0.88</td>
<td></td>
<td>1.04 (0.90–1.20)</td>
</tr>
<tr>
<td>(Q=5.71, p=0.12, I²=47.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>135 (0.79)</td>
<td>94 (0.56)</td>
<td>-1.01</td>
<td></td>
<td>1.35 (1.04–1.76)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>253 (0.95)</td>
<td>289 (1.08)</td>
<td>-0.72</td>
<td></td>
<td>0.88 (0.74–1.04)</td>
</tr>
<tr>
<td>UKPDS</td>
<td>71 (0.53)</td>
<td>29 (0.52)</td>
<td>-0.66</td>
<td></td>
<td>1.02 (0.66–1.57)</td>
</tr>
<tr>
<td>VADT</td>
<td>28 (0.83)</td>
<td>29 (0.63)</td>
<td>-1.16</td>
<td></td>
<td>1.32 (0.81–2.14)</td>
</tr>
<tr>
<td>Overall</td>
<td>497</td>
<td>441</td>
<td>-0.88</td>
<td></td>
<td>1.10 (0.84–1.42)</td>
</tr>
<tr>
<td>(Q=8.61, p=0.04, I²=65.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cardiovascular death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>115 (0.63)</td>
<td>98 (0.55)</td>
<td>-1.01</td>
<td></td>
<td>1.14 (0.87–1.49)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>245 (0.92)</td>
<td>244 (0.91)</td>
<td>-0.72</td>
<td></td>
<td>1.00 (0.84–1.20)</td>
</tr>
<tr>
<td>UKPDS</td>
<td>52 (0.39)</td>
<td>24 (0.43)</td>
<td>-0.66</td>
<td></td>
<td>0.90 (0.55–1.46)</td>
</tr>
<tr>
<td>VADT</td>
<td>64 (1.40)</td>
<td>66 (1.43)</td>
<td>-1.16</td>
<td></td>
<td>0.97 (0.69–1.36)</td>
</tr>
<tr>
<td>Overall</td>
<td>476</td>
<td>432</td>
<td>-0.88</td>
<td></td>
<td>1.02 (0.89–1.18)</td>
</tr>
<tr>
<td>(Q=0.99, p=0.80, I²=0.0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary:
ACCORD, ADVANCE, UKPDS, VADT

- A meta-analysis of ACCORD, ADVANCE, UKPDS, and VADT (total 27,049 participants with 2,370 major vascular events) showed a significant 9% reduction in these events, driven by a 15% reduction in myocardial infarction, with non-significant 10 and 4% increases in cardiovascular and total mortality, respectively.

- Hypoglycemia rates were 2.5-fold more common with intensive treatment.

- There was heterogeneity between the trials, with ADVANCE suggesting a reduction in cardiovascular mortality, the UKPDS being neutral, and ACCORD and VADT having trends to increased CV mortality in the initial trial data. In the meta-analysis, those with no history of macrovascular disease had a significant 16% reduction in CVD, but there was no CV benefit in those with such a history.

Boomgarden ZT, Cardiovascular disease and glycemic treatment. Diabetes Care 2010;33:e134-e139
So what have we learned from these landmark trials?
Landmark Trials

• Type 2 diabetes can be prevented (delayed) in individuals with pre-diabetes by lifestyle modifications or metformin.

• In people with pre-diabetes, getting them back to normal glucose tolerance is key to preventing diabetes, and weight loss is pivotal in that goal.

• Diabetes complications can be dramatically lowered in people with type 1 and type 2 diabetes by intensive insulin therapy with lasting ‘legacy’ effects over at least 20 years.
Landmark Trials

• Tight glycemic control with insulin is associated with significant increases in hypoglycemia.

• In people with type 2 diabetes and cardiovascular risk, early insulin seems not to have adverse CV outcomes (although hypoglycemia is more common).

• In people with type 2 diabetes who have had long duration diabetes and have existing CV complications, there is a risk to trying to go too low in glucose (A1C) levels. Individualize targets!
Thank You