1993 - The Diabetes Control and Complications Trial (DCCT)

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Introduction
Before we consider the DCCT and its findings, it is worth reflecting on what the situation was before that great day in June 1993 when the DCCT was unveiled. I became a consultant in 1991, and I well remember being told at that time by my colleague, Professor Gareth Beevers, “you know, Bob, there is no evidence whatsoever that what you do for your patients with diabetes makes any difference”. Professor Beevers was a leading figure in the world of hypertension and he was involved in the many studies showing the benefits of reducing blood pressure on cardiovascular and cerebrovascular outcomes.1,2 It was galling at the time, that to some extent, what Gareth said to me was true and indeed it was very difficult to argue against. All that changed with the DCCT.

The results of the DCCT were presented at the 53rd scientific sessions of the American Diabetes Association (ADA) on 13th June, 1993. I was there for the occasion and the astonishing thing, for all of us who attended that meeting in Las Vegas, was that none of us realised what was coming. The first clue that something special was happening was all the television cameras outside a lecture theatre as we approached. None of us had seen anything like this before when attending international scientific meetings and this suggested that “something was up”. We had no idea what.

DCCT design
The trial included 1,441 patients divided into a primary cohort (n=726) and a secondary cohort (n=715) (Figure 1). The primary cohort consisted of people who did not have diabetic retinopathy and the secondary cohort consisted of people who did have diabetic retinopathy. Each cohort was randomised into those who received “conventional therapy”, which amounted to whatever was the standard diabetes care delivered routinely in the United States at the time, and into another group who were labelled ‘intensive therapy’ (Figure 1). The features of intensive therapy are shown in figure 2.

Glycaemic control
By applying the measures shown in figure 2 to the intensively treated group, the mean HbA1c was reduced considerably and significantly compared to the conventional group (Figure 3). A summary of the results shown in figure 3 is that over the decade of the study the conventional group maintained HbA1c of about 9% whereas the intensively treated group maintained a HbA1c of about 7% - a 2% difference.

Diabetic retinopathy
To assess the impact of this sustained improvement in glycaemic control on diabetic retinopathy, fundus photography was used...
to assess the severity of retinopathy. For this purpose, the trialists described what was termed a "sustained three-step change". This was defined as a change observed by fundus photography of at least three steps from baseline that was sustained for at least six months. Those doing the grading were of course blinded as to which group the patients were in. Figure 4a shows the difference in sustained three-step change between the conventional and intensive arms in the primary cohort (76% reduction) and figure 4b shows the difference in the secondary cohort (54% reduction).

**Diabetic nephropathy**

Figure 5a shows the impact of the intensive therapy on microalbuminuria >40mg/24hr in the combined cohort. There was a 34% reduction in the primary cohort and a 43% reduction in the secondary cohort. Figure 5b shows the impact of the intensive therapy on macroalbuminuria >300mg/24hr in the combined cohort.

**Diabetic neuropathy**

Figure 6 shows the impact of the intensive therapy on the prevalence of neuropathy at five years. Whether it was checked by clinical examination, measurement of the autonomic nervous system, or by nerve conduction there was a significant reduction in neuropathy.

**Hypoglycaemia**

In Figure 7 the risk of severe hypoglycaemia is presented. It shows a significant increase in risk in the intensively treated group compared to the conventionally treated group (roughly a 3-fold risk).

**Risk vs. HbA1c**

Figure 8a shows a secondary analysis which was undertaken to assess the rate of retinopathy progression according to HbA1c.
It shows that the higher the HbA1c, the higher the rate of retinopathy progression. Figure 8b shows a secondary analysis which was undertaken to assess the risk of hypoglycaemia according to HbA1c exposure. It shows that the lower the HbA1c, the higher the risk of hypoglycaemia.

**Summary**

The DCCT trialists summarised the impact of intensive therapy on microvascular complications as a reduction in retinopathy of between 27% and 76%, in nephropathy of between 34% and 57% and in neuropathy of 60%. The take-home message was overall that the microvascular complications were reduced by about 60% through a maintained improvement in HbA1c of 2% (i.e., from 9% to 7%) over a decade. As shown in figure 8, the trialists also showed that the higher the HbA1c the greater the rate of retinopathy progression but, conversely, the lower the HbA1c the greater the risk of severe hypoglycaemia.

**The legacy of the DCCT**

Seventy-one years after the first injection of insulin into a person with type 1 diabetes, we finally knew from the DCCT that improving glycaemic control reduced the microvascular complications of diabetes. We also knew that utilising the intensive therapy methods employed in the DCCT increased the risk of severe hypoglycaemia. Thus emerged the challenge of finding ways to improve glycaemic control without increasing hypoglycaemia risk and this remains the challenge today, 100 years after the first use of insulin.

**Key messages**

- Before the results of the DCCT were presented at the ADA in Las Vegas in 1993, there was uncertainty as to whether improving glycaemic control reduced microvascular complications – the DCCT provided the definitive proof
- The take-home message was that, overall, the microvascular complications were reduced by about 60% through a maintained improvement in HbA1c of 2% (i.e., from 9% to 7%) over a decade
- The results also showed that the higher the HbA1c the greater the rate of retinopathy progression but, conversely, the lower the HbA1c the greater the risk of severe hypoglycaemia
- Thus emerged the challenge of finding ways to improve glycaemic control without increasing hypoglycaemia risk and this remains the challenge today, 100 years after the first use of insulin

**Figure 7.** Severe hypoglycaemia in the combined cohort comparing the intensively treated group with the conventionally treated group

<table>
<thead>
<tr>
<th>Episodes/100 patient years</th>
<th>Intensive</th>
<th>Conventional</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>62</td>
<td>19</td>
<td>3.3</td>
</tr>
<tr>
<td>Coma/Seizure</td>
<td>16</td>
<td>5</td>
<td>3.0</td>
</tr>
<tr>
<td>ER/Hospital</td>
<td>9</td>
<td>4</td>
<td>2.3</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 8.** a. The rate of retinopathy progression according to HbA1c exposure; b. Risk of hypoglycaemia according to HbA1c exposure

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**References**