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.

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Figure 1. DCCT randomisation

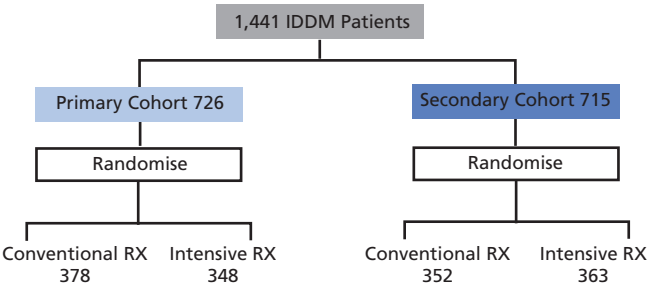
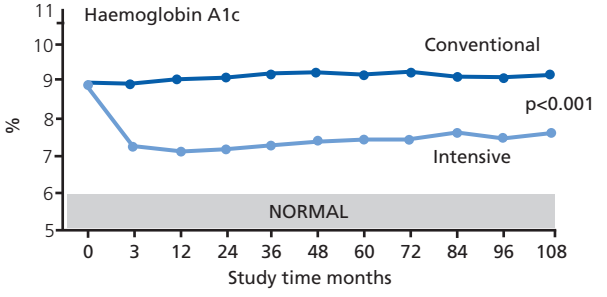


Figure 2. Intensive therapy method

- 3 or more daily injections or insulin pump
- 4 or more blood glucose tests daily
- Frequent dietary instruction to help achieve goals
- Monthly clinic visits
- Integrated tream care

Figure 3. Impact of intensive therapy on glycaemic control



Glycaemic control

By applying the measures shown in figure 2 to the intensively treated group, the mean HbA_{1c} 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 HbA_{1c} of about 9% whereas the intensively treated group maintained a HbA_{1c} 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

Figure 4. **a**. The cumulative incidence of sustained three-step change in diabetic retinopathy in the primary cohort, comparing the conventionally treated group with the intensively treated group. **b**. The cumulative incidence of sustained three-step change in diabetic retinopathy in the secondary cohort, comparing the conventionally treated group with the intensively treated group.

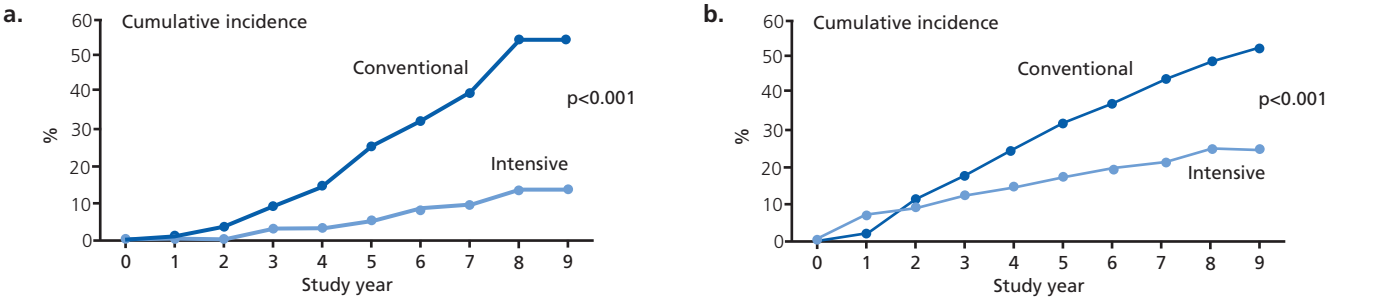
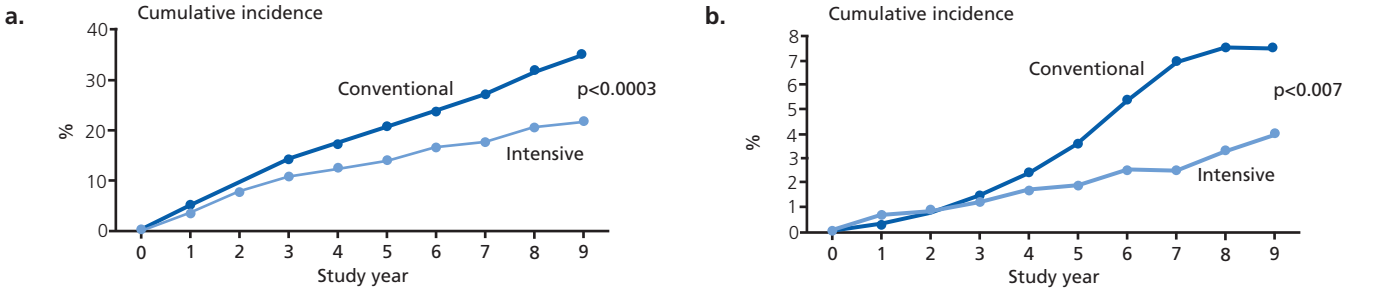


Figure 5. **a**. The cumulative incidence of microalbuminuria ≥40mg/24hr in the combined cohort, comparing the conventionally treated group with the intensively treated group. **b**. The cumulative incidence of albuminuria ≥300mg/24hr in the combined cohort, comparing the conventionally treated group with the intensively treated group.



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).

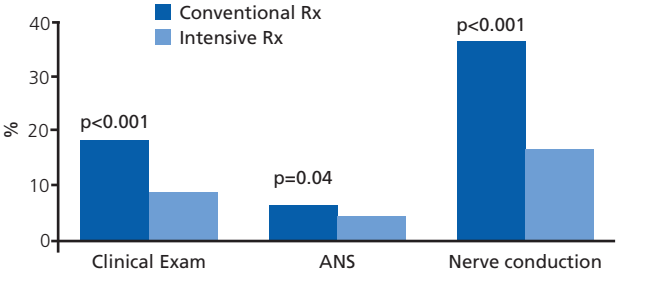
Diabetic nephropathy

Figure 5a shows the impact of the intensive therapy on microalbuminuria >40mg/24 hours 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/24 hours 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, or measurement of the autonomic nervous system or by nerve conduction there was a significant reduction in neuropathy.

Figure 6. The 5-year prevalence in neuropathy in those without baseline neuropathy as assessed by clinical examination, measurement of the autonomic nervous system, and by nerve conduction



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. HbA_{1c}

Figure 8a shows a secondary analysis which was undertaken to assess the rate of retinopathy progression according to HbA_{1c}

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

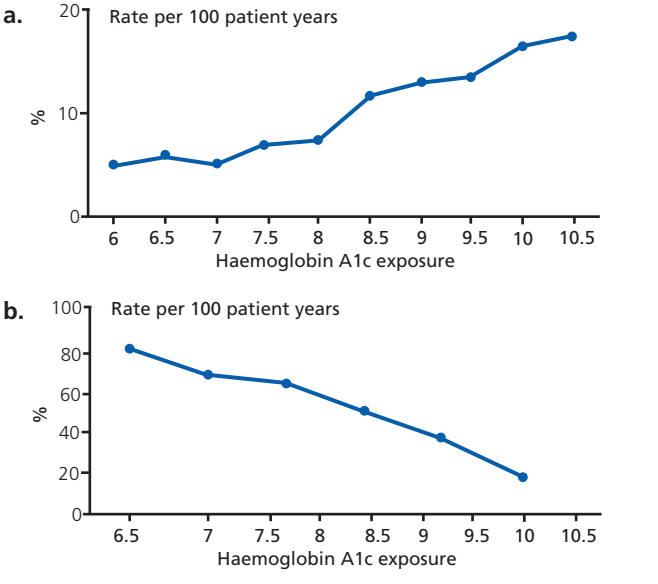
	Episodes/100 patient years		
	Intensive	Conventional	Risk ratio
Severe	62	19	3.3
Coma/Seizure	16	5	3.0
ER/Hospital	9	4	2.3
Deaths	0	0	–

exposure. It shows that the higher the HbA_{1c}, the higher the rate of retinopathy progression. Figure 8b shows a secondary analysis which was undertaken to assess the risk of hypoglycaemia according to HbA_{1c} exposure. It shows that the lower the HbA_{1c}, 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 HbA_{1c} of 2% (i.e. from 9% to 7%) over a decade. As shown in figure 8, the trialists also showed that the higher the HbA_{1c} the greater the rate of retinopathy progression but, conversely, the lower the HbA_{1c} the greater the risk of severe hypoglycaemia.

Figure 8. **a**. The rate of retinopathy progression according to HbA_{1c} exposure; **b**. Risk of hypoglycaemia according to HbA_{1c} exposure



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 HbA_{1c} of 2% (i.e., from 9% to 7%) over a decade
- The results also showed that the higher the HbA_{1c} the greater the rate of retinopathy progression but, conversely, the lower the HbA_{1c} 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

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 that first use of insulin. Three months after their presentation at the ADA in June 1993, the results of the DCCT were published in the *New England Journal of Medicine*.[3]

It was especially gratifying for me personally to be able to return to the UK from that amazing event in Las Vegas in June 1993 and to be able to tell Gareth Beevers that he was wrong!

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