

**WorldWIDE**

Worldwide Initiative for Diabetes Education

# WorldWIDE news

**We hope that you enjoyed the first issue of WorldWIDE news and we are delighted that so many people requested further information.**

The first WorldWIDE Working Group met in New York in December 2000. The aim of the 'Treatment To Glucose Goal' Working Group was to discuss the issues associated with setting and attaining treatment targets and goals. This included identifying the shortcomings in the current guidelines that impair their practical implementation, and clarifying the information conveyed to treating physicians.

## First WorldWIDE Working Group

The meeting was chaired by Professor Philip Home (UK) who presented the aims and possible outputs of the meeting and led the first session: 'Intensive therapy'.

Dr Juliana Chan (Hong Kong) presented the discussion points for the session entitled 'Which glucose goals should be targeted?'

Dr Paul Van Crombrugge (Belgium) led the third session: 'What should the target and intervention levels be?' Example case histories of people at different stages of diabetes management were presented for group discussion by Dr Alistair Emslie-Smith (UK), Professor Antonio Chacra (Brazil) and Ms Lea Sorensen (Australia).

## Intense debate

Even before the subject of guidelines was broached, the term 'intensive therapy' was hotly debated. The Working Group agreed that this term may often be misunderstood. For example, it may be construed as meaning insulin therapy alone, or just short-term therapy. Despite the fact that, for example, the 'intensive therapy' used in the DCCT included greater interaction and follow-up with the patient, the main perception of this arm of the trial is that it involved only more frequent or aggressive pharmacotherapy. By contrast, it was felt that there is a need to emphasise the fact that when considering 'intensive therapy' the clinician should also take into

account whether, for example, intensive education, encouragement and support are necessary in addition to medication requirements.

## Aiming for individual goals

The need for greater individualisation of treatment management was also discussed. It was agreed that the needs, abilities and wishes of the patient should be more carefully considered. For example, if intensive therapy is thought necessary, the clinician should consider whether the proposed goals of treatment are really appropriate for the individual. Many of these changes could be achieved through improved communication with the patient and this is a key element of good diabetes management.

## Guidelines: the simpler the better?

The UKPDS, DCCT and other studies stimulated a change in the way we think about treatment, and have prompted publication of several new sets of guidelines. However, many of the guidelines appear complex and difficult to adapt to the individual patient in the clinic. Could such guidelines be simplified to make it easier for the busy general practitioner to apply? Possibilities discussed by the WorldWIDE Working Group include simplifying the terminology used and whether more figures are quoted than are necessary or useful.

## COMPETITION

# Win!

**Registration fees for one of the main diabetes meetings in 2002!**

### How can we improve communication?

*One of the aims of WorldWIDE is to promote dialogue — between clinicians around the world, and between clinicians and patients.*

Have you found a novel phrase or figure that conveys a particular message well to colleagues or patients? Or one that made you reconsider your clinical practice? If so, we'd like to see it! Please send your entries into the WorldWIDE office by fax (+44 (0)1625 575853), email (worldwide@adelphi.co.uk) or by post (for address see back page). All entries will be judged by the WorldWIDE team. For the sender of the idea judged as best conveying a message, we will pay the registration fees for EASD, ADA, PACD6 or the Annual Scientific Meeting of the Endocrine Society of Australia in 2002. If previously unpublished, the entries may be posted on our website for your clinician colleagues worldwide to download and use for teaching purposes. The deadline for submission is 30 November 2001 and the winner will be notified by 31 January 2002.

The only rule is that you quote the source of the material where possible, whether it be from a published article, or a 'personal communication'.

**The theme for the competition is 'Glucose is toxic'**

There is obviously still much to be achieved in the choosing and communication of goals in diabetes treatment. If you have any suggestions for your colleagues on how to simplify guidelines, or how to teach others about achieving goals — have a look at our competition (above).



## Landmark Studies in Diabetes (continued from Issue 1)

Two major trials — the UKPDS and DCCT — have made a huge impact over the past decade on the way we approach diabetes management. In the first issue of WorldWIDE news we discussed the findings and questions raised by the UKPDS study. Here we review the main findings of the DCCT and the follow-up EDIC study.

### DCCT AND EDIC

#### DCCT study design

The Diabetes Control and Complications Trial (DCCT) was initiated in 1983 in the USA and Canada. Patients who had Type 1 diabetes were divided into two groups according to the degree of eye and kidney disease. One group — the primary prevention group — comprised patients who had had Type 1 diabetes for more than 1 but less than 5 years, had no evidence of retinopathy and had a urinary albumin excretion rate of less than 40 mg/24 hours. The other group — the secondary intervention group — included patients who had had Type 1 diabetes for between 1 and 15 years, had mild-to-moderate nonproliferative retinopathy and had a urinary albumin excretion rate of less than 200 mg/24 hours. Within these groups patients were subsequently randomised to receive either conventional or intensive insulin therapy.

Conventional therapy was one or two insulin injections per day. Patients in this group monitored their blood or urine glucose levels every day and were seen in clinic once every 3 months. Intensive therapy was three or more insulin doses per day by injection or pump. Patients were asked to monitor their blood glucose levels four times a day, visit the clinic once a month and contact the clinic once a week. In addition, they were set clear goals: preprandial glucose levels of 3.9–6.7 mmol/l (70–120 mg/dl) and postprandial levels of less than

10 mmol/l (180 mg/dl). The HbA<sub>1c</sub> target was to achieve a level less than 6.05%.

#### DCCT results

The trial was halted in 1993, a year ahead of schedule, because the benefits of intensive therapy were so apparent. The mean follow-up time was 6.5 years. The main findings were as follows (ref 1):

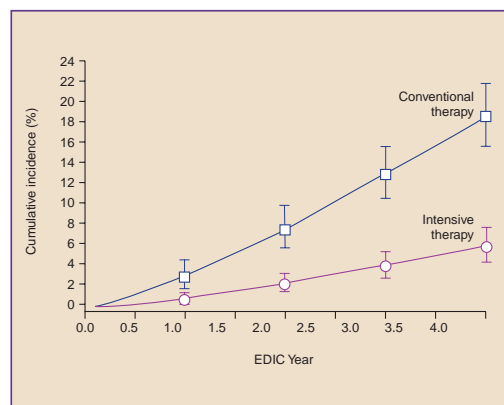
- In the primary prevention group, the risk of developing retinopathy was reduced by 76% in the cohort of patients who received intensive therapy, compared with those who received conventional therapy.
- In the secondary intervention group, the progression of retinopathy was reduced by 54% and the development of proliferative or severe nonproliferative retinopathy was decreased by 47% in the group of intensively treated patients, compared with those who were conventionally treated.
- Overall, the occurrence of microalbuminuria was reduced by 39%, and albuminuria by 54% with intensive therapy.
- Intensive treatment reduced the incidence of clinical neuropathy by 60%.
- The effects of hyperglycaemia increased exponentially over time.

The 'cost' of intensive therapy was a 2- to 3-fold increase in the incidence of severe hypoglycaemia, and an average weight gain of 10 lbs.

#### EDIC

In an observational follow-up study — the Epidemiology of Diabetes Interventions and Complications (EDIC) study (ref 2) — it was shown that the benefits of intensive control had a long-lasting impact. Patients who had been treated with conventional therapy in the DCCT trial were offered intensive therapy and

all patients were treated by their own physicians. After 4 years, the mean HbA<sub>1c</sub> level had dropped from 9.1% to 8.2% in the group of patients previously conventionally treated. In the previously intensively-treated group the mean HbA<sub>1c</sub> value had risen from 7.2% at the end of the DCCT study to 7.9% after 4 years of the EDIC study. However, although the HbA<sub>1c</sub> values for the two groups converged, the risk of progression of retinopathy (Figure 1), microalbuminuria and albuminuria was still higher in the group that had previously been treated with conventional therapy, compared with the group previously treated with intensive therapy.



**Figure 1.** Cumulative incidence of further progression of retinopathy (an increase of at least three steps from the level at the end of the Diabetes Control and Complications Trial [DCCT]) in the former conventional-therapy and intensive-therapy groups.

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### Conclusions — what did the EDIC study add to DCCT?

DCCT showed that intensive glycaemic therapy reduces the risk of development and progression of microvascular complications in Type 1 diabetes. EDIC showed that this benefit persists for at least 4 years. The DCCT and EDIC study groups recommended "the implementation of intensive therapy as early as is safely possible and the maintenance of such therapy for as long as possible."

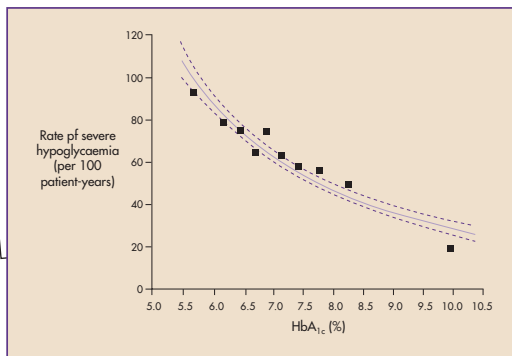
## DCCT and EDIC — Thought-provoking Studies

### A commentary by Dr Paul Van Crombrugge

As a clinician I am keen to apply the management practices found to be beneficial in well-conducted clinical trials. How can we achieve in routine daily clinical practice the excellent long-term control provided by an intensive approach as seen in the DCCT?

- After completion of the DCCT, the follow-up study (EDIC) found that the HbA<sub>1c</sub> level of the intensively-treated group increased significantly to a mean level of 7.9% (ref 2). For how long will the benefit of intensive treatment be maintained? Will the present slow rate of occurrence of complications continue in the long-term follow-up, or will we see a gradual rise to an exponential curve as in the conventional study group?
- A puzzling fact — not discussed in the original publication in the New England Journal of Medicine — is that for the same HbA<sub>1c</sub> level, the prognosis is better with intensive treatment than with conventional treatment (see Figure 2). For example, look at the curves for an HbA<sub>1c</sub> level of 9%. Should we conclude that all patients need intensive treatment? It would be interesting to analyse the available data (postprandial blood glucose levels, nutrition, lifestyle, etc.) in the DCCT, to try to unravel the reason for this remarkable finding.
- The threefold increase in hypoglycaemia is discouraging some patients from choosing intensive treatment of their diabetes. Since the DCCT, many new studies have been conducted on hypoglycaemia and have increased our practical knowledge and skills on this topic (for example, ref 4). The hypoglycaemic risk curve (see Figure 3) has probably shifted somewhat to the left with modern diabetes treatment.
- Our patients frequently ask for some more practical information on the problems associated with hypoglycaemia: is hypoglycaemia a relevant factor in car crashes, in problems in the workplace, in family life, during the practice of hobbies, etc? No information on these important aspects of diabetes management has been published from the DCCT results.
- The DCCT didn't have the power to detect a significant difference in the vascular outcome. Ultimately we will need an answer to this question, knowing the enormous effect of vascular problems on morbidity and mortality.

Paul Van Crombrugge, MD  
OL Vrouwziekenhuis, Aalst, Belgium

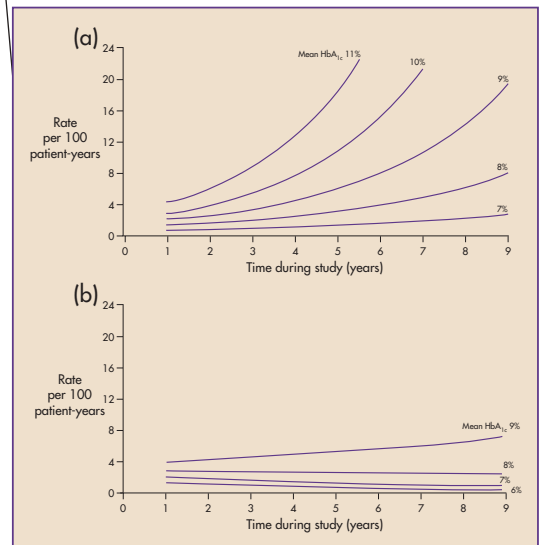


**Figure 3.** Rate of severe hypoglycaemia in the patients receiving intensive therapy, according to their mean HbA<sub>1c</sub> values during the DCCT trial.

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2. The DCCT/EDIC Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342:381-389
3. The DCCT Research Group. The relationship of glycaemic exposure (HbA<sub>1c</sub>) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 1995;44:968-983
4. Bolli G. How to ameliorate the problem of hypoglycaemia in intensive as well as non-intensive treatment of type 1 diabetes. Diabetes Care 1999;22 (Suppl. 2):B43-B52



**Figure 2.** Absolute risk of sustained retinopathy progression as a function of the updated mean HbA<sub>1c</sub> (percentage) during the study and the time of follow-up during the study (years), estimated from absolute risk regression models, (a) conventional treatment group; (b) intensive treatment group.

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## Response by Dr Bernie Zinman

The Diabetes Control and Complications Trial (DCCT) and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study documented conclusively the benefits of improved glycaemic control as measured by HbA<sub>1c</sub> on the development of the long-term microvascular complications of diabetes. In addition, the EDIC component of this study illustrated that despite achieving similar HbA<sub>1c</sub> levels in the two groups, the original intensively treated patients continued to have a more favourable outcome as compared with the conventionally treated patients. This advantage was evident 4 years after the implementation of similar therapies in both treatment groups. This observation underscores the importance of implementing intensive therapy in patients with Type 1 diabetes as soon as possible in order to obtain optimal results. Indeed, it is now our practice in our unit to implement intensive therapy regimens shortly after the diagnosis of Type 1 diabetes. As indicated, another important observation from the analysis of the DCCT results relates to the change in the risk of retinopathy over time in the conventionally and intensively treated patients for similar HbA<sub>1c</sub>. It is interesting that the time-dependent relationship to HbA<sub>1c</sub> is different in the two groups (Figure 2). Precisely why this should remain unanswered, but clearly, the HbA<sub>1c</sub> is not the complete expression for the risk of microvascular complications. Intensive therapy differed in many ways from conventional therapy. Specifically, patients were seen more frequently, were generally on insulin regimens that targeted both meal and basal replacement, and utilised more frequent SMBG, to name just a few.

We concur that since the reporting of the DCCT results, our understanding of how to implement intensive therapy, particularly in the context of patient education and the skills required for insulin dose adjustments in response to changes in nutrient intake and physical exercise, has significantly improved. In addition, the advent of improved insulins has facilitated the attainment of glycaemic control while reducing the risk of severe hypoglycaemia.

Currently, the principal goal of the DCCT/EDIC study is to evaluate the long-term impact of the various therapies on advanced microvascular disease (proliferative retinopathy, nephropathy and advanced neuropathy) as well as macrovascular disease outcomes (carotid intima-medial thickness, myocardial infarction, stroke and peripheral vascular disease). In addition, the study will examine the effect of genotype in the context of complication susceptibility or resistance. In summary, it is anticipated that the DCCT/EDIC cohort will continue to yield interesting observations as to the natural history of Type 1 diabetes and its long-term complications.

Head, Division of Endocrinology, Mount Sinai Hospital, Toronto, Ontario, Canada

Dr Bernie Zinman

## Moving Targets — the Burden of Care

Primary care physician Dr Alistair Emslie-Smith discusses the impact of the key diabetes trials on target setting in diabetes management.

The number of people with diabetes throughout the world is overwhelming medical care. Accordingly, most of the ongoing care and monitoring of people with diabetes worldwide is carried out by health professionals in primary care rather than by their colleagues in secondary care.

Randomised controlled trials such as the UKPDS, The Hypertension Optimisation Trial and the DCCT have, in recent years, clearly demonstrated the benefits in clinical outcome to be gained by the tight control of blood glucose and blood pressure. The result has been the widespread adoption of ambitious targets for control. Recommended target levels are much lower than were considered to be appropriate prior to these studies being reported.

Such targets have a significant impact on workload in primary care. As Figure 1 demonstrates, the more people with diabetes who fail to meet targets, the more will require intensive follow-up. Indeed, most people with diabetes now require longer, more frequent and more complex consultations than was thought necessary 5 years ago, as clinicians seek to help them reach the targets and to effectively address all other cardiovascular risk factors including dyslipidaemia and smoking. The need for a high level of understanding of the complex therapeutic issues involved in optimising overall metabolic control adds to

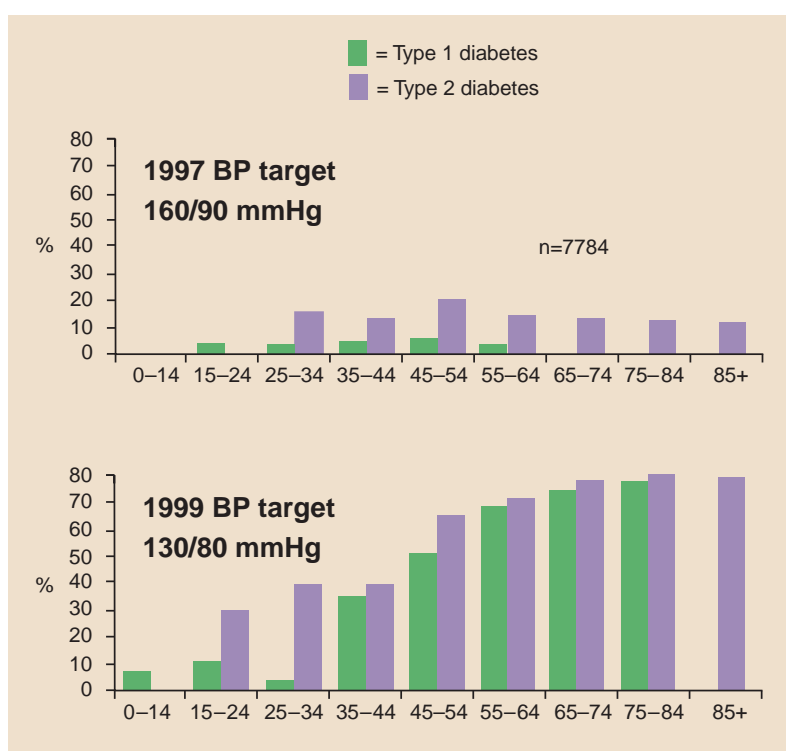
this clinical burden.

The EDIC follow-up study of the DCCT cohort has demonstrated how difficult it can be to help patients both reach and maintain blood glucose at low target levels in normal clinical practice as opposed to the special conditions of a clinical trial. Given this fact, dogged attempts to

reach target levels for all patients may be a less appropriate strategy than aiming for realistically achievable goals tailored to individuals.

**Dr Alistair Emslie-Smith**

General Practitioner  
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**Figure 1.** Population-based, regional figures showing the percentage of all patients with Type 1 and Type 2 diabetes in each 10-year age cohort, who fail to meet the evidence-based targets for blood pressure control using accepted criteria in 1997 (ref 1) (top graph) and 1999 (ref 2) (bottom graph). Personal communication — AD Morris for the DARTS/MEMO Collaboration.

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## Case History

The WorldWIDE Working Group was asked how they would manage the following case — do you have any views on their suggestions?

Patient A is a 49-year-old obese man who does not exercise, is a heavy smoker and a frequent drinker. He is hypertensive and suffers mild chronic obstructive pulmonary disease. He has previously experienced a small myocardial infarction and has osteoarthritis. At presentation he was already being prescribed six different medications. He has a poor record of hospital appointment and clinic attendance and has refused follow-up. Symptoms at presentation were fatigue and 'burning in the feet'. His general practitioner found evidence of peripheral neuropathy (in both lower limbs) but no evidence of retinopathy. A urine test revealed hyperglycaemia, and tests showed a fasting plasma glucose of 12.7 mmol/l (230 mg/dl) and an HbA<sub>1c</sub> of 9.2%. His renal function is normal, with only slight microalbuminuria. He has an atherogenic lipid profile, but his blood pressure is only slightly raised.

The group agreed that patient A needs a clear explanation of the current health risks, life expectancy and possible improvements that can be made. The level of intensity of management and the decision to proceed with treatment ultimately lies with patient A. The primary management strategy would be to encourage patient A to change behaviour, with the initial treatment goal being relief from symptoms and any improvement in glucose levels. Three main issues were discussed:

### IDENTIFICATION OF PROBLEMS

- Obesity is the main health risk: a 5–10% weight loss and cessation of smoking would be of immediate benefit
- The presence of osteoarthritis makes exercise difficult
- Administration of a statin may reduce LDL-cholesterol levels. However, a reduction in excess sugar intake and administration of a fibrate may be needed to reduce triglyceride levels

### PATIENT MOTIVATION

- Finding the issue or goal that motivates patient A is important
- Building a personal relationship and taking adequate time may keep patient A motivated
- Starting and changing therapy may be perceived by patient A as failure
- Anti-obesity drugs will only be effective if patient A is motivated to take them
- Peer-pressure may be beneficial

### TREATMENT STRATEGY

- Drugs should be administered early in the management programme. Patient A should be made aware that changes in medication may be necessary
- Metformin was suggested as the first drug to use. However, renal and liver function tests would need to be assessed
- Self-monitoring of urine glucose levels
- Increased emphasis on the importance of diet and exercise
- Advice from a dietician or referral to a diabetes clinic

Do you have a case history that may be of interest to your colleagues? We would like to hear from you. Although we cannot guarantee that your case history will be discussed, we hope to be able to feature more case histories in future issues of WorldWIDE News and on the WorldWIDE website.

Please contact us: Email: [worldwide@adelphi.co.uk](mailto:worldwide@adelphi.co.uk); Fax: +44 (0)1625 575853

By post: WorldWIDE, Adelphi Communications, Adelphi Mill, Bollington, Macclesfield, Cheshire SK10 5JB, UK

*Don't forget to include your contact details!*

## NEXT ISSUE

Dr Tim Dornan examines the current state of training for medical students and Dr Linda Siminerio discusses development of management plans for people with diabetes.

