The early noughties - Treating to Target

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80 years after the discovery of insulin, the early noughties

The era 80 years after the discovery of insulin, the early noughties, could perhaps be labelled the "Treat to Target" era. The United Kingdom Prospective Diabetes Study (UKPDS), as described elsewhere in this supplement by Professor Rury Holman,[1] showed that whilst the microvascular complications were reduced in the intensive arm, the HbA_{1c} relentlessly rose as beta cells relentlessly failed (Figure 1a) no matter whether patients were in the intensive or conventional treatment arm. The study also showed that the lower the HbA_{1c} the less likely there are to be microvascular events (Figure 1b).

Diabetes care in the UK in the 1990s

Against this background it is worth considering what diabetes care was like in the 1990s when I was a young, newly appointed consultant. The typical referral letter from GP to hospital consultant read: "Glycosuria – please do the needful". The majority of GPs considered diabetes to be a hospital problem and most patients were referred. Diabetologists were relatively few in number in those days, and most also covered endocrinology and general medicine as well as all aspects of diabetes care. The upshot was that diabetes clinics were swamped, and care was very much less than optimum. The approach to treatment of type 2 diabetes (T2DM) was not particularly aggressive (Figure 2). Patients tended to have poor glycaemic control and to remain with poor glycaemic control. Once the patient was reluctantly started on insulin, the approach to dose adjustment was lax and unaggressive, and poor glycaemic control persisted (Figure 3).

As the noughties commenced, things were starting to improve with more and more diabetes centres coming into existence, more consultant diabetologists being appointed, increasing numbers of Diabetes Specialist Nurses and primary care becoming more involved. Nevertheless, reluctance to start insulin remained and when eventually the patient was started on insulin, typically it was on twice-daily insulin mixtures and typically the dose was increased by two units for each dose when the Health Care Professional (HCP) met the patient. The frequency of the adjustments depended on availability of HCPs. Typically, oral hypoglycaemic agents (OHA) were discontinued when insulin was started.

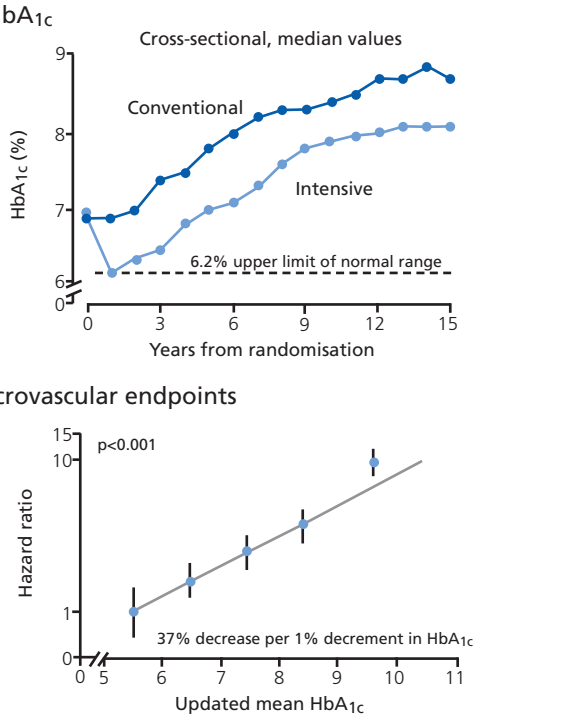

Figure 1. **a.** Change in HbA_{1c} with time in the UKPDS. HbA_{1c} relentlessly deteriorates with time, both for patients in the conventional treatment arm and in the intensive treatment arm; **b**: The hazard ratio for microvascular events at different levels of HbA_{1c} in the UKPDS. As the HbA_{1c} rises the risk of microvascular events increases

Figures 1a and 1b are adapted from the slides shown at the presentation of the UKPDS at the EASD in Barcelona in 1998.

The revolution from Finland

It was at this time that the work of Professor Hannele Yki-Jarvinen, from Finland, came to great prominence and made a considerable difference. The era and her contribution were especially memorable because of the way many of us got to know of her

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Figure 2. An illustration of the typical management of a person with T2DM during the 1990s

- Diet wait a few months
- Reinforce diet wait a few months
- Patient misses appointment - a few more months pass
- Reluctantly add OHA in low dose – wait a few months
- Patient misses appointment - a few more months pass
- Increase the OHA dose by a small amount - a few more months pass
- Reinforce diet - wait a few months
- Increase OHA again - a few more months pass
- Patient misses appointment - a few more months pass
- Increase OHA again - a few more months pass
- Add another OHA - a few more months pass
- Patient misses appointment - a few more months pass
- Increase dose of second OHA .....
- Eventually switch to insulin with reluctance .....

HbA_{1c} remains Persistently elevated whilst weeks turn into months and months turn into years

OHA, oral hypoglycaemic agents

Figure 3. An illustration of a typical approach to insulin treatment in a person with T2DM during the 1990s

- Typically, most patients on twice daily insulin mixtures
- Dose adjustments by health professional from time to time – depending on availability of health professional
- Typically, the health professional would increase each dose by 2 units at each consultation

HbA_{1c} remains Persistently elevated whilst weeks turn into months and months turn into years

work. She would present at national and international meetings with great authority and force. Like an Old Testament prophet preaching to the multitudes, she harangued her cowering audiences about how badly they were managing their patients, how awful that was for those patients, and how they could and should manage them very much better – and that it was easy to do that!

Figure 4 outlines the patient-led Treating to Target (T2T) approach that she recommended.[2-4] Her work showed that the best insulin regime was bedtime long-acting insulin with continuation of metformin.[4,5] She pointed out that if, as in the traditional approach, the insulin dose is increased by 4 IU at each two-monthly consultation with an HCP (NB in reality consultations were far less frequent than two-monthly), an increment of only 24 IU/day could be achieved in one year; whereas if the insulin dose is increased by 2 IU every three days by the patient, an increment of 240 IU/day could be achieved in one year (Figure 4b).[4] Even though T2DM is characterised by insulin resistance, it was clear that patient-led T2T would be able to find the optimum dose for most patients relatively rapidly.

The Treat to Target study

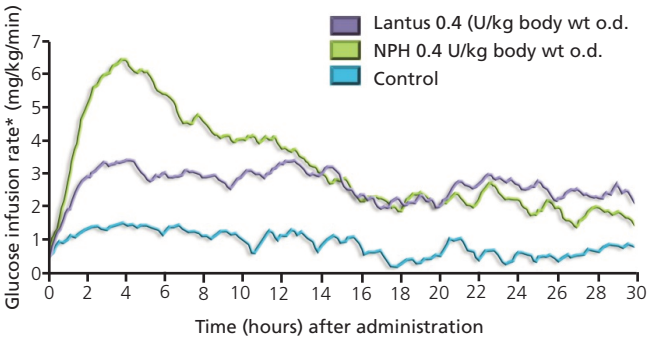
At about this time the first long-acting insulin analogue was launched, insulin glargine. Figure 5 shows the comparison of profile between insulin glargine and NPH insulin, showing a much flatter profile for the former.[6] In the wake of this, the "Treat to Target Study" was undertaken to compare insulin glargine and NPH insulin. The results were presented by Dr Julio Rosenstock and Dr Matthew C Riddle at the EASD in Budapest in 2002,[7,8] and were later published in Diabetes Care.[9] In all, 756 insulin-naïve people with T2DM with inadequate glycaemic control on one or two oral agents (sulphonylureas, metformin, thiazolidinediones) were compared in this 24-week, multicentre, randomized, parallel, open-label trial.[9] The insulin starting dose was 10 IU, and dosage was adjusted weekly by a forced-titration schedule seeking fasting plasma glucose (FPG) ≤5.6 mmol/L (≤100 mg/dL) unless prevented by hypoglycaemia. Figure 6 shows the weekly insulin forced titration algorithm that was used.[9] The study demonstrated that by intention-to-treat analysis, both insulin glargine and NPH insulin achieved good control: mean FPG fell to 6.50 and 6.68 mmol/L and mean HbA_{1c} to 6.96 and 6.97%, respectively.[7-9] 57% and 58% of patients in the insulin glargine and NPH insulin groups, respectively, ended the trial with HbA_{1c} ≤7%.[7-9] More patients treated with insulin glargine achieved HbA_{1c} ≤7.0% without experiencing nocturnal hypoglycaemia (33 vs 27%; $p<0.05$).[7-9] Treatment with insulin glargine caused less nocturnal hypoglycaemia than NPH insulin (532 vs 886 events, $p<0.002$, in 40% vs 49% of subjects; $p<0.01$).[7-9]

Figure 4. **a.** The patient-led Treat to target approach promoted by Professor Yki-Jarvinen. Professor Yki-Jarvinen maintained that when this approach was used, most patients would reach target though it might require a lot of insulin; **b.** A comparison between the potential insulin doses achieved during a year following the conventional insulin dosing approach compared to the patient-led treat to target approach of Professor Yki-Jarvinen

a.
- Start bedtime long-acting insulin 10 units
- Patient measures fasting glucose every morning
- If 3 consecutive readings > 5.5 mmol/L patient increases dose by 2 units

b.
- If the insulin dose is increased by 4 IU at each 2 monthly **consultation with a health professional** an increment of only 24 IU/d could be achieved in 1 year.
- If the insulin dose is increased by 2 IU every 3 days **by the patient** an increment of 240IU/d could be achieved in 1 year.

Figure 5. A comparison between the profiles of insulin glargine (Lantus), that of NPH insulin and normal physiological basal insulin. Trial details: A double-blind study in healthy volunteers over three days. Constant plasma glucose level was 5.0 mmol/L



*Determined as amount of glucose infused to maintain constant plasma glucose levels (hourly mean values) n=15. Figure is adapted from reference 6.

The patient-led algorithm wins

Professor Yki-Jarvinen undertook her own version of an NPH vs glargine T2T study, the LANMET study, using her patient-led titration algorithm (Figure 4a) and found a similar result.[10]

To help resolve the issue as to which T2T insulin titration algorithm was best, the USA HCP-led one (Figure 6) or the Finnish patient-led one (Figure 4a), Professor Melanie Davies undertook the AT.LANTUS study to compare the two algorithms in a head-to-head study.[11] This showed a greater improvement in HbA_{1c} with the patient-driven algorithm but with slightly more hypoglycaemia (Figures 7a and 7b).[11]

Inner-city West Birmingham

I was very inspired by the aforementioned harangues of Professor Yki-Jarvinen and became a disciple of hers. I started using a patient-led T2T approach, adapted from the Finnish protocol, throughout inner-city West Birmingham and undertook an audit.

Figure 6. The treat to target forced titration regimen used in the (Treat to Target study). See references 4-6

Start with 10 IU/day bedtime basal insulin dose and adjust weekly – clinic driven

Self-monitored FPG for two consecutive days with no episodes of severe hypoglycemia or PG ≤4.0 mmol/L (72 mg/dL)	Increase in insulin dose (IU/day)
5.6-6.7 mmol/L (100-120 mg/dL)	2
6.7-7.8 mmol/L (120-140 mg/dL)	4
7.8-10.0 (14-180 mg/dL)	6
>10.0 mmol/L (180 mg/dL)	8

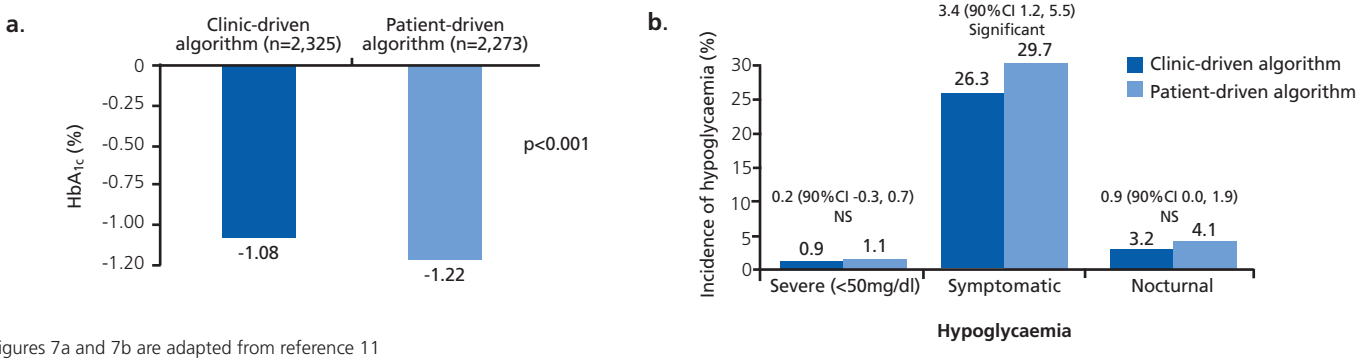
Treat to Target FPG ≤5.6 mmol/L (100 mg/dL)

We were able to conclude that in 'real world' unselected patients in an inner-city area, 41% achieved an HbA_{1c} ≤7%.[12,13] That was a remarkable finding at the time, especially considering how things had been prior to this change of approach (Figures 2 and 3). The learnings from this audit paved the way for the ABCD nationwide audit programme, which started in 2008 and has been going from strength to strength ever since.[14]

Better analogues but patient-driven T2T remains the best way

Since that time, many more agents have become available to be used before insulin is added: these include metformin, sulphonylureas, pioglitazone, gliptins, SGLT2 inhibitors and GLP-1 receptor agonists.[15] If insulin is required, we now have even longer-acting insulin analogues such as insulin degludec and glargine U300,[16] which facilitate improved glycaemic control with even less hypoglycaemia. Nevertheless, if insulin is required, a patient-driven T2T remains, in my opinion, the best way to dose-titrate for many patients.

Figure 7. **a.** In the AT.LANTUS study, significantly greater reduction in HbA_{1c} was achieved with patient-driven than with clinic-driven titration algorithms; **b.** In the AT.LANTUS study, there was no difference in the incidence of severe hypoglycaemia between clinic-driven and patient-driven titration algorithms



Figures 7a and 7b are adapted from reference 11

Key messages

- 80 years after the discovery of insulin, in the early noughties, the "treat to target" approach to insulin dosing led to a revolution in the management of people with T2DM
- Two algorithms emerged, one patient-led and the other clinic-driven. In a head-to-head study, the patient-led algorithm was marginally superior
- The patient-led algorithm was very simple: the patient administers once-daily long-acting insulin at bedtime starting with 10 units. The patient measures fasting glucose every morning and, if three consecutive readings are >5.5 mmol/L the patient increases the dose by 2 units
- The approach allows the patient to find their ideal basal insulin dose much more rapidly than previously used methods. When this approach was introduced in inner-city West Birmingham, 41% of patients achieved a HbA_{1c} ≤7%

HbA_{1c} or Time-in-Range?

As we move into the future in 2022, the question arises as to what is the best way to assess glycaemic control. It is noteworthy that in a head-to-head randomised controlled trial of insulin glargine u300 and insulin degludec,[16] Time-in-Range rather than HbA_{1c} as primary end point was used to assess glycaemic control. It would make an interesting subject for an ABCD debate: "This house supports replacing HbA_{1c} with Time-in-Range as the optimum way to assess glycaemic control from now on".

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