Simplicity cannot control HbA_{1c}: Interim results of the 4-T trial

In this section, a panel of multidisciplinary team members give their opinions on a recently published diabetes paper. In this issue, the debate focuses on the results of the first year of the Treating to Target in Type 2 Diabetes (4-T) trial.

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Results from the first year of the 3-year 4-T study were recently presented at the European Association for the Study of Diabetes annual conference and published in the *New England Journal of Medicine*. 4-T addresses important and difficult issues at the core of the treatment of type 2 diabetes. In individuals with poor glycaemic control on maximally tolerated doses of oral hypoglycaemic agents, three insulin regimens were compared as add-on therapy to the oral medications: basal insulin detemir, prandial insulin aspart and biphasic insulin aspart. Key issues relevant to this study include: when and how to use insulin in type 2 diabetes; how to titrate the dose; the role of patient education; and effects on the long-term progression of the condition. Without solving any of these questions, the 4-T 1-year results have provided useful information.

Each insulin regimen led to improvements in mean HbA_{1c}, although the improvements overall were modest, with only a small minority of participants reaching the target of 6.5 %. In comparison with similar published studies, the insulin doses used in 4-T were lower: 0.49–0.61 U/kg/day, compared with studies that recorded greater HbA_{1c} reductions where up to 0.8 U/kg/day were used. Taken together, the effects of each insulin preparation in the 4-T study at 1 year were exactly as one would expect with our existing physiology knowledge. This included basal insulin resulting in better control of fasting plasma glucose, but poor control of post-prandial glucose. Additionally, basal insulin was associated with the lowest incidence of hypoglycaemia. Prandial insulin dosing was associated with better post-prandial glucose control, but greater weight gain and a greater incidence of hypoglycaemia. Biphasic insulin had effects intermediate between the basal and prandial regimens and was also associated with more weight gain and hypoglycaemia than basal insulin.

Progression of type 2 diabetes involves complex pathophysiology and is not simply a matter of failing insulin secretion. Insulin resistance is the other key variable that adds to the challenge of metabolic control. No insulin regimen, per se, is sufficient to treat type 2 diabetes outside of concurrent efforts to minimise insulin resistance by appropriate diet, physical exercise and medication. Most diabetologists would agree that a full basal–bolus insulin regimen is the closest to ideal in both type 1 and type 2 diabetes. The active titration of any partial regimen, either basal, prandial, or pre-mixed, as in the first year of 4-T, involves compromising with regards to the risks of hypoglycaemia and weight gain. Better reductions in HbA_{1c} could no doubt have been achieved in the first year of 4-T by more aggressive and more frequent insulin dose titration, but this would have led to proportionate increases in weight and rates of hypoglycaemia.

4-T is designed to answer some of the important questions posed by its first year results. In years 2 and 3, participants' regimens will be intensified so that many more will reach a full basal–bolus regimen. When the study is completed, it will provide a key evidence base for the intensification of insulin therapy in 'typical' people with type 2 diabetes.

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Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes

Holman RR, Thorne KI, Farmer AJ et al (2007) *NEJM* [Epub ahead of print]

Control varies across more simple insulin regimens

1 This paper reports on the data from the first year of the Treating to Target in Type 2 Diabetes (4-T) trial.

2 The 4-T trial is a 3-year, open-label, multicentre, randomised, controlled clinical trial examining the safety and efficacy of adding analogue insulin (biphasic, prandial or basal) to the treatment regimen of people with type 2 diabetes on an oral treatment regimen of maximally tolerated doses of metformin and sulphonylurea for at least 4 months (or one agent if one was not tolerated).

3 Recruitment occurred between November 1 2004 and July 31 2006. Inclusion criteria were: over 18 years of age; at least 12 months duration of diabetes; HbA_{1c} 7.0–10.0 %; insulin naïve; and BMI ≤ 40 kg/m^2. Thiazolidinedione or triple oral therapy in the previous 6 months were part of the exclusion criteria.

4 Of the 936 individuals who underwent screening, 708 met the inclusion criteria and were randomly assigned to either biphasic insulin aspart bd (235), prandial insulin aspart tds (239) or basal insulin detemir regimens od unless required bd (234).

5 The primary outcome for this paper was HbA_{1c} level 1 year from baseline. The secondary outcomes included: the

proportion of individuals with an $HbA_{1c} \leq 6.5\%$; the proportion of individuals with an $HbA_{1c} \leq 6.5\%$ without hypoglycaemia during weeks 48–52; and weight gain.

6 Visits were scheduled at 2, 6, 12, 24, 38 and 52 weeks, with interim telephone contact. For each visit and telephone contact, individuals were asked to obtain three capillary glucose profiles. All used the same model of blood glucose meter. These were performed before breakfast and the evening meal for those in the biphasic and basal groups and 2 hours after meals and at bedtime in the prandial group.

7 The authors found that after 1 year, the maximum reduction in mean HbA_{1c} occurred at 24 weeks and stabilised therafter. Mean HbA_{1c} levels were similar in the biphasic group (7.3 %) and the prandial group (7.2 %; $P=0.08$) but higher in the basal group compared with both other groups (7.6 %; $P<0.001$).

8 The proportion of people with an $HbA_{1c} \leq 6.5\%$ in each group were as follows: biphasic: 17.0 %; prandial: 23.9 %; and basal: 8.1 % ($P<0.001$ for all comparisons). There were an average of 5.7 hypoglycaemic events per person per year in the biphasic group, 12.0 in the prandial group and 2.3 in the basal group.

9 Weight gain was observed on all regimens, with the least being in the basal group (+1.9 kg), followed by the biphasic group (+4.7 kg) and the greatest weight gain was observed in the prandial group (+5.7 kg; $P<0.001$).

10 Insulin doses were escalated steadily throughout the study period and at 52 weeks, the doses were similar in the biphasic and basal groups but higher in the prandial group.

11 The authors conclude that the addition of insulin to metformin and sulphonylurea therapy in type 2 diabetes is associated with clinically relevant and sustainable reductions in HbA_{1c}, but that many people may need more than one type of insulin to achieve their target blood glucose levels. The final 2 years of the trial will examine the use of complex insulin regimens in people with type 2 diabetes.

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This study raises concerns about application of results to clinical practice. It does not reflect current clinical judgement inasmuch as people were put randomly into treatment arms, instead of a specific treatment arm decided upon after an assessment of lifestyle, capabilities and preference. This assessment is normal clinical practice and takes place before people start an insulin regimen, or when one is changed. As this type of assessment did not appear to take place, one could question the appropriateness of the regimen assigned to each individual, which in turn could affect adherence and, potentially, the clinical outcomes and benefits to each person. Thus, these trial results may not reflect what could happen in the real world, although we do acknowledge why the study was structured in the way it was.

In clinical practice, the key is the individual we are working with: their wishes, their fears, their lifestyle. Clearly, one regimen does not fit all. A quality-of-life questionnaire is alluded to in the full article, but we could not find a copy to review, which would have added to the article and our knowledge.

The biggest barriers to tight control in this study were hypoglycaemia and weight gain. There was variation in the incidence rates of hypoglycaemic events and weight gain according to which regimen was used: more episodes of hypoglycaemia and greater weight gain were observed with prandial regimens while the smallest gain in weight and lowest frequency of hypos were recorded with basal regimens. This is useful information when discussing regimens with people with type 2 diabetes. As clinicians, we should acknowledge these differences and the cost to the individual of tight control. Neither hypoglycaemia nor weight gain would be seen as desirable by those using insulin and, in some cases, may cause prejudices in their job or social life.

HbA_{1c} is often used as the gold standard when any diabetes regimen is assessed. However, in practice, while this is a useful guide, it is not the be all and end all. Often, an elevated HbA_{1c} can hide frequent hypoglycaemia and rebound hyperglycaemia. In such cases, the appropriate action would be administering less insulin or changing regimens rather than increasing insulin doses to reduce HbA_{1c}, which can often happen.

Different regimens were evaluated in this study on all three parameters (episodes of hypoglycaemia, weight change and HbA_{1c}), which gives valuable and useful information. The continuation of oral medication with insulin is also useful. It is not our experience to continue with a sulphonylurea when insulin is initiated, only to continue with metformin and, more recently, to re-introduce pioglitazone if metformin cannot be tolerated. It would be clinically useful for future studies to evaluate the addition of pioglitazone to insulin treatment as, in our experience, insulin doses have significantly reduced which has enabled weight stabilisation or reduction.

A final note on this study is to point out that regular titration occurred throughout, and it may be that this regular contact and review maximised the outcomes as much as the regimen itself.

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Is there a paper that you would like to see debated in these pages? Or perhaps you want to join the debate. If so, get in touch with the journal using the contact details on the right.

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The digest gives a good synopsis of the results of the trial. In keeping with the style of these debates, I will attempt to be controversial with my review.

I can already hear the questions that will be asked of these data:

- Do they support the early, or even second-line, therapy with insulin in line with the EASD/ADA algorithm for type 2 diabetes? This question will be fuelled by the controversy of glitazones.
- Do they give insights into the question of whether baseline or postprandial glucose control is the most appropriate treatment target?
- Do they point us in the direction of a particular insulin regimen?
- Do they give insights into the choice of basal insulins?

The answers to these questions are still unfortunately and unhelpfully ambiguous. However, the 1-year data do show that insulin can lower blood glucose, but given there was an 'aggressive' escalation protocol, it is disappointing that the HbA_{1c} reduction was 1–1.3 %, which, although significant, is a value that might have been achieved with any additional agent added to a diabetes treatment regimen. Furthermore, the achieved values for HbA_{1c} of 7.2–7.6 % would straddle the line of acceptability, using the GMS guidelines, and have fallen well short if considering the aspirational JBS-2 targets. Indeed, if one looks at the 8–24 % rate of achievement of an HbA_{1c} of 6.5 % – soon to be considered the one and only target – it would appear, without needing to consider the lack of hard outcome data for insulin, that the case for use of insulin in the early treatment of people with type 2 diabetes (in the regimens described) is far from proven.

The question of baseline versus postprandial control is more difficult to unravel from the data. It would appear that post-prandial control, with pre-meal fast-acting insulin does produce marginal improvements in HbA_{1c} over basal insulin alone (7.2 % versus 7.6 %) but that the proportion achieving an HbA_{1c} below 6.5 % using this fast-acting regimen is far more impressive (23.9% versus 8.1%). These data suggest that not everyone is served equally well by this regimen, although some individuals obviously do very well (23.9 %), the implication being that others fair far worse (the only explanation for the 3-fold greater achievement of low HbA_{1c} while the average HbA_{1c} remains high). A sub-group analysis of those who do well versus those who do not has not been presented.

Additionally, side effects are objectively greater in the prandial-treated group, with higher rates of hypoglycaemia (12 versus 2 %) and greater weight gain (5.7 versus 1.9 kg). The distribution of these side effects is not offered so it is not possible to make comments about whether or not those who do well (who report a low HbA_{1c} at 1 year) have high or low side effect rates. This is of course very important in that it may define groups of individuals who would or would not benefit from this treatment design. As might be expected, the group on fixed mixed regimens seemed to steer an intermediate course between fast alone or basal alone for HbA_{1c}, achievement of HbA_{1c} below 6.5 % and complication rates.

The inference from these data is that a mixture of basal and post-prandial regimens, more aggressively administered, may give a better regimen for a majority of people with type 2 diabetes and may provide an acceptable achievement of HbA_{1c} targets. The validation of this statement will require more data, which may be available after the next phase of this trial.

Many will consider the major weakness of this study is the choice of basal insulin. Insulin detemir is not the best nor widest-used basal insulin and this adds to confusion about the generalisation of the debate. As with a number of recent publications, the use of detemir on a once- or twice-daily (as required) regimen destroys the premise that comparisons are being made with consistent basal insulin delivery and baseline glucose suppression. Conclusions on the basal-versus-prandial debate are therefore impossible. The inclusion of an insulin glargine arm would have been very helpful and has to be seen as an opportunity lost.

In summary, the study probably tells us the following:

- Insulin is not the magic bullet to perfect diabetic control.
- None of the regimens tested give acceptable long-term control to a majority of individuals.
- For some people with type 2 diabetes, post-prandial control may be very effective (pending further sub-group analysis of complications).
- A real test of the effectiveness of basal insulin therapy versus prandial insulin is not offered.
- In terms of insulin treatment, the rapid escalation to multi-dosing may be the way forward but the results of the next phase of the trial will be required.

On the basis of this study and at this time, insulin will not be my immediate second-line treatment for my patients with type 2 diabetes.

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