Complex messages from recent trials: What *are* the key messages?

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Successful management of diabetes has several layers of complexity, from diagnostic uncertainty, through complicated management decisions, to identifying how to motivate and empower individual patients to make lifestyle choices and adhere to medication. Ever since the UKPDS reported that multifactorial interventions have a favourable impact on mortality for people with type 2 diabetes (UKPDS Group, 1998), there has been an interest in how treatment options can be maximized to deliver a reduction in the morbidity and mortality associated with the complications of diabetes. Recently, three major trials have reported conflicting findings around the central question of whether or not intensive, multifactorial intervention improves outcomes in type 2 diabetes (Steno-2, ACCORD [Action to Control Cardiovascular Risk in Diabetes] and ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation]). In addition, the DESMOND programme recently reported an improvement in some important outcomes but not in blood glucose control (Davies et al, 2008). This editorial considers these new evidence and the potential impact on the management strategies for primary care teams.

The Steno-2 study addressed an important question, partially also addressed by the UKPDS: 'Do multifactorial interventions have an impact on mortality in type 2 diabetes?' (Gaede et al, 1999). Although Steno-2 was conducted in the Danish secondary care setting, it involved a small cohort of typical, high risk, primary care patients, and 13-year follow up data were recently published (Gaede et al, 2008). Gratifyingly, it showed that multifactorial interventions, tight glucose regulation, use of renin–angiotensin system blockers, aspirin, and lipid-lowering agents are all important and worthwhile interventions. The investigators highlighted how poorly the non-intensive intervention group fared, 50% of whom were dead at the 13-year follow-up point. In the UK, many of these interventions are already encouraged through the payment-by-results system of the Quality and Outcomes Framework.

Two other diabetes trials have generated controversy, rather than help answer key questions. The blood glucose lowering part of the ACCORD trial, in patients with type 2 diabetes at especially high risk of heart disease, was stopped prematurely because of a higher mortality rate in the patients in the intensive arm versus the standard arm. The trial was a study of strategy, rather than specific therapies, and many glucose-lowering drugs were used to reach glycaemic targets. Investigators were able to rule out hypoglycaemia, effects of any single oral drug such as rosiglitazone, or a combination of drugs as the cause for the increased mortality. However, insulin was used to pursue the aggressive targets, and this seems to confound the findings of the DIGAMI-1 study which supported intensive insulin use in patients with ischaemic heart disease and diabetes (Malmberg, 2004) and did not find this higher mortality rate.

The ACCORD trial has similarities to the ADVANCE trial, which was designed to answer two questions in patients with type 2 diabetes. Firstly: does intensive blood pressure lowering treatment improve outcomes? And secondly: does intensive glycaemic control improve outcomes? The blood pressure arm reported positively last year supporting the data from the Steno-2 study (ADVANCE trial investigators, 2007). The intensive glycaemic control arm has yet to report but preliminary data do not support the ACCORD trial findings.

The intensive glycaemic control arms in these studies aimed for HbA_{1c} levels well below 7.0%; it is unlikely that primary care teams will want to pursue such aggressive targets. However, it

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is interesting to reflect that we still do not yet know the full implications of aggressive blood glucose management, and the effects of intensive insulin use on patients at high risk of ischaemic heart disease. It has lead commentators to speculate that using insulin to counter insulin resistance aggressively in type 2 diabetes may not be a safe strategy (Unger, 2008).

It is not clear what structured education the participants had in, for example, the Steno-2 study, but the recent results from the DESMOND randomised controlled trial have made teams reflect on how structured education programmes facilitate achievement of HbA_{1c} targets (Davies et al, 2008). Both the DAFNE programme for people with type 1 diabetes, and the X-PERT programme for people with type 2 diabetes confirmed the benefits of glycaemic control in encouraging self management (DAFNE Study Group, 2002; Deakin et al, 2006; respectively). The DESMOND randomised controlled trial performed across 13 primary care centres over a 1-year period, resulted in improvements in outcomes such as weight loss and smoking cessation, but, compared with the control group, no improvement in HbA_{1c} was observed.

The team carrying out this research reflected that their study had been done in an NHS culture of high recording of patient data and aggressive and effective targeting of outcome goals, and that this may explain the lack of difference in HbA_{1c} targets in the two study arms. It may be that structured education has less impact on this. While this reflects well on contemporary primary diabetes care and this study is just the sort of research we need in primary diabetes care, the diabetes national service frameworks have encouraged patient education and empowerment for everyone with diabetes.

In summary, the DESMOND randomised controlled trial underlines that it is important our patients feel empowered by continuous education, and that softer outcomes are not forgotten in the rush to pursue aggressive targets. Moreover, the Steno-2, ACCORD and ADVANCE trials suggest that pragmatic targets of HbA_{1c} may be the most sensible option for most of our patients with type 2 diabetes in the current climate: while aggressive multifactorial interventions targeted at cardiovascular risk remain paramount. ■

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