Optimising the care of patients with type 2 diabetes and cardiovascular disease:

Translating evidence-based medicine into practice

This report is from a conference that took place on 23 May 2007 at The Odeon Cinema, The Printworks, Manchester. The event was supported by an educational grant from Takeda UK.

Introduction

People with type 2 diabetes have a much higher incidence of cardiovascular disease (CVD) than the general population – some studies have suggested that this risk is as much as four times greater. CV complications are often present at diagnosis of type 2 diabetes, reflecting the abnormal metabolic parameters that have pre-existed the emergence of the condition. This meeting took place to help address the management of this population in primary care, with a strong focus on evidence-based practice. Practice-based commissioning and what it could mean to everyday practice was also discussed. The meeting was supported by an educational grant from Takeda UK.

'Who *should* look after the person with diabetes? Wouldn't it be better to prevent it? Has the Quality and Outcomes Framework (QOF) been a good thing? How are general practices doing with regard to the QOF? What about patient empowerment? *And*, what of all of the politics?', began Eugene Hughes (GP, Isle of Wight; and Chair of this meeting). Dr Hughes was highlighting the many aspects of diabetes care that must be considered by all healthcare professionals when managing the person with diabetes: 'The answers to these [questions] are not necessarily the main point, rather that we constantly consider them. It is hoped that this meeting will go some way to answering the second question, at least!'

Several studies have had as their primary end point the prevention of type 2 diabetes or, more strictly, slowing the progression of pre-diabetes and therefore delaying the condition's diagnosis. Some were discussed and are summarised below.

Preventing diabetes using lifestyle interventions

The Finnish Diabetes Prevention Study and the US-based Diabetes Prevention Program both demonstrated a 58% reduction in the risk of developing diabetes (respectively: Tuomilehto et al, 2001; Diabetes Prevention Program Research Group, 2002).

Tuomilehto and colleagues' (2001) study included 522 overweight people (350 women; mean age: 55 years; mean BMI: 31 kg/m^2) with impaired glucose tolerance. All were randomised to receive advice and counselling aimed at weight loss – this included advice on saturated fat and fibre intake, and physical activity levels – or no intervention. The study participants were followed up for a mean of 3.2 years. The intervention group had a significantly lower risk of developing diabetes: 58% ($P<0.001$).

A follow-up to Tuomilehto et al's study published recently reported that those in the intervention group continued to be at a lower risk of developing diabetes after

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Eugene Hughes

the counselling was stopped (Lindstrom et al, 2006).

The US Diabetes Prevention Program had a larger study population: 3234 (Diabetes Prevention Program Research Group, 2002). All had raised fasting and postprandial plasma glucose levels. The participants were randomised to one of three groups: placebo, metformin or lifestyle intervention. The lifestyle intervention group had goals of at least 7% reduction in weight and 150 minutes of physical activity a week. Compared with placebo, the lifestyle and metformin groups had a 58% and a 31% lower incidence of diabetes at study end (mean follow up was 2.8 years).

Preventing diabetes using pharmacotherapy

More recently, the DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) trial demonstrated that rosiglitazone is able to lower the incidence of diabetes in a high-risk population. A total of 5269 people with impaired fasting glucose, impaired glucose tolerance or both, and aged over 30, years were randomised to receive rosiglitazone or placebo. Follow up was for a median of 3 years. Diabetes was diagnosed at study end in 11.6% of the intervention group and 26.0% of the placebo (*P* for difference <0.0001; The DREAM Trial Investigators, 2006).

Evidence-based prevention of CV disease

Haffner et al (1998) showed that people with diabetes have a similar risk of CV events to those without diabetes but with previous myocardial infarction.

Turner et al (1998) demonstrated that the following five factors are potentially modifiable risk factors for coronary artery disease.

- Raised concentrations of LDL cholesterol.
- Lowered concentrations of HDL cholesterol.
- Hypertension.
- Hyperglycaemia.
- Smoking.

This study also showed that myocardial infarction is associated with the same risk factors, except that it is associated with raised diastolic blood pressure rather than systolic. 'It is therefore imperative that CV risk is reduced in people with diabetes,' stated Miles Fisher.

There have been studies conducted to assess the effect of pharmacotherapy on risk modification (some of which were discussed at the meeting and will be elaborated on herein); however, there is a dearth of evidence for the long-term effect of lifestyle intervention on CV risk modification. The outcomes of the Look AHEAD (Action for HEAlth in Diabetes) study are eagerly awaited.

The Look AHEAD study

The US-based Look AHEAD study began in 2001 and is scheduled to complete in 2012. Its two main goals are a ≥7% weight loss from baseline and increasing moderately intense physical activity to ≥175 minutes a week (The Look AHEAD Research Group, 2006).

This multicentre, randomised controlled trial has randomised 5145 participants to a lifestyle intervention or an enhanced usual care condition (that is, diabetes support and education). In order to ensure as many participants as possible adhere to their suggested lifestyle regimens, the study research group have devised an algorithm. This has three levels of care and support, with the third being the most intensive with regard to healthcare and patient input, and also the most costly.

Intensifying antidiabetic therapy

Data from such pivotal trials as the DCCT and the UKPDS were used to inform the formation of an algorithm that advocates intensifying any and all therapies for people with type 2 diabetes (Nathan et al, 2006).

Pharmacotherapy of diabetes

Recent 'landmark' trials in people with diabetes with an aim of reducing specific risk factors have been conducted and published. These include:

- Improving hyperglycaemia, PROactive (Dormandy et

al, 2005).
- Improving dyslipidaemia, TNT (LaRosa et al, 2005).
- Improving hypertension, ASCOT (Dahlof et al, 2005; Poulter et al, 2005).

These trials are discussed in more detail below.

PROactive study

Below is a brief summary of this trial as discussed at this meeting.

- This was a prospective, multicentre, randomised controlled trial in which 5238 people with type 2 diabetes and evidence of established macrovascular disease were randomised to receive either pioglitazone (maximum of 45 mg/day, titrated up from 15 mg/day; n = 2605) or placebo (n = 2633) in addition to their existing medications.
- The study's primary end point was the time from randomisation to a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome plus endovascular and surgical interventions.
- The main secondary end point was the time to the composite of all-cause mortality, stroke or non-fatal myocardial infarction.
- The proportion of participants reaching the composite primary end point was lower at the end of the study in the pioglitazone group (n = 514/2605) compared with placebo (n = 572/2633), but failed to reach statistical significance (hazard ratio [HR]: 0.90; 95 % confidence interval [CI]: 0.80–1.02; *P* = 0.095).
- The proportion of patients reaching the main composite secondary end point was also lower in the pioglitazone group (n = 301/2605) compared with the placebo group (n = 358/2633). In this case, the difference was statistically significant (HR: 0.84; 95 % CI: 0.72–0.98; *P* = 0.027).
- At the start of the study, two-thirds of patients were not using insulin. During the course of the trial, 11 % of the non-insulin users treated with pioglitazone (n = 183/1741) began to use insulin compared with 21 % of the non-insulin users in the placebo group (n = 362/1737; HR: 0.47; 95 % CI: 0.39–0.56; *P* < 0.0001).
- The authors concluded that in patients with type 2 diabetes who are at high risk of CV events, pioglitazone treatment can reduce the composite of all-cause mortality, non-fatal myocardial infarction and stroke. Furthermore, pioglitazone treatment reduces the need for insulin in addition to other glucose-lowering regimens.

TNT

The TNT (Treating to New Targets) trial hypothesised that more intensive lowering of cholesterol with atorvastatin 80 mg versus 10 mg would further reduce CV events. A total of 10 001 participants with previous CVD were randomised to atorvastatin 80 mg or 10 mg, and were followed for a median of 4.9 years.

During the trial, mean LDL cholesterol was 2.0 mmol/l and 2.6 mmol/l for the 80 mg and 10 mg groups, respectively. A significant reduction in major CV events (the primary end point) by 22 % was observed (*P* < 0.001).

Shepherd et al (2006) analysed the TNT data further with respect to people with type 2 diabetes. They found that in 1501 people (15 % of whom had a history of CVD), there was a 25 % reduction in major CV events in the atorvastatin 80 mg group (*P* = 0.026).

ASCOT

The Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT–BPLA) compared the newer drug combination of amlodipine and perindopril with the older regimen of atenolol with bendroflumethiazide in people with hypertension who had at least three other CV risk factors.

The primary end point was non-fatal myocardial infarction and fatal CHD. Of the 19 257 participants, 5145 had diabetes, hypertension and other CV risk factors. Mean follow up was 5.5 years.

No statistical significance

Miles Fisher

Gwen Hall

Azhar Farooqi, OBE

was attained in the primary end point. However, the secondary end points did reach significance, including: total CV events and procedures were reduced by 16% ($P<0.0001$); and CV mortality was reduced by 24% ($P=0.0010$). The incidence of diabetes, a tertiary end point, was significantly reduced by 30% ($P<0.0001$).

Miles Fisher concluded that there is much evidence for a variety of approaches to reducing CV risk in people with diabetes. These include: the UKPDS and PROactive trials for hypoglycaemic therapy, especially metformin and pioglitazone; ASCOT and TNT for reduction of hypertension and dyslipidaemia; and antiplatelet therapy, which, owing to time constraints, was not elaborated upon at this meeting.

'True trial evidence for lifestyle changes and their effect on risk reduction is lacking, although its benefits are well recognised. It is hoped that the Look AHEAD study will provide data to help prove what is already known', Gwen Hall concluded. 'However, the ultimate aim of all healthcare professionals should be to prevent the onset of diabetes.'

Practice-based commissioning: What it means for general practice

Azhar Farooqi (OBE and GP, Leicester) discussed Practice-Based Commissioning in the final presentation of the conference. He described it as 'determining how the healthcare budget is used, and it is expected that it results in a "good deal" for the taxpayer and the patient'.

As a minimum, commissioning should involve a needs assessment, a specification of how to meet the need, how the practice intends to procure services to deliver the specified needs, and proactive monitoring. There are a number of tools available for the healthcare professional to aid them in commissioning services. Perhaps the foremost is the *Diabetes Commissioning Toolkit* (DoH, 2006).

This toolkit was led by the Primary Care Diabetes Society (PCDS) in partnership with a number of other organisations:

- ABCD (Association of British Clinical Diabetologists)
- DoH (Department of Health)
- Diabetes UK
- NDST (National Diabetes Support Team)
- YHPHO (the Yorkshire and Humber Public Health Observatory).

The toolkit is aimed at NHS commissioners of diabetes services at the PCT and primary care levels, and can be used by diabetes networks.

The toolkit is currently undergoing a pilot implementation in three NHS trusts:

- Manchester (North Locality) and Bury PCT and Pennine Acute Trust
- Leicester
- Hereford.

This pilot project aims to support health communities to redesign diabetes services, inform the development of the toolkit in order that future versions are fit for purpose, and to gather information on how the toolkit can be used in 'real life'.

The trial sites are all different from each other, with differing issues and problems. Presently, needs assessments have been carried out at each site, service gaps and deficits have been identified and services have been specified. Further workshops are planned as each site is at a different stage to the others.

In conclusion, Eugene Hughes, stated that: 'We [the meeting faculty] hope that we have provided you with enough food for thought. We hope that you will go away and consider how current and future evidence can inform the development of diabetes services for your locality.' ■

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