Statins, safety studies and sharing good practice

Pam Brown
GP in Swansea

The diabetes indicators in the Clinical Commissioning Group (CCG) Improvement and Assessment Framework were amongst those published on the My NHS site in early September along with the indicators on dementia and learning disabilities. The media picked up that out of 209 CCGs in England, 71% were rated as needing improvement in helping people manage their diabetes. CCGs were rated on the numbers achieving the NICE-recommended treatment targets each year, and the numbers who attend structured education within 12 months after diagnosis. CCGs were categorised as "Top performing" (25/209; 12%), "Performing well" (34/209, 16%), "Needs improvement" and "Greatest need for improvement" on their diabetes care. Around 40 CCGs that had less than 25% of practices participating in the National Diabetes Audit did not have their scores published and were automatically placed in the category "Greatest need for improvement – poor participation". Numbers attending structured education within the first year after diagnosis ranged from 0% (two CCGs) to 21.8%, while top-achieving CCGs recorded up to 48% of patients achieving all the NICE-recommended targets. CCGs were also given an overall 2015 year-end rating from "Outstanding" (10, 5%), "Good" (82, 39%), "Requires improvement" (91, 44%), and "Inadequate" (26, 12%).

New data confirm old beliefs

As we read new clinical papers, we often have a sense of déjà vu, as they seem to confirm things we thought had been proven years before. A recently published, large observational study (Hine et al, 2016) of 650 000 adults using the Royal College of General Practitioners' Research and Surveillance database confirms what I certainly believed – that people with diabetes are more prone to infections, particularly fungal and yeast infections, and that poorer glycaemic control increases this risk. Surprisingly, the authors stated that this had not been investigated in large studies previously as most had failed to document pre-infection glucose control. People with poor glycaemic control (defined as HbA_{1c} >69 mmol/mol [8.5%] in this study) had more bacterial and fungal infections than those with good control, and those with type 2 diabetes had more infections of all kinds apart from herpes simplex, than those without diabetes. Genital and perineal infections, skin and soft tissue infections and urinary tract infections (UTIs) showed strongly a positive correlation with type 2 diabetes. Those with diabetes did not suffer more viral upper respiratory tract infections, influenza illnesses or gut infections than those without diabetes.

The authors postulate that several factors are likely to contribute to the increased risk of infections, including: hyperglycaemia resulting in impaired immune pathways; neuropathic bladder changes resulting in increased catheterisation and more UTIs; foot ulcers often becoming infected; and sodium–glucose cotransporter 2 inhibitor treatment increasing risk of mycotic infections. The authors suggest that those with diabetes may also be more likely to consult than those without diabetes when they develop infections, although the lack of documented increased risk of most viral infections amongst those with type 2 diabetes would argue against this having a significant contribution.

Evidence for efficacy and safety of statin therapy

Although we know that statin therapy saves lives, encouraging patients to share our belief and take the drugs takes time and effort. A *Lancet* review of statin therapy (Collins et al, 2016) published online in September revisits the evidence from both randomised controlled trials (RCTs) and observational studies, quantifying risk and benefits and aiming to help healthcare professionals, patients and the general public make informed decisions about therapy.

The authors conclude that large-scale evidence from RCTs demonstrates that statin therapy reduces the relative risk of major vascular events

by around 25% for each 1 mmol/L reduction in LDL-cholesterol therapy during each year of treatment, after the first year.

Although absolute benefit depends on initial absolute risk, at a population level, lowering LDL-cholesterol by 2 mmol/L for 5 years in 10 000 people would typically prevent major cardiovascular events in 1000 people (10% absolute benefit) when used for secondary prevention and 500 events if used for primary prevention. Larger absolute benefits would accrue with longer therapy.

Serious adverse events that may occur are myopathy (muscle pain and weakness combined with raised creatine kinase enzymes), new type 2 diabetes and possibly haemorrhagic stroke. Five years' treatment of 10 000 people would typically result in only five cases of myopathy, 50–100 new cases of type 2 diabetes and five to ten haemorrhagic strokes, but these adverse effects have already been incorporated in the estimates of benefits. In addition, symptomatic adverse events such as muscle pain without enzyme changes occur in an additional 50–100 patients for each 10 000 people treated for 5 years – an absolute harm of 0.5–1%. The authors contend that most of these are misattributed to the statin. An interesting perspective from the review is that any myopathy caused is likely to be rapidly reversible on stopping statin therapy, whereas the major cardiovascular events and deaths potentially preventable by treatment are obviously irreversible if allowed to occur.

Some of these adverse event rates, such as muscle pain without enzyme changes, seem lower than we perceive our patients' experience and lower than has been suggested in commentaries in reputable journals previously (Redberg and Katz, 2012). The review shares thought-provoking data on the potential impact of adverse media coverage resulting in people choosing not to take statins. For example, in the European SHARE (Survey of Health, Ageing and Retirement in Europe) study (Borsch-Supan et al, 2013) only 42% of those over 50 with prior cardiovascular disease (CVD) were taking statins, with large variations between countries from 27–29% in Estonia and Slovenia to 55–56% in Belgium, Denmark and Netherlands. In a recently published UK Clinical Practice Research Datalink study (Mattthews et al, 2016) looking at usage in 2014–15, only 60% of those with a recent cardiovascular event started statins and of those with a recent 10-year CVD risk score >20% recorded on the practice computer system, only around 25% started statin therapy. Collins et al's 30-page review provides a good grounding in the principles of evidence-based medicine, outlines the benefits and limitations of different study types and discusses the evidence for statin therapy in relation to public health and our daily practice. I hope you will encourage one of your team to read it and share its contents, and that armed with the knowledge it provides we will be motivated to search out high risk people not taking statin, and encourage them to start or restart therapy in line with NICE guidelines.

More CVD safety studies published

Two new glucagon-like peptide-1 (GLP-1) receptor agonist cardiovascular safety studies, along with a 1-year review of the EMPA-REG OUTCOME study (Zinman et al, 2015), were presented and discussed at the EASD meeting in September 2016. These studies, along with other ongoing CVD safety studies with glucose-lowering drugs, use either a primary combined 3-point Major Adverse Cardiac Events endpoint (MACE: cardiovascular death, non-fatal myocardial infarction [MI], non-fatal stroke) or a 4-point MACE endpoint, with the addition of hospitalisations for unstable angina. Since populations recruited to the cardiovascular safety studies for different drugs differ even within a single class such as the GLP-1 receptor agonists, direct comparison between safety studies is not possible. These are designed to be non-inferiority studies. Investigators strive to keep glycaemic control the same in both groups, so intensification of glucose lowering can occur to try to keep HbA_{1c} in the control group as close as possible to the active treatment group throughout the study. This should not be misinterpreted as poor glycaemic efficacy of the active drug versus placebo.

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study (Marso et al, 2016b) was a randomised controlled trial involving 9340 patients with type 2 diabetes and high CVD risk treated with liraglutide versus placebo in addition to standard treatment, with follow-up for a median

"This issue's CPD module focuses on foot assessment, provides guidance on how to classify feet and the appropriate action when any abnormality or ulceration occurs."

of 3.8 years. The 3-point MACE primary endpoint occurred in 13% fewer people in the treated group (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.78–0.97), with $P<0.001$ for non-inferiority and $P=0.01$ for superiority. There was a significant 22% reduction in cardiovascular deaths and significant 15% reduction in all-cause mortality. Rates of non-fatal MI and stroke and hospitalisations for heart failure were non-significantly lower in the liraglutide group. There was a non-significant signal for retinopathy increase in the group treated with liraglutide.

The Trial to Evaluate Cardiovascular and other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6; Marso et al, 2016a) explored the non-inferiority of semaglutide, a GLP-1 receptor agonist not yet available in the UK, versus placebo, in terms of cardiovascular safety. A total of 83% had CVD, chronic kidney disease or both at entry to the study. This demonstrated a primary outcome of a significant 26% reduction in 3-point MACE (HR, 0.74; 95% CI, 0.58–0.95), with $P<0.001$ for non-inferiority driven by a significant non-fatal stroke risk reduction of 39% (HR, 0.61; 95% CI, 0.38–0.99; $P=0.04$), and with no significant differences in cardiovascular or all cause death between the two groups. Secondary endpoints were a 36% reduction in new or worsening nephropathy in the semaglutide group and a small significant increase in retinopathy (HR, 1.76; 95% CI, 1.11–2.78; $P=0.02$).

We will bring you an overview and discussion of the results from currently published cardiovascular safety studies in a future issue of the Journal.

Revisiting important areas of care and service delivery

In this issue, we have the opportunity to revisit important areas of diabetes care and service delivery, including pre-conception care in our audit (page 216), insulin safety (page 208), your feedback from the previous survey (page 213), confidentiality (page 227) and the impact of the Super Six model 5 years after its implementation (page 221). You can read the biographies of the candidates standing for election to the PCDS Committee in November on page 231 so that you can choose who is most likely to help PCDS fulfil our aims over the next 3 years.

Amputation rates remain high in people with diabetes and we have discussed previously the vital role we can all play in reducing amputations. Our CPD module (page 234) focuses on foot assessment, providing guidance on how to classify feet and the appropriate action when any abnormality or ulceration occurs. The module reminds us of the importance of identifying those who cannot undertake their own self-assessment, either because they cannot reach their feet or because they are blind or have significant visual impairment. For such people it is important that we identify and train others who can examine their feet or ensure regular foot assessments with a healthcare professional.

As we near the end of this year's PCDS Smart Update meetings titled *Individualising diabetes therapy in a confusing landscape: A point-by-point plan to help you optimise your consultation*, we felt it would be useful to share the key messages we discussed and debated in the meetings with a wider audience than just those who were able to attend. You can read the meeting report in the centre pages of the Journal.

Finally, we are excited to announce the launch of four new PCDS e-learning modules funded and supported by an educational grant from NHS Wales. These modules cover topics such as pre-diabetes and diabetes prevention and pre- and post-pregnancy care. There are also two modules aimed at community teams, including healthcare support workers, working with older people with diabetes. These modules are now available via www.learning.wales.nhs.uk/login/index.php for colleagues in Wales and through www.diabetesonthenet.com/cpd for healthcare professional across the rest of the UK. ■

Borsch-Supan A, Brandt M, Hunkler C et al (2013) Data resource Profile: the Survey of Health, Ageing and Retirement in Europe (SHARE). *Int J Epidemiol* **42**: 992–1001

Collins R, Reith C, Emberson J et al (2016) Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 8 Sep [Epub ahead of print]

Hine J, De Lusignan S, Burleigh D et al (2016) Association between glycaemic control and common infections in people with type 2 diabetes: a cohort study. *Diabet Med* 22 Aug [Epub ahead of print]

Marso S, Bain S, Consoli A et al (2016a) Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 15 Sept [Epub ahead of print]

Marso S, Daniels G, Brown-Frandsen K et al (2016b) Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* **375**: 311–22

Matthews A, Herrett E, Gasparrini A et al (2016) Impact of statin-related media coverage on use of statins: interrupted time series analysis with UK primary care data. *BMJ* **353**: 13283

Redberg R, Katz M (2012) Healthy men should not take statins. *JAMA* **307**: 1491–2

Zinman B, Wanner C, Lachin J et al (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* **373**: 2117–28