PCDS
Primary Care Diabetes Society

The latest news and views from the Primary Care Diabetes Society

Why NICE needs to change: Defining a new prescribing pathway

NICE developed its guidance for the management of type 2 diabetes in adults (NG28) several years ago, with its publication in December 2015. The guidance was based on current evidence at the time and it tried to highlight best practice in prescribing. Cost was included in the recommendations, but to be considered only following an individualised assessment of the person with diabetes.

Since the development of NG28, there have been launches of further medications in the sodium–glucose cotransporter 2 inhibitor (SGLT2i) and once-weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA) classes. The guidance has been altered to account for these therapies, with a review published in September 2017. With the newer therapies, however, a number of cardiovascular (CV) safety trials have subsequently been undertaken and published.

Cardiovascular safety trials are placebo-controlled trials, often using a high-risk study population. The aim of these trials is to demonstrate CV safety. The first trials that were published investigated the dipeptidyl peptidase-4 (DPP-4) inhibitors. The first of these, SAVOR-TIMI, studied saxagliptin in participants with type 2 diabetes who had a history of, or were at risk for, CV events. It found no evidence for CV harm, but a concern of hospitalisation with heart failure compared to placebo (Scirica et al, 2013). The results of EXAMINE, which studied the effects of alogliptin in a population with type 2 diabetes and acute coronary syndrome, suggested a non-statistically significant trend with heart failure (White et al, 2013), while the TECOS study with sitagliptin showed no association with heart failure (Green et al, 2015). It remains unclear why the link with heart failure in SAVOR-TIMI was found. Uncertainty remains whether this was trial design, selection of participants or specific reaction to the individual drug rather than a class effect.

The SGLT2i therapies have been studied and, surprisingly, have shown not only CV

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safety, but evidence to suggest protection. The trials (EMPA-REG OUTCOME [Zinman et al, 2015] and CANVAS [Neal et al, 2017]) have raised interest that these therapies can reduce morbidity and mortality, and may offer benefit in secondary prevention. It remains unclear whether they can give benefit with primary prevention. The mode of action to give CV protection remains unclear. It has been suggested that it may involve several elements:

- Decrease in blood pressure by reducing arterial stiffness, vascular resistance and osmotic diuresis.
- Decrease in body weight, resulting in less visceral adiposity.
- Decrease in uric acid and oxidative stress.
- Shift in myocardial fuel energetics.

Studies involving the GLP-1 RA class have shown some variation between the different drugs. The GLP-1 analogues derived from the human type have demonstrated both CV safety and benefit. Once again, there are several theories behind the mechanism.

- Prevention of atherogenesis.
- CV benefits from weight loss.
- Improved cardiac function
  - Improved cardiac glucose uptake and improved left ventricular function.
- Effects on blood vessels
  - Improving blood flow with vasodilation, reducing smooth muscle hypertrophy and plaque stability.

The CV outcome trials have offered hope of protecting our at-risk population from worsening harm and death. Many guidelines around the world have started to change to include this compelling evidence. In particular, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) have jointly suggested that, for patients who have significant CV risk, SGLT2 inhibitors or GLP-1 analogues should be used much earlier in intensification of diabetes therapies (Davies et al, 2018).

NICE are not due to review the NG28 guidelines until 2021. In light of the new evidence and national guideline changes, the PCDS has asked NICE to review its guidance earlier and to bring it in line with international expert opinions. You can read our letter on the following page. ■

Davies MJ, D'Alessio DA, Fradkin J et al (2018) Management of hyperglycemia in type 2 diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* **61**: 2461–98

Green JB, Bethel MA, Armstrong PW; the TECOS Study Group (2015) Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* **373**: 232–42

Neal B, Perkovic V, Mahaffey KW et al; the CANVAS Program Collaborative Group (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* **377**: 644–57

NICE (2017) *Type 2 diabetes in adults: management*. NICE, London. Available at: https://www.nice.org.uk/guidance/ng28 (accessed 30.01.19)

Scirica BM, Bhatt DL, Braunwald E et al; the SAVOR-TIMI 53 Steering Committee and Investigators (2013) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* **369**: 1317–26

White WB, Cannon CP, Heller SR et al; the EXAMINE Investigators (2013) Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* **369**: 1327–35

Zinman B, Wanner C, Lachin JM et al; the EMPA-REG OUTCOME Investigators (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* **373**: 2117–28

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Dear Sir David Haslam

The Primary Care Diabetes Society is the largest representation for Primary Care with an interest in diabetes. The current active membership of the PCDS is 18,000 healthcare professionals working in diabetes outside of a hospital environment. We are writing to express our concern regarding the NG28 guidelines. These guidelines were produced in 2015. Since their publication, there has been new evidence that suggests a review leading to a change in recommendations.

Cardiovascular disease is the largest cause of death within the diabetic population. Evidence has shown that expected life expectancy is reduced by as much as 10 years due to early death from cardiovascular disease.[1] Despite setting individualised targets of blood pressure, cholesterol and glucose control, there remains a significant gap between death rates when compared to a non-diabetic population.[2]

Studies such as the UKPDS[3] have shown that intensive management from the diagnosis can offer long-term benefits. Other studies, such as ADVANCE[4] and ACCORD[5] have led to the recommendation of individualised targets. These studies were available during the writing of the current guidance and are referenced in NG28.

Since the publication of NG28, there have been many studies, in particular cardiovascular outcome studies. Some of these have raised potential concern regarding the use of certain agents and association of heart failure (SAVOR-TIMI 53[6]), while others have suggested that some agents have a unique protective action on secondary prevention over and above glucose lowering (EMPA-REG[7], CANVAS[8], LEADER[9] and SUSTAIN[10]).

With the evidence presented from the cardiovascular outcome studies, there has been a significant change in many national guidelines and recommendations, in particular SIGN, ADA and EASD.

The current NICE guideline does not reflect current evidence and is now considered outdated. The PCDS has significant concerns that best care is no longer reflected in the NG28 Guidance. We now feel that we have to recommend the alternative guidelines rather than NICE. These alternative guidelines have separated cardiovascular disease as a significant condition and emphasise the earlier use of SGLT2 inhibitors or GLP-1 analogues.

We ask that NICE should make an early review of the NG28 guidance as it is out of line with other learned bodies and we feel that we cannot continue to support its adoption in its current form.

Yours sincerely

Clare Hambling David Millar-Jones

1. PROactive. Roper et al. *BMJ* 2001;**322**: 1389–93
2. THIN. Lind et al. *Diabetologia* 2013;**56**: 2601–8
3. UKPDS 34. UKPDS Study Group. *Lancet* 1998;**352**: 854–65
4. ADVANCE. ADVANCE Collaborative Group. *N Engl J Med* 2008;**358**: 2560–72
5. ACCORD. ACCORD Study Group. *N Engl J Med* 2008;**358**: 2545–59
6. SAVOR-TIMI 53. Scirica et al. *N Engl J Med* 2013;**369**: 1317–26
7. EMPA-REG OUTCOME. Zinman et al. *Cardiovasc Diabetol* 2014;**13**: 102
8. CANVAS. Neal et al. *Am Heart J* 2013;**166**: 217–23
9. LEADER. Marso et al. *N Engl J Med* 2016;**375**: 311–22
10. SUSTAIN. Marso et al. *N Engl J Med* 2016;**375**: 1834–44