A new age in management of type 2 diabetes treatment

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Approximately half of all deaths in people with type 2 diabetes are caused by heart disease. The life expectancy of people with type 2 diabetes at high cardiovascular (CV) risk is reduced by approximately 12 years. Therefore, addressing the burden of CV disease is fundamental to the management of diabetes.

In the last 12 months, we have seen results from three trials showing a reduction in CV events from agents in three different classes of antidiabetes medication, possibly heralding the start of a new paradigm with respect to the choice of second- and third-line antidiabetes therapies. The first was empagliflozin, a sodium–glucose cotransporter 2 inhibitor, in the EMPA-REG OUTCOME trial. This agent reduced CV mortality by 38% and all-cause mortality by 32% compared with placebo in people with type 2 diabetes at high CV risk (Zinman et al, 2015).

In the second study, IRIS (Insulin Resistance Intervention After Stroke), pioglitazone reduced the rate of recurrent stroke or myocardial infarction in people with insulin resistance by 24% compared to placebo (Kernan et al, 2016). It also reduced the risk of progression to diabetes in this population, as shown in the article summarised on the facing page.

The third study, LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation), is summarised alongside. In this CV safety trial, the glucagon-like peptide-1 receptor agonist liraglutide reduced the rates of major CV events in people with type 2 diabetes at high CV risk by 13% compared with standard care.

These positive CV outcomes are very encouraging and clearly have important implications for the treatment of people with type 2 diabetes. However, research is still at an early stage. The studies raise a number of questions. In the EMPA-REG OUTCOME trial, the mechanism behind the reduction in CV mortality is still not completely clear. Furthermore, in all three studies, the generalisability of the results to other patient groups at lower CV risk is not yet known. And particularly in the case of empagliflozin and liraglutide, it is not known whether these positive results are a class effect or particular to the agents in the trials.

While it is too early to speculate on the future impact of these trials, they may well result in a significant change in how type 2 diabetes is treated. At this time, there is still universal agreement that, for most people, metformin remains the drug of choice for first-line therapy. The options for second- and third-line treatment have expanded considerably in the last decade and we have been encouraged to individualise choice of such medication taking into account many factors, including patients' attitudes and expected adherence, risks associated with hypoglycaemia, duration of diabetes, life expectancy, important comorbidities, established vascular complications and support systems (Inzucchi et al, 2015).

With these new studies demonstrating improved CV outcomes, possible or probable CV benefit beyond any effect related to improved glycaemia is likely to become an additional consideration in the choice of therapy beyond metformin. For high-risk patients, it is quite likely that this consideration will become the most important when choosing one medication or class over the alternatives. And given that the benefits seen with empagliflozin are probably linked to haemodynamic changes while the benefits from liraglutide are more related to modified progression of atherosclerotic disease, combining these two agents in high-risk patients may have even greater synergistic benefits in improving CV outcomes. As further studies are completed, the implication of these three studies will become clearer. ■

Inzucchi SE, Bergenstal RM, Buse JB et al (2015) Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* **38**: 140–9

Kernan WN, Viscoli CM, Furie KL et al (2016) Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med* **374**: 1321–31

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

New Engl J Med

LEADER trial: Cardiovascular outcomes of liraglutide

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓✓

1 Details of LEADER, a cardiovascular (CV) outcomes trial designed to compare the long-term safety of liraglutide (a glucagon-like peptide-1 analogue) with standard care in people with T2D, were published simultaneously at ADA 2016 and in the *New England Journal of Medicine*.

2 In this double-blind trial, 9340 people with T2D and high CV risk were randomly assigned to receive liraglutide (n=4668) or placebo (n=4672) in addition to standard care. The primary composite outcome in the time-to-event analysis was the first occurrence of death from CV causes, non-fatal myocardial infarction (MI) or non-fatal stroke.

3 The primary outcome occurred in significantly fewer liraglutide recipients than placebo recipients (13.0% vs 14.9%; hazard ratio [HR], 0.87; P<0.001 for non-inferiority; P=0.01 for superiority).

4 Fewer individuals died from CV causes in the treatment group (4.7%) compared with placebo (6.0%; HR, 0.78; P=0.007). Furthermore, the rate of all-cause death was lower with liraglutide (8.2% vs 9.6%; HR, 0.85; P=0.02).

5 There were fewer hospitalisations for non-fatal MI, non-fatal stroke and for heart failure in the treatment group, although the difference between the groups was not significant.

6 The number needed to treat to prevent one event in 3 years was 66 for the primary outcome and 98 for death from any cause.

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

ADA 76th Scientific Sessions

Diabetes Care

Pioglitazone and diabetes prevention

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓✓

1 The Insulin Resistance Intervention after Stroke (IRIS) trial revealed that pioglitazone reduces the rates of stroke and myocardial infarction after ischaemic stroke or transient ischaemic attack (TIA) in people without diabetes who have insulin resistance (IR).

2 In this analysis of the IRIS cohort, the authors evaluated pioglitazone's effect on glycaemic parameters and on the prevention of diabetes.

3 A total of 3876 people without diabetes who had experienced a recent ischaemic stroke or TIA and scored >3.0 on the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) were randomly assigned to receive pioglitazone (45 mg daily) or placebo. Baseline levels of fasting plasma glucose (FPG), HbA_{1c}, insulin and HOMA-IR were recorded.

4 Surveillance for the onset of diabetes was by annual interview and FPG testing.

5 During a median follow-up of 4.8 years, diabetes developed in 73 individuals (3.8%) in the pioglitazone group compared with 149 (7.7%) in the control group (hazard ratio (HR), 0.48; 95% confidence interval [CI], 0.33–0.69; $P<0.0001$).

6 The absolute risk reduction was greatest for individuals with impaired FPG, increased HbA_{1c} or worse HOMA-IR at baseline.

7 This is the first single trial of a glucose-lowering drug to show prevention of both progression to diabetes and major cardiovascular events as prespecified outcomes. Pioglitazone was, however, also associated with higher risks of weight gain, oedema and bone fracture.

Inzucchi SE, Viscoli CM, Young LH et al (2016) Pioglitazone prevents diabetes in insulin-resistant patients with cerebrovascular disease. *Diabetes Care* 27 Jul [Epub ahead of print]

ADA 2016

Faster-acting insulin aspart in adults with uncontrolled T2D

1 At ADA 2016, the results of two trials of faster-acting insulin aspart (faster aspart) in adults with T2D were presented.

2 The Onset 2 trial evaluated over a 26-week period the efficacy of faster aspart vs insulin aspart (IAsp) in adults with T2D uncontrolled on basal insulin and oral antidiabetes drugs. After optimising basal insulin during an 8-week run-in, participants were randomised to treatment with mealtime faster aspart or mealtime IAsp.

3 Faster aspart demonstrated non-inferiority in reducing HbA_{1c} and a significant lowering of 1-hour postprandial glucose (PPG) levels when compared with IAsp, without increasing overall hypoglycaemia.

4 The Onset 3 trial assessed the efficacy of a basal–bolus (BB) regimen with mealtime faster aspart vs a once-daily basal regimen of detemir, glargine or isophane insulin over an 18-week period. Participants underwent an 8-week run-in to optimise their insulin therapy before being randomised to one of the treatments.

5 The BB arm demonstrated superiority in reduction of HbA_{1c} from baseline over the basal arm, possibly as a result of the significantly greater reduction in 2-hour PPG levels that were recorded in the former.

6 The rates of hypoglycaemia and of weight gain were greater in the BB arm than the basal arm.

Bowering K, Case C, Harvey J (2016) Faster-acting insulin aspart vs insulin aspart as part of basal-bolus therapy improves postprandial glycaemic control in uncontrolled T2D in the double-blinded Onset® 2 trial. *ADA 76th Scientific Sessions*: abstract 240-OR

Rodbard H, Tamer SC, Velazquez MV (2016) Adding faster-acting insulin aspart to basal insulin significantly improved glycaemic control: the Onset® 3 trial. *ADA 76th Scientific Sessions*: abstract 241-OR

ADA 2016

Novel flash glucose sensing and hypoglycaemia

1 The results of the IMPACT clinical trial, which examined the impact of new sensor technology on hypoglycaemia compared to conventional self-monitoring of blood glucose (SMBG), were presented during a poster discussion at ADA 2016.

2 Participants ($n=241$) were adults with well-controlled T1D (HbA_{1c}, <58 mmol/mol [<7.0%]) of an average duration of 22 years. The intervention group ($n=120$) used Abbott's Freestyle Libre flash glucose sensor and reader system, while the control group ($n=121$) used the Freestyle Lite SMBG system.

3 After 6 months, there was a significant reduction in time spent in hypoglycaemia (blood glucose <3.9 mmol/L) of 38.0% in the intervention group compared with the control group (mean difference [±standard error], –1.24±0.239 hours/day; $P<0.0001$). The time spent with blood glucose levels <2.2 mmol/L was reduced by 65.3% ($P=0.0003$).

4 Time spent in hyperglycaemia (>13.3 mmol/L) in the intervention group was significantly reduced by –0.37±0.163 hours/day, while time in range (3.9–10.0 mmol/L) significantly increased by 1.0±0.30 hours/day ($P=0.0006$). No differences in mean glucose or HbA_{1c} levels were noted.

5 Despite 13 device-related adverse events (resulting in five participants withdrawing), treatment satisfaction and quality-of-life scores significantly improved with the Libre.

Bolinder J, Antuna R, Geelhoed-Duijvestijn N et al (2016) Using novel flash glucose-sensing technology reduces hypoglycemia in individuals with type 1 diabetes. *ADA 76th Scientific Sessions*: abstract 868-P

"This is the first single trial of a glucose-lowering drug to show prevention of both progression to diabetes and major cardiovascular events as prespecified outcomes."