Updates from the 2018 EASD and AHA meetings

Stay abreast of the latest news that could influence diabetes care. Pam Brown, Editor-in-Chief of *Diabetes & Primary Care*, reports from EASD 2018 and Sean Delaney shares breaking news from AHA 2018 Scientific Sessions.

This issue's breaking news comes from the 54th Annual Meeting of the European Association for the Study of Diabetes (EASD) and the American Heart Association (AHA) 2018 Scientific Sessions (see below). Several presentations had accompanying research papers simultaneously published in peer-reviewed journals. Here we share some of the key new research findings reported at the two conferences, with links to the online published papers.

EASD Annual Meeting

The 54th Annual Meeting of the EASD was held on 1–5 October in Berlin, Germany. The scientific programme included more than 1200 talks and presentations on the latest results in diabetes research.

ADA/EASD consensus report on management of hyperglycaemia in type 2 diabetes

This consensus report updates the American Diabetes Association (ADA)/EASD position statements issued in 2012 and 2015, and places greater focus on self-management; putting the patient at the centre of all discussion and decision-making to improve engagement; and addressing clinical inertia, medication adherence and persistence. There is increased focus on lifestyle interventions, including nutrition, which may be difficult to implement in the UK, where there is scarcity of access to dietitians and patchy expertise amongst primary care teams. The choice of glucose-lowering medication is informed by new evidence from cardiovascular outcome trials (CVOTs) that have been published in the last 2 years.

All patients start with metformin, and the consensus development group took a decision to recommend metformin monotherapy initially, rather than combination therapy for those with high HbA_{1c} as recommended by other guidelines.

The consensus document makes use of detailed algorithms and initially focuses on identifying and managing those people who have had previous cardiovascular disease (CVD) or chronic kidney disease (CKD). This group is then managed depending on whether it is CVD or CKD that predominates, and the CVD group is further subdivided by whether the individual has atherosclerotic CVD or heart failure. Management of these groups prioritises the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1 RAs) with proven cardiovascular benefits.

People without CVD or CKD are divided into three slightly arbitrary categories according to treatment goals: overwhelming need to prevent hypoglycaemia, compelling need to prevent weight gain or promote weight loss, and need to keep costs low. Since preventing hypoglycaemia and avoiding weight gain are important in everyone with type 2 diabetes, unless there are significant cost constraints it is unlikely that there will be much inclination to manage using the low-cost part of the algorithm, which recommends adding a sulfonylurea or pioglitazone, and then insulin. Those for whom hypoglycaemia avoidance is important (ideally everyone) can choose between dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 RAs, pioglitazone or an SGLT2 inhibitor, and if weight is important the choice is between an SGLT2 inhibitor and a GLP-1 RA.

The consensus development group specifically chose not to include glycaemia targets within the document in order to ensure that clinicians would personalise glycaemic goals with patients. Those who feel less confident about doing this may choose to use the tool provided in the previous ADA/EASD guidelines, which helps with decision-making.

Additional key recommendations include the following:

- Foundation therapy should be metformin and lifestyle management, including diabetes self-management education and support.
- Monotherapy is preferred initially. If HbA_{1c} is more than 16 mmol/mol (1.5%) above target, then adding two therapies simultaneously could be considered, but if side effects develop it will be difficult to establish which drug has caused them.
- When injectable therapy is required, the use of GLP-1 RAs should be prioritised over insulin since the long-acting GLP-1 RAs are as effective as insulin and cause weight loss rather than gain. Consider insulin if the patient is catabolic or if the diagnosis is uncertain.

Those who are highly symptomatic may need insulin at least initially.

- To intensify injectable therapy, add basal insulin and then one prandial insulin dose. Guidance is provided on which therapies to stop and which can be safely continued when injectables are introduced.
- Bariatric surgery guidance is unchanged from previous position statements.

A useful table summarises the advantages, disadvantages and special considerations for each of the available therapies.

Clinicians developing the consensus identified knowledge gaps, such as whether metformin should always be used first, whether early combination therapy is useful, whether SGLT2 inhibitor and GLP-1 RA effects in CVD prevention are additive, and how to manage younger and older people with type 2 diabetes.

E-learning modules which will facilitate implementation of the consensus were also launched at the EASD conference.

Click here to access the full report.

Click here to access the E-learning modules.

CARMELINA trial results

The CARMELINA study, the CVOT for the DPP-4 inhibitor linagliptin, demonstrated the cardiovascular safety of linagliptin compared with placebo in a clinically relevant type 2 diabetes population at high risk of both CVD and renal disease. The primary endpoint of three-point MACE (a composite of cardiovascular death, non-fatal myocardial infarction (MI) or non-fatal stroke) had an HR of 1.02 (95% CI, 0.89–1.17) compared with placebo.

Originally the primary endpoint had been four-point MACE, including hospitalisations for unstable angina; however, this was changed during the study to bring the endpoint in line with other DPP-4 inhibitor CVOTs. Analysis of the four-point MACE similarly demonstrated CV safety, with an HR of 1.00 (95% CI, 0.88–1.13). Likewise, there was no significant difference between linagliptin and placebo for the individual components of three-point MACE. All-cause mortality was high in the study but there was no difference between the groups, with an HR of 0.98 (95% CI, 0.84–1.13). The secondary endpoint, a composite of death due to renal failure, end-stage renal disease or sustained reduction of ≥40% decrease in eGFR from baseline, was also not significantly different between groups. The composite microvascular endpoint demonstrated a small benefit in favour of linagliptin, with an HR of 0.86 (95% CI, 0.78–0.95), which was largely driven by a reduction in albuminuria progression.

At the start of the study, 57% of the 6991 participants had established CVD, 62.3% had an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2, and 33% had both CVD and CKD. This study therefore had a much higher proportion of participants with CKD than CVOTs of other DPP-4 inhibitors (<10% in TECOS [for sitagliptin] and 15% in SAVOR-TIMI [for saxagliptin]). This was a very high-risk population, with more than 850 MACE events over 2.2 years, and more than 50% of these were cardiovascular deaths.

Heart failure is more common in people with an eGFR <60 mL/min/1.73 m^2, and hospitalisation for heart failure (HHF) was a prespecified secondary outcome of the study. Even though 28% of the population in this trial had heart failure at baseline, there was no significant increase in risk of HHF in those treated with linagliptin compared to placebo, with an HR of 0.90 (95% CI, 0.74–1.08). A similar finding was observed with sitagliptin in TECOS; however, in SAVOR-TIMI, there was a slightly increased risk of HHF with saxagliptin (HR, 1.27; 95% CI, 1.07–1.51).

Glycaemic equipoise between the two groups was not quite achieved, with an HbA_{1c} difference of 4 mmol/mol (0.36%) in favour of linagliptin across the study. More patients required insulin initiation with placebo than with linagliptin (729 vs 555 participants).

The study did not identify any unexpected adverse events. There were no significant differences in cancers, hypoglycaemia or severe hypoglycaemia between the groups, but there were higher rates of pancreatitis and bullous pemphigoid (which were previously known side effects) in those treated with linagliptin.

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The CAROLINA study, a CVOT comparing the impact of linagliptin versus glimepiride, is due to report in 2019.

Harmony Outcomes trial results

In the Harmony Outcomes trial, the once-weekly injectable GLP-1 RA albiglutide reduced the primary endpoint of three-point major adverse cardiovascular events (MACE; a composite of CVD death, myocardial infarction [MI] or stroke) by a significant 22% (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.68–0.90) compared with placebo in a population with type 2 diabetes and established CVD. This reduction in the composite endpoint was driven by a reduction in fatal and non-fatal MI (HR, 0.75; 95% CI, 0.61–0.90). The primary endpoint rate was 4.57 per 100 person-years in the albiglutide group and 5.87 per 100 person-years in the placebo group, translating to a number needed to treat of 50 over a median of 1.6 years to prevent one major cardiovascular event.

The study recruited 9463 people aged 40 years and over with type 2 diabetes and previous CVD (70% coronary arterial disease, 20% heart failure), who were randomised to weekly albiglutide injections of 30–50 mg (based on

glycaemic control and tolerability) or to placebo. Albiglutide has a half-life of 5 days, allowing weekly dosing.

There was no significant difference in the risk of acute pancreatitis (10 cases with albiglutide and seven with placebo), pancreatic cancer (seven with albiglutide and six with placebo), medullary thyroid cancer (zero cases in both groups) or other major adverse events between the groups. There was no increased incidence or worsening of retinopathy in the albiglutide group but there was an increase in injection site reactions. This study had a high rate of new cardiovascular events, even though more than 80% of participants were on statins and more than half were on renin–angiotensin system blockers and aspirin. Lipids and urinary albumen excretion were not measured. In this study, the HbA_{1c} reduction was 8.7 mmol/mol (0.80%; 6.9 mmol/mol [0.63%] at 8 months), and in phase 2/3 studies the weight loss was less than with some other GLP-1 RAs, at 1.5–2.0 kg.

CVOTs of GLP-1 RAs have included different populations with differing cardiovascular risk, and have shown inconsistent results. The authors of Harmony Outcomes stated that this new evidence confirms that people with type 2 diabetes and established CVD should receive either a GLP-1 RA or an SGLT2 inhibitor with evidence of reducing future CV risk. This recommendation is also made in the new ADA/EASD guideline launched at the conference.

Providing commentary on the study, David Matthews, Professor of Diabetic Medicine at the University of Oxford, applauded GSK for continuing to fund this study to its conclusion in order to ensure further insight into the cardiovascular effects of this class of drugs, despite taking the decision not to market albiglutide in July 2018. It is as yet uncertain whether this product will be marketed in the UK by another company.

The findings were presented at EASD and published simultaneously in *The Lancet*.

Click here to access the article.

Novel dual GIP/GLP-1 receptor agonist: Phase 2 trial

LY3298176, a novel dual gastric inhibitory polypeptide (GIP) and GLP-1 receptor agonist administered subcutaneously once weekly, has demonstrated significantly better HbA_{1c} lowering and weight loss compared with both placebo and an active comparator, the GLP-1 RA dulaglutide, in a 26-week, double-blind, phase 2 trial. Participants in the study had a BMI of 23–50 kg/m^2 (mean, 32.6 kg/m^2), and a baseline HbA_{1c} of 53–91 mmol/mol (7.0–10.5%), and were randomised to receive 1 mg, 5 mg, 10 mg or 15 mg of LY3298176; 1.5 mg of dulaglutide; or placebo, in addition to their current therapy with metformin and/or diet and exercise.

Mean reductions in HbA_{1c} were dose-dependent, with no evidence of plateau across the dose range tested, and ranged from 11.6 mmol/mol (1.06%) with the 1-mg dose of LY3298176 to 20.6 mmol/mol (1.89%) in those treated with the 15-mg dose, compared with 13.2 mmol/mol (1.21%) with dulaglutide 1.5 mg and an increase of 0.7 mmol/mol (0.06%) in those treated with placebo. Mean weight loss in those treated with LY3298176 ranged from 0.9 kg with the 1-mg dose to 11.3 kg with the 15-mg dose, compared to 0.4 kg with placebo and 2.7 kg with dulaglutide.

The study population had a mean duration of type 2 diabetes of 9 years and a mean age of 57 years. Overall, 81.7% completed the allocated treatment and data were available at completion for 89% of participants. Higher doses of the dual agonist were titrated to minimise gastrointestinal side effects, as would be recommended for some GLP-1 RAs. There were no new significant adverse events with LY3298176 that have not been seen with GLP-1 RAs. Gastrointestinal adverse event rates with the dual agonist were dose-related, ranging from 23.1% with the 1-mg dose to 66% with the 15-mg dose; however, most were mild to moderate in severity and transient. There were more discontinuations in the group treated with the 15-mg dose and during titration. There were no severe hypoglycaemic events, and mild/moderate hypoglycaemia events were similar in frequency in those treated with the dual agonist compared to dulaglutide. The authors concluded that LY3298176 may be a useful new therapeutic option in type 2 diabetes.

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CAMELLIA-TIMI trial results

In the CAMELLIA-TIMI study, lorcaserin, a selective serotonin 2C receptor agonist with proven appetite suppression and weight-loss effects, demonstrated cardiovascular safety earlier in 2018 (Bohula et al, 2018). Prespecified primary and secondary metabolic endpoints from this study were presented at the EASD meeting and simultaneously published in *The Lancet*. A total of 12 000 overweight or obese people with established CVD (age ≥40 years) or high cardiovascular risk (age ≥50 years with diabetes and one other cardiovascular risk factor) were randomised to lorcaserin or placebo and followed for 3.3 years. At baseline, 6816 participants (56.8%) had diabetes, 3991 (33.3%) had prediabetes and 1193 (nearly 10%) had normoglycaemia. The primary metabolic endpoint was time to incident diabetes in those with prediabetes at baseline, and secondary endpoints were incident diabetes in all those without diabetes, achievement of normoglycaemia in those with prediabetes and change in HbA_{1c} in those with diabetes.

Weight loss was moderate amongst those treated with lorcaserin; the mean placebo-subtracted weight loss was 2.6 kg (95% CI,

2.3–2.9) in those with diabetes at baseline, 2.8 kg (95% CI, 2.5–3.2 kg) for those with prediabetes and 3.3 kg (95% CI, 2.6–4.0 kg) for those with normoglycaemia. Lorcaserin reduced the incidence of type 2 diabetes by 19% in those with prediabetes (HR, 0.81; 95% CI, 0.66–0.99), and by 23% in those without diabetes (HR, 0.77; 95% CI, 0.63–0.94). In those with diabetes, there was a net decrease in HbA_{1c} of 3.6 mmol/mol (0.33%) in those with good control at baseline, and 5.7 mol/mol (0.52%) in those with poor control (HbA_{1c} >64 mmol/mol). In those with diabetes, severe hypoglycaemia with serious complications was rare, but was at least three times as common with lorcaserin (0.4% vs 0.1%), occurring in all but one case in those treated with insulin and sulfonylureas. Significantly more people on lorcaserin achieved at least 5% weight loss, with rates ranging from 37.4% in those with diabetes at baseline to 39.7% in those with prediabetes and 42.3% in those with normoglycaemia, compared with 16–17% of those receiving placebo in each group.

To put these results into context, orlistat treatment resulted in a mean weight loss of 3 kg after 4 years and reduced the risk of incident diabetes by 37% in obese people with prediabetes, while liraglutide 3 mg resulted in a 4.3% net weight loss and a 79% reduction in incident diabetes at 3 years.

Click here to access the article.

Link to an accompanying commentary.

PIONEER 1 study

An oral formulation of the GLP1-RA semaglutide is under development. The new drug is coformulated with an absorption enhancer, known as SNAC, that promotes absorption across the gastric epithelium. Safety and efficacy results from PIONEER 1, a 26-week, phase 3a, randomised, placebo-controlled trial of the agent in drug-naïve patients uncontrolled on diet and exercise demonstrated significant reductions in HbA_{1c} across 3 mg, 7 mg and 14 mg doses, with a reduction in HbA_{1c} of 16 mmol/mol (1.5%) in those on the 14 mg dose compared to 1 mmol/mol (0.1%) in those on placebo. In the intention-to-treat analysis, significant weight loss was demonstrated with the 7 mg and 14 mg doses of oral semaglutide versus placebo (2.3 kg and 3.7 kg vs 1.4 kg). As anticipated, the most frequent side effect was nausea, an effect that was dose-dependent.

To ensure effective absorption, oral semaglutide needs to be taken daily, on an empty stomach, first-thing in the morning, with post-dose fasting for at least 30 minutes. The presenters highlighted that this may prove challenging to achieve on a daily basis, meaning that some may prefer a once-weekly injection of semaglutide, which has similar efficacy and tolerability.

Additional studies using oral semaglutide as dual and triple therapy and a CVOT are ongoing and were summarised in the meeting.

PCDE symposium at EASD 2018

The Primary Care Diabetes Europe (PCDE) symposium focused on optimal primary care management of younger and older people with type 2 diabetes, and harnessed the expertise of international speakers Didac Mauricio, Sam Seidu, Kamlesh Khunti and Guy Rutten, with lively interaction between the speakers, the Chairs, Xavier Cos and Pinar Topsever, and the audience.

Younger people with type 2 diabetes

Professor Mauricio reminded us that, amongst younger people diagnosed with type 2 diabetes, complication rates are actually higher than in those with type 1 diabetes of a similar age. Early age of type 2 diabetes onset is associated with very high risk of complications, mortality and morbidity, which will all have significant impact not just on the person with diabetes but on their families and workplace. Glycaemic control is worse in those with type 2 diabetes aged <45 years compared to those aged 45–70 years, and around 30% in some studies are only managed with lifestyle and less invasive therapies. This group also tends to have high levels of smoking and obesity. Blood pressure control is similar to that in older groups, but lipid management is often poor. Retrospective review of those who died at an early age demonstrates that they were poorly managed or did not adhere to treatments, and were often not treated to tight targets. "There is an urgent need for prevention in this group and for tight control of blood pressure, glycaemia, lipids and lifestyle changes once the disease is diagnosed", concluded Professor Mauricio.

Dr Seidu stressed that younger people with type 2 diabetes are highly likely to have complications already present at the time of diagnosis. Studies have demonstrated that up to 28% have microalbuminuria at diagnosis, a much higher rate than in those with type 1 diabetes of a similar age, and there is a higher rate of progression to nephropathy than in older people. In the Leicester cohort with type 2 diabetes aged 18–35 years, 16% have depression and many are self-harming.

Dr Seidu postulated several reasons why younger people may receive less active treatment – in young women this may relate to concerns about pregnancy risk and the teratogenicity of statins and angiotensin-converting enzyme inhibitors. However, he concluded that the evidence base is now developing and suggests that early, aggressive treatment for glycaemia, blood pressure and lipids is particularly important in this group, which is the opposite of current practice.

In the discussion, it was highlighted that many of the younger people with type 2 diabetes have developed it due to having severe mental illness and being treated with antipsychotics that increase diabetes risk. This group is less likely to

adhere to medication, attend structured education or make lifestyle changes, and they are likely to become more depressed and distressed by the diagnosis, adding to existing mental health problems. This makes them a particularly important group to identify, although hard to manage.

Since younger people with type 2 diabetes are generally managed in primary care, Professor Khunti proposed that PCDE should consider developing a position statement raising awareness of type 2 diabetes in this group and stressing the importance of early diagnosis and intensive management.

In November 2018, the ADA released a position statement on the comprehensive care of younger people with type 2 diabetes. It is available at **http://bit.ly/2K4jd0h** and published in the December issue of *Diabetes Care*.

Older people with type 2 diabetes

Professor Guy Rutten reminded the audience that the ACCORD, VADT and ADVANCE studies started us thinking about outcomes and management in older people with type 2 diabetes, and highlighted that older age and longer duration of diabetes may require different management from that of younger groups. Comorbidities are common and many have cognitive decline, frailty and sarcopenia, and are at much higher risk of disability, falls and death than younger people. In the CVOTs that did include older people, there were the same benefits as in younger groups. However, it is less clear what the best blood pressure target should be and, although a 2018 *BMJ* paper supports the benefits of statin therapy at age 75 years, there is not the same benefit in people aged 85 years and older (Ramos et al, 2018).

Professor Rutten's comprehensive consultation model and other resources can help clinicians deliver patient-centred and individualised care to older people with type 2 diabetes and other chronic conditions (Rutten et al, 2018). He concluded that in primary care we should be proactive and take the lead, and have at least an annual conversation with older people, discussing the benefits and dangers of their treatment and helping them make informed decisions about their care. Although this may seem like a time-consuming model, he stressed it can be tackled step by step, and is likely to save time and deliver improved care in the longer term.

Professor Khunti reminded the audience that clinical inertia is not just about failing to intensify therapy but also includes failing to deintensify treatment when this is appropriate. He shared PROACTIVE, the PCDE's person-centred approach to individualised glycaemic goals in older people, which will be available on the PCDE website at the end of 2018 or early 2019. He highlighted the paucity of involvement of older people in the key type 2 diabetes studies – for example, UKPDS only involved those aged 25–65 years; VADT included those up to 75 years but only if they were deemed to have a life expectancy of more than 7 years; and ACCORD included those aged 40–79 years.

Audits have demonstrated that, unfortunately, many older patients with tight glycaemic control are also on drugs such as sulfonylureas or insulin, which put them at high risk of hypoglycaemia. "Sadly there is no evidence that fewer elderly are managed with insulin than in the younger age groups, despite their being at greater risk of serious impact from hypoglycaemia and the fact that hypoglycaemia admissions in those over 70 remain higher than in younger people. Since we have good therapies which are safer in the elderly, it is worrying that we are still not using them", stressed Professor Khunti.

The PROACTIVE guidance provides pragmatic mnemonics and tools to calculate frailty index, and offers advice when considering adding new medications in older people (NEW MEDS) and how to safely deintensify therapy (DEINTENSIFY). We will share the link to the position statement when it is published.

UKPDS – review of the first 40 years

The UK Prospective Diabetes Study (UKPDS), a 20-year randomised controlled study of glucose and blood pressure treatments in 5102 people with newly diagnosed type 2 diabetes, began in December 1977, with the original results published in 1998 and the long-term follow-up in 2008. The 40th anniversary of the trial was celebrated with a symposium. The studies compared normal and tight control, with an HbA_{1c} difference of 9.8 mmol/mol (0.9%) between the arms, which was maintained throughout the trial, although HbA_{1c} gradually rose in both groups.

Describing the original study, Professor Rury Holman reminded delegates that, following previous trials, there had been concerns regarding combining drug treatments and, therefore, the intensive treatment arms received either a sulfonylurea (n=1573), basal insulin (n=1156) or metformin (n=342). Since metformin was licensed only for use in overweight or obese people, its use was restricted to those with a body weight >120% of normal. The control group was managed with diet alone (n=1138). Glycaemic rescue therapy could only be added if fasting plasma glucose rose to >15 mmol/L or there were hyperglycaemia symptoms, very different from the lower treatment intensification thresholds seen in control groups in studies today.

Conference attendees were reminded that UKPDS was designed to look at the total burden of disease, and the 21 adjudicated endpoints covered "the totality of bad things which happen to people with type 2 diabetes". The study has so far yielded more than 100 publications (in basic science, clinical and

public health), with the original 1998 outcomes paper (UKPDS 33) cited more than 15 000 times and the metformin paper (UKPDS 34) cited more than 6000 times.

Key messages from UKPDS:

- More than 50% of people already had complications at diagnosis.
  - 21% retinopathy, 18% abnormalities on ECG, 14% foot pulses absent or ischaemic foot.
- Hyperglycaemia progresses in type 2 diabetes, as demonstrated by rising HbA_{1c}.
  - This began at around 1 year in the treated groups and continued throughout the 10 years of the study, regardless of therapy.
- Beta-cell function was estimated to be around 50% of normal at diagnosis and entry to the study.
  - This declined linearly in the diet group and initially increased but then declined in the sulfonylurea and metformin groups, and averaged a 4% decline per year, demonstrating that this was responsible for the progressive hyperglycaemia.
- A strong relationship between mean glucose exposure and microvascular and macrovascular complications was demonstrated.
  - Microvascular complications increased 15-fold from normal HbA_{1c} levels to levels of 97 mmol/mol (11.0%).
  - MI risk doubled across the HbA_{1c} range, likely because more than just glycaemia is involved in the increased risk of CVD.
- Having hypertension and type 2 diabetes was described as "double jeopardy", as the combination increased the risk of all diabetes-related endpoints (relative risk, 1.45; 95% CI, 1.32–1.60).
  - A randomised blood pressure arm was added during the study to further explore the impact of different blood pressure treatments.

Publication of the metformin study changed first-line glycaemic therapy, particularly for overweight or obese people. Metformin, a little-used treatment prior to UKPDS, remains the monotherapy recommendation in all global guidelines. Later publications demonstrated the well-known "legacy effect", or metabolic memory, whereby tight early glycaemic control provides long-lasting microvascular and macrovascular benefits, even if control deteriorates after the first 10 years.

Professor David Matthews sought to put UKPDS into perspective and address four common misconceptions:

- *"We cannot trust the UKPDS results about intensive glucose control – another trial showed that lowering HbA_{1c} to normal led to an increase in death rates."* UKPDS studied people newly diagnosed with type 2 diabetes, with only 2% having established CVD, whereas at entry to the ACCORD study, participants had had diabetes for an average of 10 years, they were older and a significant proportion already had established CVD. There were fundamental differences in treatment strategies, with UKPDS using single therapies and insulin rescue while in ACCORD there was more aggressive use of multiple therapies to attempt to drive the HbA_{1c} down to normal levels; more than 50% of the intensive treatment group had HbA_{1c} <48 mmol/mol (6.5%) and a quarter had levels <42 mmol/mol (6.0%). Thus, UKPDS remains an important trial because it is the only one to address early tight control and to demonstrate the significant benefits from this.
- *"The UKPDS used old-fashioned glucose-lowering techniques which are irrelevant in today's new drug environment."* UKPDS looked at a policy of tight early glycaemic control and found this to be beneficial compared with normal management, irrespective of the drugs used. Today, tight control can be achieved safely using newer drugs, and this may result in even greater benefit.
- *"The metformin arm of UKPDS was underpowered, enrolling only 342 subjects – we don't know that the results were true."* It is the number randomised that is important, and this was 753, significantly greater than in STENO-2, which only included a total of 160 people, 80 in each group. If the study had been underpowered then there would have been a type 2 statistical error and no difference would have been seen between the arms. This was not the case.
- *"Many recent trials of new glucose-lowering agents showed no difference in cardiovascular outcome – lowering glucose cannot, therefore, be very important."* In CVOTs, the regulator demands glycaemic equipoise between the groups, expecting no difference in cardiovascular outcomes to prove the drug is doing no harm. The DPP-4 inhibitor trials, such as TECOS and CARMELINA, were designed as safety studies, not to demonstrate the impact of glucose-lowering on cardiovascular risk. Where cardiovascular benefit is seen in the CVOTs (e.g. in EMPA-REG OUTCOME or LEADER), this is being achieved by a mechanism other than glucose-lowering.

Professor Matthews concluded with a tribute to Robert Turner, lead clinician of UKPDS, who sadly died shortly after the initial trial was completed. Using the words of Professor Philip Home, from his 2008 review of UKPDS (Home, 2008), he said:

"The UKPDS has obviously been unusually influential in the development of treatment guidelines, clinical education and the thinking of healthcare professionals. By inference, it must be responsible for a significant part of the improvement in health outcomes for people with type 2 diabetes in the last decade."

AHA 2018 Scientific Sessions

by Sean Delaney

The AHA 2018 Scientific Sessions were held on 10–12 November in Chicago, IL, USA. Highlights included the much anticipated DECLARE-TIMI 58 study, the third CVOT with an SGLT2 inhibitor and the largest to date. Given that the study reported positive results in September, DECLARE was one of the most highly attended events of the meeting.

DECLARE-TIMI 58

The results, presented on Saturday 10 November by Dr Stephen Wiviott, were done so to a full auditorium. In the primary safety outcome analysis, dapagliflozin met the prespecified criterion for non-inferiority compared with placebo, with respect to the composite MACE (CV death, MI or ischaemic stroke), with an upper boundary of the 95% confidence interval (CI, <1.3; *P*<0.001 for non-inferiority).

The investigators then assessed the co-primary efficacy endpoints of MACE and CV death/hospitalisation for heart failure (HHF): dapagliflozin did not lead to a lower rate of MACE compared with placebo (8.8% vs 9.4%, respectively; hazard ratio [HR], 0.93 [95% CI, 0.84–1.03; *P*=0.17]). It did, however, result in a lower rate of the composite of CV death or HHF (4.9% vs 5.8%, respectively; HR, 0.83 [95% CI, 0.73–0.95; *P*=0.005]). Similar to the CANVAS and CANVAS-R study with canagliflozin, the reduction of the composite of CV death/HHF, appeared to be driven primarily by the HHF benefit (HR, 0.73 [95% CI, 0.61–0.88]). This result was consistent across subgroups, demonstrating that dapagliflozin reduced HHF regardless of a history of atherosclerotic CVD or HF at baseline.

Since only one of the primary efficacy outcomes was significant, analyses of other outcomes can only be hypothesis generating. However, it should be noted that a secondary composite renal endpoint of ≥40% decrease in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2, new end-stage renal disease, or death from renal or cardiovascular causes, was significantly reduced by dapagliflozin, compared with placebo (4.3% vs 5.6%, respectively; HR, 0.76 [CI, 0.67–0.87; *P*<0.001]). Moreover, one component of this (combination of 40% decrease of eGFR to <60 mL/min/1.73 m^2, occurrence of end-stage renal disease, or renal death) occurred in just 3.7% of the dapagliflozin arm compared with 7% of the placebo (HR, 0.53 [CI, 0.43–0.66]). The other secondary endpoint of death from any cause was numerically lower in those treated with dapagliflozin compared with placebo, but did not reach significance (6.2% vs 6.6%, respectively; HR, 0.93 [CI, 0.82–1.04; *P*=0.2]). This was in contrast to that seen in EMPA-REG OUTCOME, where empagliflozin resulted in significantly lower all-cause mortality compared with placebo (8.3% vs 5.7%; HR, 0.68 [CI, 0.57–0.82; *P*<0.001]).

A question of population?

Although the reduction of the composite of CV death or HHF may not have been of the same magnitude seen in EMPA-REG OUTCOME or CANVAS, it should be noted that DECLARE patients, unlike those in EMPA-REG OUTCOME or CANVAS, were derived largely from a primary prevention cohort, with 10 186 harbouring multiple risk factors for CVD while just 6974 had established CVD. In CANVAS, approximately one-third of patients did not have established CVD at enrolment, whereas in DECLARE this accounted for almost two-thirds of the study population. DECLARE was the first SGLT2 inhibitor CVOT to enrol such a large proportion of patients without established CVD, demonstrating dapagliflozin's ability to lower HHF in a large primary prevention cohort. Though direct comparisons cannot be made with other studies, owing to differences in trial design and study populations, the lack of benefit on MACE seen in DECLARE may possibly be explained by the larger, healthier patient population enrolled.

Similarly, it has been posited that the non-significant reduction of death from any cause may be due to the restrictive exclusion criteria used in DECLARE, as patients with a creatinine clearance <60 mL/min were excluded. In contrast, patients with an eGFR down to 30 mL/min/1.73 m^2 were included in EMPA-REG OUTCOME. This is notable because SGLT2 inhibitors appear to have greater benefits in patients with chronic kidney disease, so excluding these patients may have limited the benefits.

Safety and key learnings

Dapagliflozin also had a reassuring safety profile in DECLARE, with no signs of increased stroke, amputation or fracture. One further unexpected observation, was the possible decrease in the occurrence of bladder cancer with dapagliflozin compared with placebo (0.3% vs 0.5%, respectively; *P*=0.02). An explanation for this was not offered, although it is an interesting observation given previous suggestions of increased risk in smaller studies, and warrants further investigation.

Dapagliflozin did lead to a significant increase in the incidence of DKA (0.3% vs 0.1%, respectively; *P*=0.02) and genital infections (0.9 vs 0.1%, respectively; *P*<0.001), a risk common to all SGLT2 inhibitors. This appears to be one of the few drawbacks of the class as a whole.

To wrap-up his presentation, Dr Wiviott summarised some of the salient points taken from DECLARE and other SGLT2 inhibitor CVOTs. From what we now understand, the SGLT2

inhibitors appear to have moderate benefits on atherosclerotic MACE and these are confined mainly to those with established CVD. However, there is a lowering of HHF risk and possible renal composite risk, both of which appear to be independent of baseline CVD or prior heart failure.

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Further insight into the cardiovascular benefit of antidiabetes agents

In the wake of so many CVOTs, attention has now turned to the mechanistic nature of these agents – indeed, there are many elegant theories currently already undergoing intense investigation. Multiple small, exploratory studies presented at the AHA gave some additional insight and are worth mentioning.

Following on from EMPA-REG OUTCOME, the EMPA-HEART Cardiolink 6 study explored the effect of empagliflozin on left ventricle (LV) remodelling:

- Patients with type 2 diabetes with stable coronary artery disease (CAD) with or without prior heart failure were randomised 1:1 to empagliflozin or placebo and followed over six months for change in LV mass index using cardiac magnetic resonance (CMR). Empagliflozin led to a significant regression in LV mass index compared with placebo (–2.6 vs –0.01 g/m^2, respectively; *P*=0.01). The greatest improvement among patients in LV mass index was >60 g/m^2 (*P* for interaction=0.007). Only 6% of patients had heart failure in this study, suggesting that empagliflozin results in salutary effects on LV remodelling among patients with stable CAD but normal ejection fraction and without a clear history of HF. This may provide further clues on the mechanisms underlying the benefit these agents have on heart failure.

Meanwhile, two additional studies focussed on the atherosclerotic impact of SGLT2 inhibitors and DPP-4 inhibitors:

- Building on an increasing body of pre-clinical evidence, Tatsuaki Murakami and colleagues showed, in a small study, compelling data that dapagliflozin improves endothelial function and reduces arterial wall thickening, independent of glucose lowering. In this study, patients with type 2 diabetes and stable CAD, who were already on a statin or a sartan, were randomised to either dapagliflozin or enhanced conventional antidiabetes agents without an SGLT2 inhibitor. They quantified flow-mediated endothelium-dependent dilatation (FMD) of the brachial artery after transient forearm occlusion, and also quantified intima–media thickness of brachial artery (IMT) using high-resolution ultrasonography. In the dapagliflozin group, FMD significantly increased (from 3.5±2.6% to 6.5±2.5%; *P*<0.01) and IMT significantly decreased (from 0.33±0.06 mm to 0.31±0.04 mm; *P*=0.04), while both FMD and IMT remained unchanged in the comparator, indicating that SGLT2 inhibitors may have novel benefit in reducing residual risk in progressive atherosclerosis in type 2 diabetes.
- In a second study by the same authors, using the same study design, they assessed the DPP-4 inhibitor, linagliptin. Fifty patients with type 2 diabetes and stable CAD were randomised in the same manner. In this study, linagliptin led to an improvement of FMD from baseline (3.8±1.6% to 6.8±2.5%; *P*<0.01) and IMT (from 0.34±0.11 mm to 0.31±0.10 mm; *P*=0.03), while remaining unchanged in the active comparator. Furthermore, IMT of the common carotid artery did not increase in the dapagliflozin arm (from 1.11±0.38 mm to 1.09±0.37 mm; *P*=0.15) but significantly increased in active comparator (from 1.09±0.45 mm to 1.17±0.49 mm; *P*=0.03). ■

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