Updates from EASD 2017

Stay abreast of the latest news that could influence diabetes care. Pam Brown, Editor-in-Chief of *Diabetes & Primary Care*, rounds up the latest national and international news and clinical research stories.

This issue's breaking news comes from the 53rd Annual Meeting of the European Association for the Study of Diabetes (EASD), held in Lisbon on 11–15 September. This year's conference programme combined basic science and clinical practice, and encouraged lively interaction between speakers and the 15 000 delegates. Several presentations had accompanying research papers simultaneously published in peer-reviewed journals. Here we share some of the key new research findings reported at EASD, with links to the online published papers.

Exenatide once weekly meets safety objective but fails to significantly reduce cardiovascular events

The EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial was conducted in nearly 15 000 people, of whom 73% had established cardiovascular (CV) disease. Exenatide just failed to demonstrate significant improvement in the primary outcome of three-point major adverse cardiac events (MACE; CV death, non-fatal myocardial infarction [MI] and non-fatal stroke) compared with placebo (hazard ratio [HR], 0.91 [95% confidence interval (CI), 0.83–1.00]).

Over a median of 3.2 years, exenatide once weekly was confirmed to be non-inferior to placebo for the three-point MACE outcome, meeting its primary CV safety objective. The incidences of acute pancreatitis, pancreatic cancer and medullary thyroid cancer were similar between the exenatide and placebo groups. Death from any cause was reduced by 14% in the exenatide group (HR, 0.86 [95% CI, 0.77–0.97), although, owing to hierarchical testing and the non-significant MACE finding, this cannot be considered statistically significant.

Experts discussed possible reasons why the three-point MACE endpoint was not significantly reduced in this study while reductions were achieved in the CV outcome trials of other drugs in the glucagon-like peptide-1 (GLP-1) receptor agonist class, LEADER (liraglutide; Marso et al, 2016a) and SUSTAIN-6 (semaglutide; Marso et al, 2016b). The study authors proposed that the shorter treatment (2.4 vs 3.5 years) and follow-up durations (3.2 vs 3.8 years), the slightly lower baseline HbA_{1c} levels compared with the LEADER cohort (64 vs 72 mmol/mol [8.0% vs 8.7%]) and the rates of discontinuation in EXSCEL (some related to difficulties with the original injector device) may have contributed to the findings. In addition, the significant use of drugs such as sodium–glucose cotransporter 2 (SGLT2) inhibitors and other GLP-1 receptor agonists, which are known to reduce CV events, in the placebo group may have reduced the likelihood of achieving a significant difference in CV risk between the two groups.

In LEADER, all-cause mortality was reduced by 15% with liraglutide compared with placebo, similar to the 14% reduction observed with exenatide once weekly in EXSCEL, but there was no reduction in all-cause mortality in SUSTAIN-6. In the ELIXA study (Pfeffer et al, 2015), lixisenatide also failed to demonstrate superiority in its MACE endpoint.

Link to paper: http://dx.doi.org/10.1056/NEJMoa1612917

Continuous glucose monitoring in women with type 1 diabetes improves neonatal outcomes

The CONCEPTT (Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial) randomised controlled trial demonstrated that use of continuous glucose monitoring (CGM), in addition to capillary glucose monitoring, during pregnancy in women with type 1 diabetes was associated with improved glycaemic control in the mothers and significantly improved neonatal outcomes. Women with access to CGM demonstrated slightly lower HbA_{1c}, increased time in the recommended glycaemic range and less time spent in hyperglycaemia than women relying solely on capillary glucose testing. The number of hypoglycaemic episodes was similar in the two groups. The incidences of large-for-gestational-age babies and neonatal intensive care admissions lasting >24 hours were both reduced by around 50%.

Only six women would need to be treated to prevent one large-for-gestational-age baby or one neonatal intensive care unit admission lasting >24 hours, and only eight need to be treated to prevent one case of neonatal hypoglycaemia.

The CONCEPTT study recruited 215 pregnant women and 110 planning pregnancy, and randomised them to CGM and capillary glucose testing or capillary glucose testing alone. No differences were found in those who had access to CGM during preconception rather than pregnancy.

The study authors and an associated editorial in *The Lancet* propose that CGM should now be made available to all women

with type 1 diabetes during the first trimester of pregnancy.

Amongst mothers with type 1 diabetes, birth defects are twice as common and the risk of large-for-gestational-age babies, stillbirth and very high birthweight is three, five and ten times higher, respectively. While 6% of babies from mothers without diabetes are admitted to neonatal intensive care units, 40% of those from mothers with type 1 diabetes require intensive care, incurring extra costs and disrupting breastfeeding. Women with diabetes are, therefore, advised to maintain as tight glucose control as possible in the preconception period and throughout pregnancy to reduce risk of poor outcomes.

Link to paper: http://dx.doi.org/10.1016/S0140-6736(17)32400-5

Link to editorial: http://dx.doi.org/10.1016/S0140-6736(17)32449-2

Caffeine consumption linked to dose-dependent effect on all-cause mortality in women

Data from the US NHANES (National Health and Nutrition Examination Survey) study conducted between 1999 and 2010 demonstrate that caffeine consumption in women with diabetes is inversely proportional to the risk of all-cause mortality, with HRs of 0.49 for <100 mg caffeine per day, 0.43 for 100 mg to <200 mg per day and 0.34 for ≥200 mg per day. There was no association between caffeine consumption and all-cause mortality in men, or between caffeine intake and CV or cancer-related mortality in men or women.

There were differences depending on the source of the caffeine; women with diabetes consuming more caffeine from coffee had lower risks of CV and all-cause mortality, while those consuming more caffeine from tea had a lower risk of cancer-related mortality. There were no significant associations between mortality and caffeine consumption from soft drinks.

The authors conclude that encouraging women with diabetes to consume more caffeine may reduce their mortality risk, but that further studies are needed to confirm their findings. Coffee consumption has previously been associated with decreased risk of mortality and development of type 2 diabetes in the general population, but this is the first report of the relationship between caffeine consumption and mortality in people with diabetes.

Link to poster: https://is.gd/iCWx4L

Sodium intake associated with risk of type 2 diabetes

A Swedish, population-based study compared incident cases of type 2 diabetes (*n*=1136) and latent autoimmune diabetes in adults (LADA; *n*=355) with 1379 matched controls without diabetes. The results demonstrated that, above 2.3 g, each extra gram of sodium consumed per day was associated with a mean 65% increased risk of developing type 2 diabetes.

When participants were divided into three groups of sodium consumption – low (<2.3 g), medium (2.3–2.9 g) and high (>2.9 g) – those in the highest consumption group had a 72% higher risk of developing type 2 diabetes than those in the lowest group. Mechanisms postulated for the increased risk included weight gain, hypertension, decreased magnesium intake (resulting in reduced insulin sensitivity) and an association between sodium intake and a generally unhealthy diet and lifestyle.

Each additional gram of sodium intake increased the risk of LADA by 82%, and those at high genetic risk of LADA were almost three times more likely to develop the condition with a daily sodium intake of >2.9 g than if consuming <2.3 g per day. A postulated mechanism is that increased sodium intake may increase inflammation and act as a trigger for autoimmunity and LADA. These findings may be particularly important in preventing LADA amongst genetically susceptible people.

Dietary salt intake was identified using a validated food frequency questionnaire. Those with higher sodium intake ate less fruit and vegetables, and more processed meat. Salt is 40% sodium, so each 2.5 g of salt consumed contains 1 g of sodium.

Link to presentation: https://is.gd/2X6YUW

Adjunctive treatments in type 1 diabetes improve glycaemia but increase risk of ketoacidosis

DEPICT-1 (Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes) was a 24-week, randomised controlled trial of dapagliflozin 5 mg or 10 mg versus placebo, in conjunction with insulin therapy, conducted in 833 people with inadequately controlled type 1 diabetes (HbA_{1c} ≥61 mmol/mol [7.7%]). Both doses of dapagliflozin significantly reduced HbA_{1c} by 4.6 and 4.9 mmol/mol (0.42% and 0.45%), respectively, versus placebo.

Hypoglycaemia occurred in similar numbers in each of the three groups, and severe hypoglycaemia occurred in 8% and 6% of the dapagliflozin 5 mg and 10 mg groups, respectively, not significantly different compared with 7% of placebo recipients. There were reductions in weight and insulin dose in the dapagliflozin groups. Adjudicated, definite diabetic ketoacidosis (DKA) occurred in four (1%) and five people (2%) in the dapagliflozin groups, and in three people (1%) in the placebo group. A 28-week extension study is ongoing.

Similarly, a 24-week, phase III, double-blind trial of sotagliflozin (a combined SGLT1 and SGLT2 inhibitor) 400 mg/day in 1402 people with type 1 diabetes demonstrated a significantly higher achievement of the primary endpoint (HbA_{1c} <53 mmol/mol [7.0%] with no episode of severe hypoglycaemia or DKA) compared with placebo (28.6% vs 15.2% of participants). There was a significantly lower rate of documented hypoglycaemia in the sotagliflozin group and similar rates of severe hypoglycaemia between the groups. However, the rate of DKA was significantly higher in the sotagliflozin group

(21 participants; 3%) compared with the placebo group (four participants; 0.6%).

These are the first published phase III trials of a selective SGLT2 inhibitor and a combined SGLT1/SGLT2 inhibitor as adjunctive therapy to insulin in people with type 1 diabetes, and the authors suggest these agents may offer future benefits in this population. However, in an accompanying editorial in the *New England Journal of Medicine*, David Nathan, Director of the Diabetes Center at Massachusetts General Hospital, highlights that, although small reductions in HbA_{1c} may translate into reduced microvascular event rates, as was demonstrated in the DCCT (Diabetes Control and Complications Trial), increased DKA risk is likely to persist over time, and short-term studies do not allow quantification of the relative benefits and risks of these adjunctive treatments. The author believes that future improvements in treatment of type 1 diabetes will result from better insulins and delivery systems, rather than from adjunctive oral drug therapies.

Link to dapagliflozin paper: http://dx.doi.org/10.1016/S2213-8587(17)30308-X

Link to sotagliflozin paper: http://dx.doi.org/10.1056/NEJMoa1708337

Link to editorial: http://dx.doi.org/10.1056/NEJMe1711296

Acarbose in impaired glucose tolerance does not reduce cardiovascular events

In a randomised, double-blind, placebo-controlled trial in 6522 Chinese individuals with CV disease and impaired glucose tolerance (the ACE [Acarbose Cardiovascular Evaluation] trial, acarbose failed to significantly reduce the risk of a five-point MACE endpoint (CV death, non-fatal MI, non-fatal stroke, hospitalisation for unstable angina or hospitalisation for heart failure). Of a large group of secondary outcomes, which included the individual five-point MACE components, the conventional three-point MACE, death from any cause, development of diabetes and development of impaired renal function, only development of diabetes was significantly reduced, by 18% (HR, 0.82 [95% CI, 0.71–0.94]). Not surprisingly, gastrointestinal side effects were the most common reason for discontinuation, occurring in 7% of treated participants and 5% of the placebo group.

An associated *Lancet* editorial concludes that the ACE trial confirms the benefits of acarbose in reducing progression from impaired glucose tolerance to type 2 diabetes (Nauck et al, 2017), as was previously suggested by the smaller STOP-NIDDM study (Chiasson, 2006), although ACE failed to confirm the CV benefits suggested by the latter study. As an alpha-glucosidase inhibitor, acarbose reduces postprandial glucose excursions. Therefore, at least in people with impaired glucose tolerance rather than type 2 diabetes, the postulated increased CV risk associated with high postprandial glucose levels has not been confirmed in this study.

Link to paper: http://dx.doi.org/10.1016/S2213-8587(17)30309-1

Link to editorial: http://dx.doi.org/10.1016/S2213-8587(17)30318-2

Further analyses from the DEVOTE trial

Previously, the DEVOTE trial demonstrated that insulin degludec was non-inferior to insulin glargine in terms of CV events and mortality, and was associated with lower rates of severe hypoglycaemia, in people with type 2 diabetes (Marso et al, 2017). At EASD, the investigators presented results of two observational, epidemiological analyses based on the original trial data.

DEVOTE 2 demonstrated that individuals with higher day-to-day fasting glycaemic variability had a similar risk of MACE to those with lower variability, but had an increased risk of severe hypoglycaemia and all-cause mortality. In DEVOTE 3, those who had severe hypoglycaemia were found to have the same risk of MACE as those who did not; however, they had a doubling of future risk of total mortality and CV mortality. However, as these were observational studies, they cannot clarify whether the relationships were causal.

Link to DEVOTE 2: https://doi.org/10.1007/s00125-017-4423-z

Link to DEVOTE 3: https://doi.org/10.1007/s00125-017-4422-0

Link to accompanying editorial: https://doi.org/10.1007/s00125-017-4421-1

Cardiovascular events similar with sulfonylureas or pioglitazone added to metformin

The TOSCA.IT (Thiazolidinediones or Sulfonylureas Cardiovascular Accidents Intervention Trial) pragmatic, randomised clinical trial was stopped early at 57.3 months' median follow-up on the basis of a futility analysis. Among 3028 people assigned to pioglitazone or sulfonylureas (glimepiride 2–6 mg in 48%, gliclazide 30–120 mg in 50%, glibenclamide in 2%), the primary endpoint (all-cause mortality, non-fatal MI, non-fatal stroke or urgent coronary revascularisation) occurred in 7% of participants, or 1.5 per 100 person-years, in both treatment groups. At baseline, 11% of participants had had a previous CV event and the mean HbA_{1c} was 61 mmol/mol (7.7%). Secondary endpoints included two expanded CV composite endpoints, one of which included heart failure and new or worsening nephropathy. Heart failure was added as a standalone endpoint at the recommendations of the Data and Safety Monitoring Board during the study.

Significantly fewer people had hypoglycaemia in the pioglitazone group than in the sulfonylurea group (10% vs 34%), as expected, and those treated with pioglitazone had better durability of glycaemic control, with significantly lower treatment failure rates (13% vs 20% failed to achieve an HbA_{1c} of <64 mmol/mol [8.0%]). Moderate weight gain of <2 kg occurred in both groups, with no significant differences between

the groups in the rates of heart failure, bladder cancer (although the study was not powered to identify this), new or worsening nephropathy, or fracture.

The choice of primary endpoint makes it difficult to compare these results with other studies. Annual CV event rates were low in this study, possibly related to the low number of participants with previous CV events, and the authors suggest this may have influenced the lack of CV differences between treatments. An accompanying editorial reminds us that lower CV event rates among people with type 2 diabetes are now more likely due to effective preventive measures, such as use of statins and antihypertensive agents, and that the lower doses of drugs used and appropriate discontinuation of therapy (which was more common in the pioglitazone group) may have contributed to the low rates of side effects (Fonseca and Lovre, 2017).

Guidelines continue to recommend the addition of sulfonylureas or pioglitazone as an add-on to metformin to achieve early tight glycaemic control, but there have been concerns about the potential side effects of these two drug classes. One study that may shed light on this issue is CAROLINA, a CV outcome trial comparing linagliptin with glimepiride (Marx et al, 2015). Other CV outcome trials have only used placebo as a comparator, allowing other treatments to be added to retain control.

Link to paper: http://dx.doi.org/10.1016/S2213-8587(17)30317-0

Link to editorial: http://dx.doi.org/10.1016/S2213-8587(17)30320-0

Multifactorial intervention reduces stroke but fails to significantly reduce CV risk

The J-DOIT (Japan Diabetes Optimal Integrated Treatment) study was a multifactorial intervention trial with the aim of preventing macrovascular complications and mortality. Compared with conventional therapy, intensive control of glycaemia, blood pressure and LDL-cholesterol only achieved a non-significant 19% reduction in the primary outcome (a composite of MI, stroke, revascularisation and all-cause mortality). This reached a significant 24% difference after adjustment for baseline risk factors.

The study, conducted from 2006 to 2016, achieved a mean of 8.5 years' treatment in 2540 people with type 2 diabetes. All of the participants (mean age, 59 years) had hypertension and/or dyslipidaemia, and 11% had a previous history of CV disease. Mean achieved HbA_{1c}, blood pressure and LDL-cholesterol levels were significantly lower in the intensive therapy group (51 mmol/mol [6.8%], 123/71 mmHg and 2.2 mmol/L, respectively) than in the conventional therapy group (55 mmol/mol [7.2%], 129/74 mmHg and 2.7 mmol/L).

Cerebrovascular events were reduced by 58% in the intensive therapy group; however, there were no differences in CV events and all-cause mortality between the groups. Onset or progression of nephropathy, one of the secondary endpoints, was also significantly reduced by 32% in the intensive therapy group.

Link to session: https://is.gd/jOEb72

PCSK9 inhibition with evolocumab reduces CV risk in people with or without diabetes

In a pre-specified analysis of the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) study looking at diabetes status at baseline, the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab significantly reduced the primary endpoint (CV death, MI, stroke, hospital admission for unstable angina or coronary revascularisation) by 17%, and the key secondary endpoint (CV death, MI or stroke) by 18%, in people with diabetes. In those without diabetes at baseline, evolocumab did not have any significant effect on glycaemia or increase the risk of new diabetes, including in those with prediabetes. Overall, 40% (11 031) of participants had diabetes at baseline; of the remaining 60%, 10 344 had prediabetes and 6189 were normoglycaemic.

Link to paper: http://dx.doi.org/10.1016/S2213-8587(17)30313-3 ■

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