51st Annual Meeting of the European Association for the Study of Diabetes

Stockholmsmässan, Stockholm, Sweden

All abstracts and posters and most of the oral presentations and highlight sessions can be viewed online at www.easdvirtualmeeting.org. Sessions for online viewing can be accessed using the presentation reference in blue (e.g. http://www.easdvirtualmeeting.org/contentsessions/2023). Abstract and poster references in green can be found via www.easdvirtualmeeting.org or *Diabetologia* (2015) 58(Suppl 1): S1–S607

The European Association for the Study of Diabetes (EASD) supports a tradition of prestige award lectures at its annual conference, all receiving enthusiastic audience responses. Two are summarised herein as well as other highlights from the 5-day conference.

Understanding phenotypes of prediabetes

In the Claude Bernard Lecture, Professor Häring (Germany) postulated on why some people are unable to increase insulin secretion in response to insulin resistance. Taking stock of his work with the Tubingen family study (>3000 participants) he reported that those who were homozygous for the *TCF7L2* gene single nucleotide polymorphism were unable to increase insulin secretion in response to insulin resistance and glucose loads and progressed from pre-diabetes to type 2 diabetes. Interestingly, participants with the wild-type (normal) gene, responded almost twice as well to treatment with a glucose-like peptide-1 (GLP-1) receptor agonist – suggesting that this is also a mechanism of "incretin resistance".

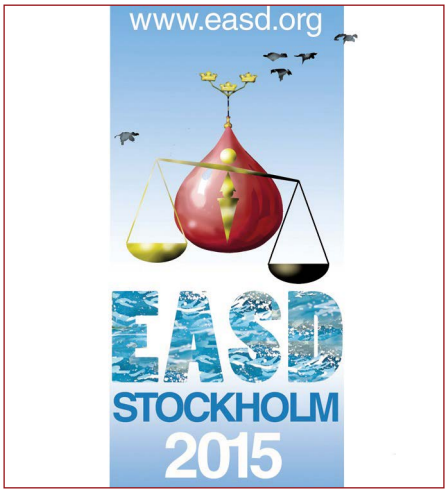
He drew attention to ectopic fat deposition, noting that people with impaired glucose tolerance commonly have fatty liver and that we now know there is crosstalk between the liver and accompanying perivascular fat deposition in the pancreas. The hepatokine fetuin-A, which exacerbates lipotoxicity in the islet, is thought to mediate this crosstalk (92). Indeed, increased plasma fetuin-A is predictive of type 2 diabetes. Exercise is the mainstay of treatment for fatty liver and Professor Häring reminded us that some of these individuals are exercise non-responders, making the condition harder to treat. A study in 20 obese people at high risk of type 2 diabetes showed that 8 weeks of supervised exercise failed to improve insulin sensitivity in 60% of participants despite improving fat mass and cardiorespiratory fitness (526).

Finally, he shared recent research exploring insulin resistance in the brain, which is believed to occur very early in life. The Häring group is currently undertaking scans of fetal brains *in utero* to ascertain if such changes are already visible.

Size, sites and cytes

In the Minkowski Lecture, Professor Matthias Blüher (Germany) reflected on the role of adipose tissue in the regulation of body weight, posing the question: "Is adipose tissue a patient's friend or enemy?"

He recognised that achieving and maintaining a healthy body weight is one of the most challenging goals in the treatment of diabetes and that excess accumulation of adipose tissue increases



the risk of type 2 diabetes. However, he also highlighted that a congenital deficiency of adipose tissue can be associated with type 2 diabetes and fatty liver. Professor Blüher commented on how our understanding of adipose tissue has changed from believing it to be an inert storage organ to now realising that it is a dynamic organ producing more than 600 adipokines with crosstalk and signalling to all other major organs and tissues, but notably those involved in glucose metabolism, appetite and satiety. There is also emerging understanding of the role of the brain in these communications.

Professor Blüher has extensive experience of the FIRKO (Fat-specific Insulin Receptor Knock Out) mouse, which has in-built protection against obesity and glucose intolerance, and

he hopes that this model will facilitate an understanding of the association with insulin resistance and longevity in humans. His development of an adipose bank in Leipzig, Germany, has helped in the understanding of the sub-group of obese individuals who are metabolically "healthy". The individual obesity-related risk is not determined by fat mass alone ***(size)***. He pointed out that contemporary magnetic resonance imaging scanning has made it possible to appreciate the effect of adipose tissue distribution ***(sites)*** in risk. He also commented that adipose dysfunction may be triggered by an inability to increase fat mass via recruitment of new adipocytes ***(cytes)***, which activates pathological cellular mechanisms including insulin resistance. He pointed out that high-quality imaging had improved understanding of the role of macrophages in obesity-induced inflammation. In conclusion, Professor Blüher was optimistic that the emerging science of adipose tissue dysfunction may be more productive in the prevention of metabolic diseases than in achieving extensive weight loss.

EASD debates

EASD debates are designed to be entertaining and stimulate thought. They present different ways of looking at the same data and literature and give participants an opportunity to present a brief oral rebuttal to their opponent at the end of the debate. Online viewing of these debates is highly recommended.

Dogmata debate

Is insulin resistance always bad for you?

Professor Ele Ferrannini (Italy) defended the status quo, whilst Professor David Matthews (UK) challenged the dogma (2023).

Professor Ele Ferrannini highlighted the adverse effects of insulin resistance and possible mechanisms, describing the effects of insulin resistance on a variety of metabolic pathways and clinical features such as increased lipid oxidation, emphasising that insulin resistance constrains the ability to switch from one substrate to another (e.g. from free fatty acids to glucose). He illustrated this by explaining how insulin resistance aggravates hypertension, impaired endothelial function, and increased oxygen need by cardiac muscle. He described how many of these features occurred even in well-controlled diabetes and pointed to mounting evidence for an association between Alzheimer's disease and diabetes, focussing on the potential role of insulin receptors throughout the brain in this association. Professor Ferrannini concluded that insulin resistance is mostly bad for you.

Professor Matthews' central argument was that insulin resistance should not be labelled as a "defect" but recognised as a normal adaptive response to certain physiological situations in which the metabolic changes can be helpful to the body's homeostatic function, accepting that extreme cases of insulin resistance *are* pathological (Semple et al, 2011).

This debate illustrated the enormous variability in insulin resistance amongst people with diabetes and without diabetes: a 23-fold difference in insulin resistance between people without diabetes has been reported (Ferrannini et al, 1997). Unpublished data (Chew and Matthews) using HOMA (Homeostasis Model Assessment) modelling showed that East Asian people are more insulin resistant than non-Asians; yet the insulin resistance in East Asian people is not labelled as "pathological".

Professor David Matthews highlighted that insulin resistance predicts diabetes in later life but surprisingly does not predict death (Welsh et al, 2014). He also considered from an ontological perspective how the body communicates using insulin and adapts its responsiveness. Insulin resistance is the inevitable consequence of a system of signalling between remote parts of the body that still allows local responses. So insulin resistance is physiological but can simply go wrong when people are exposed to modern life. In other words, insulin resistance is not always bad for you.

Do we need triple and quadruple therapies?

Professor Ralph DeFronzo (USA) opened this lively and practically focussed debate (2025) by emphasising that multiple defects in type 2 diabetes will require

multiple therapies to target as many of the defects as possible. He highlighted the problem with a "treat to fail approach" of multiple late additions of therapies to arrest the progressive hyperglycaemia of type 2 diabetes. He noted that current initial treatment with metformin or a sulphonylurea does not target lesions in the beta-cell and described beta-cell preservation with thiazolidinediones and GLP-1 receptor agonist therapies. He described his own data showing that newly diagnosed individuals initiated on triple therapy (metformin, pioglitazone and exenatide) had improved HbA_{1c}, fewer hypoglycaemic episodes and greater durability of glycaemic control than people receiving conventional step-wise treatment intensification (Abdul-Ghani et al, 2015). His take-home message was that in order to keep HbA_{1c} under control, initiate treatment with multiple drugs which target a range of pathological defects of the disease.

Professor Thomas Pieber (Austria) countered this argument with a discussion on the lack of cardiovascular (CV) benefits seen in glucocentric trials, in all but the metformin arm of the UKPDS. He highlighted a poor mortality outcome in the tight control arm of ACCORD where individuals were on multiple treatments. He lamented that recent CV outcome safety studies with dipeptidyl-peptidase 4 (DPP-4) inhibitors and GLP-1 receptor agonists had shown no CV risk reduction whilst conceding that these trials were not designed to do so. Professor Pieber concluded that multiple interventions were needed to improve CV outcomes, but that, as tight glycaemic control only has a small impact on CV outcome, use of multiple glucose-lowering therapies is not needed. He also discussed appropriate HbA_{1c} targets. His argument was weakened by an absence of consideration about microvascular complications – clearly a major reason for effective glycaemic control.

Devices

EASD/ADA symposium (2032)

Professor Steve Russell (USA) described a portable bi-hormonal system with insulin and glucagon cartridges used wirelessly in conjunction with a glucose-sensing device connected to an iPhone, to guide rates of automated insulin and glucagon infusion. The system uses autonomously adaptive algorithms (held in the iPhone), which require only patient body weight at set-up and respond to easy user inputs via the iPhone. This system has improved glycaemic control (without increasing insulin) with minimal hypoglycaemia in people aged 6–76 years with type 1 diabetes. Patients were highly satisfied with the bionic pancreas and registration trials are planned for 2017.

Dr Lalantha Leelarathna (UK) summarised advances in artificial beta-cell research in Europe. The artificial beta-cell is essentially a single-hormone closed-loop system utilising the same principles as the bionic pancreas. Several recent studies have shown the benefits of this system in different groups of adults and children with type 1 diabetes in a range of situations (home, hotel, school etc. [Thabit et al, 2015; 918; 987]). All studies showed reduced glucose variability, improved HbA_{1c} and reduced hypoglycaemia. Portable bi-hormonal pumps are also being studied in Europe and comparisons between single and bi-hormonal systems are awaited. Cost effectiveness is a potential issue due to the price of glucagon. Also, Dr Leelaranthna noted that bionic approaches are not trouble-free.

Professor Lutz Heinemann (Germany) drew attention to the issues surrounding insulin pump therapies, including the current regulatory and reporting framework in the EU and USA, noting the paucity of "real world" data. He summarised the content of the EASD/American Diabetes Association (ADA) statement on insulin pumps and said it was hoped that a more rigorous, standardised and transparent approach to safety would be implemented (Heinemann et al, 2015).

Trial expansions

ACCORD
Action to Control Cardiovascular Risk in Diabetes

DUAL
DUal Action of Liraglutide and insulin degludec

ELIXA
Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes After Acute Coronary Syndrome During Treatment with AVE0010 (Lixisenatide)

EMPA-REG OUTCOME
Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients

TECOS
Trial to Evaluate Cardiovascular Outcomes with Sitagliptin

UKPDS
United Kingdom Prospective Diabetes Study

Changing treatment paradigms

This session offered useful insights to the implementation of pump therapy and the organisational support required (193–198). Presentations by the Steno team (Denmark) described patient pathways for insulin pump and glucose sensor use (193; 196).

In adults, treatment with continuous subcutaneous insulin infusion (CSII) generally lowers HbA_{1c} by ~3.3 mmol/mol (0.3%) compared to multiple daily injection (MDI) therapy, with greater reductions observed early after introduction of CSII, particularly in patients with significantly elevated HbA_{1c} at initiation. The Steno team usually observe HbA_{1c} reductions of 5.5–7.7 mmol/mol (0.5–0.7%) over a year after CSII initiation (the duration of most reported pump studies).

In a 6-year follow-up study of people with type 1 diabetes initiated on CSII therapy, there was a fall in HbA_{1c} of 5.5–7.7 mmol/mol (0.5–0.7%) over a year and a reduction in total insulin doses. There was no increase in body weight and HbA_{1c} reduction was

9.5 mmol/mol (0.9%) after 2 years and insulin dose was 23% lower than at pump initiation, with benefits persisting for 6 years (193). A CSII study over 3 years among people with type 1 diabetes in Greece also demonstrated improved glycaemic control without weight gain, reduced hypoglycaemic episodes and good tolerability (916). A 5-year US observational study in 13 people with type 2 diabetes who were poorly controlled was similarly positive (155).

Younger and more distressed individuals are more likely to discontinue glucose sensor use, despite significantly improved HbA_{1c}. It is important then that after 1 year, 75% of participants in a particular study were using a sensor-augmented pump (SAP) and their distress scores had decreased significantly, suggesting SAP use helped address patient distress (196).

A study in the Netherlands indicated that CSII could be cost effective compared to MDI in uncontrolled type 2 diabetes as it reduced complications (~50% of costs), and increased life expectancy and quality of life (53).

Other management options

The IntroDia study analysed 3628 physician–patient conversations at diagnosis of type 2 diabetes in 26 countries and noted that perceived physician empathy was associated with improved patient wellbeing, less diabetes distress and greater adherence to lifestyle strategies and medication (893). Analysis of 861 patients in the USA whose first HbA_{1c} was >53 mmol/mol (7%) at 6–12 months after initiating metformin found those who transitioned to no adherence or full adherence had an HbA_{1c} increase of 6.9 mmol/mol (0.63%) or decrease of 4.4 mmol/mol (0.40%) respectively (95% confidence interval [CI], 2.95–10.82 mmol/mol [0.27–0.99%]; $P<0.001$) (889).

Identification via the UK Clinical Practice Research Datalink (CPRD) database of people with type 2 diabetes on one or more anti-diabetic medication showed that after 1 year, more patients persisted with oral anti-diabetic therapy than with GLP-1 receptor agonist therapy (87% versus 70% respectively). However, adherence was similar between GLP-1 receptor agonist dosage regimens (799).

A retrospective study from the IMS LRX database in Germany of people with type 2 diabetes initiated on exenatide once weekly (n=5449) or liraglutide (n=24 648) showed that adherence to therapy was 66% ($P<0.0001$) better with exenatide once-weekly, and that older individuals (>50 years of age) were strikingly more adherent (795). Another study noted that people on fixed-dose combination tablets were more likely to be adherent compared to those on loose-dose combination therapy (57.0% versus 50.7%; $P<0.0001$ [358]).

Sodium–glucose cotransporter 2 inhibitors

As the newest oral glucose-lowering class in clinical use, the sodium–glucose cotransporter 2 (SGLT2) inhibitors were of particular interest, with studies looking at renal function noting that there is a transient reduction of estimated glomerular filtration rate (eGFR) on treatment initiation and improvements in albuminuria over time (164; 185; 747). It has also been suggested that improved blood pressure may, in part, reflect reduced arterial stiffness (751; 753). In a 6-month observational study, these agents did not have an adverse effect on bone metabolism in type 2 diabetes (767), and two studies allayed concerns regarding dehydration with these agents in hot climates (756) and during the Ramadan fast (757). Genital infections, a recognised side-effect of SGLT2 inhibitor therapy, have been shown to decrease with protracted use (758).

EMPA-REG OUTCOME results

The CV safety trial EMPA-REG OUTCOME assessed CV outcomes with empagliflozin as add-on to usual therapy in adults with type 2 diabetes and established CV disease, a BMI of ≤45 kg/m^2 and eGFR ≥30 mL/min/1.73 m^2 (2030). The study was event driven, requiring 691 events to achieve a 95% CI for a hazard ratio (HR) <1.3 (the value mandated by the US Food and Drug Administration as indicative of CV safety), and powered to show non-inferiority but with an opportunity to demonstrate CV superiority. By 2015, there were 772 primary outcome events (3-point major adverse cardiovascular events [MACE] comprising a composite of CV deaths, fatal and non-fatal myocardial infarction and non-fatal stroke) over a median observation period of 3.1 years.

In total, 7020 people, in 42 countries, were randomised in a 1:1:1 ratio to receive placebo or 10 mg or 25 mg of empagliflozin once daily. Baseline, demographic and clinical characteristics were similar in all groups with equivalent proportions of participants receiving similar CV risk treatments and about 50% of individuals receiving insulin. Empagliflozin was in general well tolerated (the exception being increased genital infections), and there were few differences in adverse events between placebo and both treatment groups.

The primary (3-point MACE) and main secondary outcomes (3-point MACE plus hospitalisation for angina) comparing placebo with pre-planned, pooled empagliflozin data are shown in *Table 1*. Treatment with empaglifozin was superior to usual care, with a reduction in events being evident within the first few months of treatment – unusual in a study investigating CV safety. SGLT2 inhibitors are multi-tasking agents that offer benefits additional to reducing hyperglycaemia (speculate as you please on the reasons for this positive outcome on CV risk).

End sessions

The TECOS results, originally reported at the ADA conference in June 2015, were updated with sub-analyses which supported

Table 1. Summary of primary and secondary endpoints in EMPA-REG OUTCOME study.

	Empagliflozin 10 or 25 mg od (*n*=4867) %	Placebo (*n*=2333) %	Hazard ratio (95% CI)	*P* value (significant if *P*<0.05)
3-point MACE	10.5	12.1	0.86 (0.72–0.99)	–
Non-inferiority	–	–	–	<0.001
Superiority	–	–	–	0.04
4-point MACE	12.8	14.3	0.89 (0.78–1.01)	–
Non-inferiority	–	–	–	<0.001
Superiority	–	–	–	0.08
All-cause death	5.7	8.3	0.68 (0.57–0.82)	<0.001
Cardiovascular death	3.7	5.9	0.62 (0.49–0.77)	<0.001
Non-fatal myocardial infarction	4.5	5.2	0.87 (0.70–1.09)	0.22
Silent myocardial infarction	1.6	1.2	1.28 (0.70–2.33)	0.42
Non-fatal stroke	3.2	2.6	1.24 (0.92–1.67)	0.16
Hospitalisation for heart failure	2.7	4.1	0.65 (0.50–0.85)	0.002
Hospitalisation for heart failure or death from cardiovascular causes, excluding stroke	5.7	8.5	0.66 (0.55–0.79)	<0.001

3-point major adverse cardiovascular event (MACE)=composite of cardiovascular death and non-fatal myocardial infarction and stroke; 4-point MACE=3-point MACE plus hospitalisation for additional cardiovascular problem; CI=confidence interval; od=once daily.

the wider published observations for this CV safety trial. Particularly, sitagliptin can be safely used to improve glycaemic control in people with type 2 diabetes without concern for worsening heart failure or causing pancreatic cancer (2045). A session on the ELIXA trial affirmed the CV safety data presented at ADA last June.

The DUAL programme is investigating the use of a fixed-dose combination injection (IDegLira – insulin degludec and liraglutide) in different clinical scenarios for type 2 diabetes (2042). In summary, switching to IDegLira improved body weight control and reduced HbA_{1c} and improved patient important outcomes (assessed in DUAL III and V). Results from DUAL V were reported at this meeting (836), and DUAL VI and VII are ongoing.

There were several studies at the EASD conference showing the utility of SGLT2 inhibitors in type 2 diabetes as monotherapy and in combination with other oral agents, GLP-1 receptor agonist and insulin. SGLT2 inhibitors in the treatment of type 1 diabetes was considered a trending topic and this session described the benefits of this approach and addressed concerns regarding euglycaemic ketoacidosis (2170). Delegates were reminded that the utility of insulin goes beyond glycaemic control and Professor Anne Peters (USA) shared her protocol for off-label use of SGLT2 inhibitors in type 1 diabetes.

For a front row seat at EASD 2015 go to the virtual meeting site, select a presentation and be informed and entertained in complete comfort. ■

Authorship and funding statement

Caroline Day was the principal author of this report. Pam Brown, Grainne Connelly, Alia Gilani, Gwen Hall, Katharine Higgins, Greg Jones, Colin Kenny, Mayank Patel and Garry Tan also contributed to the writing of the report. This article has been funded by Janssen, part of the Johnson & Johnson Family of Diabetes Companies. Janssen had no editorial control over the article. Janssen sponsored the attendance of the authors to the EASD meeting.

Abdul-Ghani MA, Puckett C, Triplitt C et al (2015) Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. *Diabetes Obes Metab* **17**: 268–75

Ferrannini E, Natali A, Bell P et al (1997) Insulin resistance and hypersecretion in obesity. European Group for the Study of Insulin Resistance (EGIR). *J Clin Invest* **100**: 1166–73

Heinemann EL, Fleming GA, Petrie JR et al (2015) Insulin pump risks and benefits: a clinical appraisal of pump safety standards, adverse event reporting and research needs. A Joint Statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. *Diabetologia* **58**: 862–70

Semple RK, Savage DB, Cochran EK et al (2011) Genetic syndromes of severe insulin resistance. *Endocr Rev* **32**: 498–514

Thabit H, Tauschmann M, Allen JM et al (2015) Home use of an artificial beta cell in Type 1 diabetes. *New Engl J Med* 17 Sept [Epub ahead of print]

Welsh P, Preiss D Lloyd SM et al (2014) Contrasting associations of insulin resistance with diabetes, cardiovascular disease and all-cause mortality in the elderly: PROSPER long-term follow-up. *Diabetologia* **57**: 2513–20