Extended commentary from the American Diabetes Association 2015 meeting

Dr Mike Gwilt[1] and Dr Caroline Day[2] take a closer look at the 75th Annual Scientific Sessions of the American Diabetes Association, Boston, MA, June 4–9, 2015

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Table 1 Awards at ADA 2015

Award	Recipient
National Scientific & Health Care Achievement Awards	
Banting Medal for Scientific Achievement Award	Philipp E Scherer, Texas, USA
Outstanding Scientific Achievement Award	Pere Puigserver, Massachusetts, USA
Albert Renold Award	Richard N Bergman, California, USA
Outstanding Achievement in Clinical Diabetes Research Award	David M Nathan, Massachusetts, USA
Outstanding Physician in Clinical Diabetes Research Award	Lori Lafel, Massachusetts, USA
Outstanding Educator in Diabetes Award	Linda M Delahanty, Massachusetts, USA
Harold Rifkin Award for Distinguished International Service in the Care of Diabetes	Karl Eric Morgensen, Denmark
Kelly West Award for Outstanding Achievement in Epidemiology	K M Venkat Narayan, Georgia, USA
Professional Interest Group Award Lectures	
Edwin Bierman Award (Complications)	George L King, Massachusetts, USA
Norbert Freinkel Award (Pregnancy)	Elisabeth R Mathiesen, Denmark
Roger Pecorara Award (Foot care)	Karel Bakker, The Netherlands
Richard R Rubin Award (Behavioural Medicine & Psychology)	Robert Anderson, Michigan, USA
Association Officers Leadership and Service Recognition	
Charles H Best Medal	Janel L Wright
Rachmiel Levine Medal for Service	David G Marrero
Banting Medal	Samuel Dagogo-Jack
Charles Kopke Medal	Richard Farber

Introduction

The world's largest diabetes congress

The 75th Annual Scientific Sessions of the American Diabetes Association was held in the Boston Convention and Exhibition Center, close to the city's harbour. The meeting, attended by some 18,000 delegates and acclaimed as the world's largest diabetes congress, opened with 17 'Meet The Expert' sessions, followed by a multiplicity of symposia, oral sessions, and major award lectures (Table 1). There were also presentations and displays of posters and more than 3000 abstracts were published in association with the meeting.[1,2] The abstracts themselves are available at www.abstractsonline.com/pp8/#!/3699 and most posters can be viewed at www.ada.apprisor.org.

Check out the data

In the following commentary the references cited refer to the numbers of the abstracts, which also denotes presentation format: for example, 1-OR was an oral presentation, 386-P was a poster and 2374-PO shows that the material was in published-only format[1] whilst 1-LB describes a Late Breaking poster.[2] For ease of reading we have not spelt out trial acronyms in the text and you can find these in Table 2.

Cardiovascular safety

The so-called cardiovascular outcomes trials – a requirement of the US Food and Drug Administration (FDA) – have been conducted over a relatively short time period with regard to opportunity to observe potential cardiovascular benefit (in the UKPDS it took 6 years for the cardiovascular benefit of metformin to become apparent). Thus, it is no surprise that all the cardiovascular outcomes trials presented to date have shown non-inferiority (as opposed to superiority) for major adverse cardiovascular events (MACE). ELIXA and TECOS, which were granted an afternoon of back-to-back symposia, also reassuringly showed non-inferiority for MACE. Neither trial demonstrated any suggestion of adverse cardiovascular outcomes, either on their prespecified primary and secondary composite endpoints, the single-outcome components of the composites, or any other exploratory outcomes, including pancreatic cancer, pancreatitis and infection. The cardiovascular outcomes meta-analysis of phase 2/3 trials with dulaglutide also offers reassurance (1127-P), as do sub-analyses from SAVOR/TIMI-53 and EXAMINE.

But how representative are these trials for people with diabetes seen in routine practice? An analysis of the eligibility of the general US population for cardiovascular outcomes trials with incretin agents showed that only 28% of the current US population with diabetes would have qualified for any of the trials (1201-P). In the routine care setting the proportion of patients who would have been eligible are: 21% for SAVOR (saxagliptin), 9% for CARMELINA (linagliptin), 5% for CAROLINA (also linagliptin), 4% for TECOS (sitagliptin) and 0.5% for EXAMINE (alogliptin). This is due to the selection of patients at high cardiovascular risk to provide a timely conclusion to an event-driven trial and to ensure adequate power to exclude the possibility of adverse cardiovascular outcomes

Table 2 Trial acronyms

CARMELINA	Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus
CAROLINA	Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes
DECARTES	Durable Effect of PCSK9 Antibody Compared with Placebo Study
DECLARE–TIMI58	Dapagliflozin Effect on CardiovascuLAR Events–Thrombolysis in Myocardial Infarction Study group 58
ELIXA	Evaluation of LIXasenatide in Acute coronary syndrome
EXAMINE	EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome
SAVOR–TIMI53	Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus–Thrombolysis in Myocardial Infarction Study group 53
SCALE	Satiety and Clinical Adiposity – Liraglutide Evidence
TECOS	Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin
UKPDS	UK Prospective Diabetes Study

in high-risk patients. Nevertheless, this poster raises the question of just how representative are these trials of the general patient population seen in routine clinics.

DECLARE-TIMI58 is the ongoing cardiovascular outcomes trial of the SGLT2 inhibitor, dapagliflozin. A previously described pooled analysis (21 phase 2b/3 trials in type 2 diabetes patients treated with dapagliflozin for ≤4 years) demonstrated no excess of MACE with dapagliflozin. New research presented here showed that there was also no increase in cardiovascular events with this agent in a subgroup of older patients (≥65 years) with cardiovascular disease and hypertension (15-OR).

A cardiovascular outcome trial with the GPR40 agonist fasiglifam was terminated early due to undue risk of liver toxicity. At study termination (mean drug exposure was 221 ± 134 days), 3,207 subjects at high cardiovascular risk had been enrolled and the study's primary endpoint (composite cardiovascular death, nonfatal myocardial infarction and stroke or hospitalisation for angina) had occurred in 40 subjects (2.5%) in each group (111-LB).

PDE5 inhibitors and myocardial infarction

Analysis of five primary care diabetes registers identified 857 men with total testosterone of ≤12 nmol/L and free testosterone ≤0.25 nmol/L who were followed for a mean of 5.8 years. Increased mortality was observed in men with untreated low testosterone levels. Men receiving testosterone therapy (long-acting testosterone undecoanoate) showed a 62% reduction in mortality, despite being at greater cardiovascular risk at baseline and twice as likely to be taking a PDE5 inhibitor (9-LB). Analysis of 42 primary care records identified 7,860 men with type 2 diabetes diagnosed before 2007. Follow up in 2014 showed that PDE5 inhibitor use in men at high cardiovascular risk was associated with a significant reduction in overall mortality and the risk of death was reduced by 50% in 432 men who had an incident myocardial infarction (7-LB).

PCSK9 inhibitors

These drugs represent the next major step forward in the management of dyslipidaemia, reducing in LDL-C in excess of 50%, even added to intensive statin treatment. Evolocumab and alirocumab are the agents most advanced in development, and each has received positive opinions from both the European Medicines Agency and the FDA, so marketing authorisation is pending.

In a pooled analysis of four phase 3 trials in patients with or without type 2 diabetes, treatment for 12 weeks with evolocumab (given by either 2-weekly or monthly injections) induced reduced LDL-C by 57–62% (257-OR). Alirocumab (2-weekly injections) similarly induced reductions in LDL-C of 59–63% in people with or without type 2 diabetes in the Odyssey Long Term trial (1296-P). Reassuringly, 12 month data from the DESCARTES study affirmed the lipid lowering efficacy of evolocumab in patients regardless of glycaemic status and recorded no notable changes in glycaemic status, new onset diabetes (a concern with statin use) or other key safety issues (258-OR).

DPP4 inhibitors

Sub-analyses explored the effects of saxagliptin or alogliptin on outcomes in subpopulations from SAVOR (cancer [11-OR], race/ethnicity [15-LB], lymphocyte count [1239-P], liver enzymes [1227-P]) and EXAMINE (ACE inhibitor use [12-OR], ischaemic outcomes and hospitalisations [13-OR]). There was no cancer signal for DPP4 inhibition and we now know that a lower lymphocyte count is a risk factor for adverse cardiovascular outcomes. Otherwise, none of these analyses revealed a subgroup with outcomes different from the main analyses of the trials. Interestingly, data from SAVOR suggested that sulphonylurea treatment did not promote adverse cardiovascular outcomes (504-P), which has long been a source of controversy in diabetes pharmacotherapy.

Vildagliptin provided better overall daily glucose control (as measured by continuous glucose monitoring [CGM]) than sitagliptin (942-P) or saxagliptin (1230-P), although vildagliptin and sulphonylureas exerted similar effects on glucose variability (1286-P).

Little was presented this year on sitagliptin, the first-in-class, but a 12 week study showed that this agent given at 50 mg/day reduced circulating CD4+ T cells – especially the proportion of Th17 and Tregs cells, but numerical data were not provided (1252-P). With regard to DPP4 inhibition in general, large database studies or meta-analyses provided further evidence of a lack of association of DPP4 inhibition with pancreatitis (1703-P). Addition of a DPP4 inhibitor to insulin therapy has again been shown to improve glycaemic control without additional hypoglycaemia or weight gain (1245-P).

New agents in development include gemigliptin (127-LB), retagliptin (1188-P), teneligliptin (1251-P) and gosogliptin (1269-P). Omarigliptin, the first once weekly DPP4 inhibitor improved glycaemic control in Japanese patients with type 2 diabetes when used as add-on therapy to metformin, a sulphonylurea, a meglitinide, a thiazolidinedione or an α-glucosidase inhibitor (1231-P).

GLP-1 receptor agonists

Duration of action and effects on heart rate

It would appear that the GLP-1 agonist class contains at least two subdivisions, based on duration of action: shorter acting agents are

more effective on postprandial glycaemia and longer acting agents tend to be more effective on fasting plasma glucose. Also, increased heart rate has always been a concern with the GLP-1 agonist class. Shorter-acting agents (lixisenatide, exenatide BID) induced smaller (1–3 bpm) and relatively transient (1–12 h) increases in heart rate, while longer-acting agents (liraglutide, exenatide QW and dulaglutide) exerted larger increases (6–9 bpm) that lasted into the night (2566-PO). A head-to-head comparison of lixisenatide versus liraglutide showed that the latter increased sympathetic activation in line with effects on heart rate throughout the day, whereas the increase in heart rate and sympathetic drive with lixisenatide only occurred transiently after dosing (282-OR).

Efpeglenatide, a very long-acting GLP-1 agonist, induced smaller increases in heart rate than liraglutide (278-OR), so there may yet prove to be subdivisions within the longer-acting GLP-1 agonists. Increased heart rate was identified as a risk factor for adverse cardiovascular outcomes many years ago. Whether this proves to be an issue with the longer acting agents (in particular) remains to be seen.

Long-acting GLP-1 receptor agonists

PB119 has a half-life about 50–70 h, permitting at least a QW dosing regimen. This long duration of action is due to addition of a long polyethylene glycol chain to exenatide (275-OR).

Efpeglenatide (*née* HM11260C or ^{LAPS}Exendin-4) is essentially exenatide attached to two non-glycosylated immunoglobulin Fc fragments, via a flexible polyethylene glycol linker. This agent has a half-life of about 150 h and is effective weekly (278-OR) or even monthly (105-LB). Efpeglenatide can be co-formulated with ^{LAPS}insulin (insulin115, based on glargine) to make ^{LAPS}Combo (172-OR). A "superagonist" mechanism of efpeglenatide involves retaining GLP-1 receptors on the cell surface for added efficacy (1116-P) and this agent is thought to have potential as an anti-obesity agent in obese non-diabetic people (303-LB).

Attachment of elastin-like polypeptides to bioactive proteins provides a further way to enhance their duration of action. The length of the polypeptide determines the precise temperature at which a phase transition occurs that causes the molecule to drop out of solution. Thus, a stable, clear solution in a vial at 25°C becomes a slowly-dispersing, long-acting depot in the warmer environment of the subcutaneous tissue. PE1039 is a "super long-acting" analogue of human insulin and PB1023 is a once weekly GLP-1 agonist, each based on this technology and which can be co-administered (168-OR).

GLP-1 agonist plus insulin

When the GLP-1 agonists were introduced it was generally thought that they would only be effective early in the course of diabetes, due to their enhancement of glucose-dependent insulin release. Today, we know that adding a GLP-1 agonist to insulin for a patient with advanced type 2 diabetes will markedly improve glycaemia (especially postprandially), permit substantial reductions in the dose of insulin, limit insulin-induced weight gain (and often induce weight loss) and reduce the frequency of hypoglycaemia. GLP-1 agonists might reduce glucose variability when given with insulin in patients with type 2 diabetes, as shown by studies with GLP-1 agonists involving CGM (167-OR, 1110-P).

There were 25 clinical reports on combinations of a GLP-1 agonist with insulin, including the fixed-dose combinations (FDCs), LixiLan® (lixisenatide + glargine; e.g. 169-OR, 107-LB), and IDegLira® (degludec + liraglutide) and reports on exenatide QW and BID, and dulaglutide. It would appear that the signal transduction mechanisms following activation of insulin (glargine in this case) and GLP 1 receptors (lixisenatide) remain entirely separate, with no cross talk between them (1113-P).

Most presentations on currently approved GLP-1 agonists concerned data cuts in special populations, although dulaglutide may have modestly improved renal function in type 2 diabetes (1114-P).

GLP-1 receptor agonists in type 1 diabetes

In insulin-treated type 2 diabetes, addition of a GLP-1 agonist has reduced weight gain and insulin dose, so that there may be merit in GLP-1 agonist usage in type 1 diabetes. In the LIRA-1 trial liraglutide (1.8mg QD) reduced body weight (~ 6 kg versus placebo over 6 months) and daily insulin requirement in overweight, poorly controlled patients with diabetes. There was no change in the hypoglycaemia rate or in HbA_{1c} compared with placebo (277-OR). These observations were consistent with those of a similar trial (with liraglutide 1.2mg QD) in normal weight patients (279-OR). However, in another study in type 1 diabetes, the addition of liraglutide (1.8mg QD) reduced insulin dose by 20% and HbA_{1c} by 0.45% (1141-P). Liraglutide has also been shown to reduce glucose variability under closed loop conditions (220-OR).

GLP-1 receptor agonists as anti-obesity agents

Liraglutide 3.0 mg is now approved for therapeutic use within the management of obesity. This dose of liraglutide reduced body weight irrespective of body mass index (BMI) at baseline in the SCALE Diabetes Trial (307-LB) and improved patient-reported outcomes vs. placebo in this population (2219-P). Liraglutide may be useful for non-responders to bariatric surgery (2233-P, 2560-PO).

Dual peptide receptor agonists

HM12525A is a dual GLP-1-glucagon agonist, and uses the LAPS technology (described earlier) to link versions of these peptides together via a human immunoglobulin Fc protein. Phase I data show that the pharmacokinetic properties of this agent support the once-weekly dosing schedule of its GLP-1 agonist relatives (173-OR). MOD-6031, a long-acting preparation of oxyntomodulin (a peptide co-secreted with glucagon that activates both glucagon and GLP-1 receptors) is in preclinical development, where it has been shown to inhibit food intake and induce weight loss (1136-P).

Attaching long fatty acid chains to derivatives of GLP-1 and GIP can generate full co-agonists at these peptides' receptors, in mice, with a half-life of about 4–20 hours (2086-P). Linking GLP-1 and GIP to Fc proteins also produces a dual agonist which is effective in preclinical models (2350-P). ZP-DI-70 is another dual GLP-1/GIP dual agonist in preclinical investigation (2061-P).

Novel insulins

Basal insulins

Comparison of the ultra long-acting insulin degludec with glargine was the subject of several presentations which supported the current usage of degludec. A number of presentations focused specifically on Asian patient populations. One presentation concluded that U200 degludec had a larger effect on FPG and a lower incidence of hypoglycaemia than standard U100 glargine (1040-P) – hardly surprising and a comparison with U300 glargine may have been more equitable.

The snappily-named 'Basal insulin lispro pegylated' (BIP), was the subject of at least 17 oral or poster presentations. This agent has a liver-preferential action; suppressing endogenous hepatic glucose production similarly to glargine, but showing less peripheral activity (89-LB). BIP also elevated some liver enzymes during treatment (989-P), which will be a note of caution for the future.

Other presentations on BIP included demonstrations of larger effects on glycaemia than glargine in insulin-naïve type 2 diabetes patients (93-OR), type 2 diabetes patients on background oral therapies (984-P), type 2 diabetes patients using a basal-bolus regimen (985-P) or in type 1 diabetes patients (95-OR, 986-P). A pooled analysis revealed a lower in-

cidence of nocturnal hypoglycaemia with BIP than glargine (988-P). BIP was more effective at reducing glycaemic variability than glargine (94-OR), but counter-regulatory hormonal responses to BIP and glargine were similar (993-P). Other studies focused mainly on binding kinetics, pharmacokinetic/pharmacodynamic studies, dosing flexibility and effects on lipids.

The therapeutic effect of glargine U300 was the subject of 10 presentations, including demonstrations of better sustained glycaemic control with less hypoglycaemia compared with U100 glargine (98-OR, 987-P) or NPH or BID glargine (1021-P). Meta-analyses supported a superior therapeutic profile of U300 glargine versus U100 glargine, premix or NPH insulin (99 OR, 1030-P). Other studies stratified datasets for age, gender, BMI or diabetes duration.

Several weekly basal insulins are in development, including Insulin115 (also known as HM14270) which reported preclinical and pharmacokinetic modelling data (96-OR, 86-LB). PE0139, which is insulin attached to an elastin-like polypeptide, displayed a peakless weekly profile in type 2 diabetes patients (100-OR). AB101 (a microsphere formulation of pegylated human insulin) produced a slow onset and sustained insulin levels in several species and did not cause acute hypoglycaemia (97-OR). The glargine analogue, Elin-H, is comprised of glargine with a histidine moiety attached to the B chain; this modification has extended the duration of action to at least 36 hours, compared with 20–24 hours with glargine (84-LB).

Biosimilar insulins

Of 19,600 insulin-treated Asian patients in 11 countries, 7% were using biosimilar insulin, with usage ranging from 6.5% in Vietnam to 60% in India. These patients were mainly younger, heavier and poorly controlled. Biosimilar use was associated with higher insulin dose and HbA_{1c} in a multivariate analysis (1023-P).

Studies of the *in vitro* properties of the glargine biosimilar LY glargine (LY LY2963016) did not show any significant differences with glargine itself (1033-P) and antibody responses in people with type 1 and type 2 diabetes were also similar to those receiving glargine (1029-P). In euglycaemic clamp studies in non-diabetic subjects, the glargine biosimilar MK-1293 showed bioequivalence with glargine (1026-P).

Prandial insulins

Most of the interest surrounding rapid acting insulin related to the absorption properties of Faster Acting Insulin Aspart (general pharmacodynamic studies, effects in young people with type 1 diabetes, suitability for use in pumps and mechanistic studies focusing on the contribution of nicotinamide to the therapeutic profile). The concentrated rapid insulin BIOD-531 was studied in type 2 diabetes patients (92-LB, 977-P) and pump users (1016-P). Other new rapid insulins featured were Ultra-Rapid BioChaperone Insulin Lispro (BC LIS), which was faster acting than lispro (979-P), and it was reported that the biosimilar, SAR342434, showed bioequivalence with Humalog insulin (1022-P).

Inhaled insulins

The limited long-term safety data for the newly-approved Technosphere® insulin (Afrezza®) led the authors of a meta-analysis to conclude that this product should be reserved for "non-pregnant, non-smoking, adult patients with diabetes, free of pulmonary disease, who are needle-phobic and would otherwise delay initiating or intensifying insulin" (96LB). However it would appear unnecessary to restrict its use in people with upper respiratory tract infections, as these do not affect the absorption of this inhaled insulin (94-LB).

Dance-501 is an aerosolised human insulin with similar within-subject variability to lispro (978-P). Variations in particle size within the aerosol do not influence within-subject variability in the response to this novel insulin (1028-P).

Oral insulin

Ingestion of the oral insulin ORMD-0801 by type 1 diabetes patients before meals reduced prandial insulin requirements and positively impacted on fasting glucose, though no benefit was reported for post-prandial glucose (1058-P). Oral insulin is hypothesised to partially restore insulin signalling in the liver, before dilution of the insulin in the general circulation.

Devices

Meters and pumps

A comparison of 17 blood glucose meters found wide variations in performance with seven meeting the ISO15197: 2003 criteria and only two meeting the updated 2013 criteria. There was no correlation between accuracy and cost of test strip (72-LB). A comparison of six meters drew similar conclusions but suggested that the magnitude of variation may not be clinically significant, according to their performance on the Consensus Error Grid (944-P). Elsewhere, the Contour® Next USB, Freestyle InsuLinx® and OneTouch® Verio™ IQ systems met the ISO15197: 2013 criteria (938-P). The Abbott Navigator® II and Dexcom G4® meters performed identically under open or closed loop conditions in type 2 diabetes patients (956-P). PixoTest does away with the need for a meter entirely, as the patient simply uses their smartphone camera to read a test strip contained within a box physically attached to the lancet (176-OR).

Previous studies (e.g. STAR-3) have shown optimising sensor-augmented pump (SAP) therapy requires patients to wear a glucose sensor for most of the time, and a recent study in newly diagnosed type 1 diabetes patients has added further confirmation, with frequent users of CGM having significantly lower HbA_{1c} (1.1%) at 1 year than infrequent CGM users (355-OR). The Medtronic Threshold Suspend feature, an important intermediate technology between SAP and closing the loop, suspends insulin delivery for up to 2 hours if hypoglycaemic blood glucose levels are imminent. Frequent use of Threshold Suspend increased blood glucose during the day by about 4 mg/dL in the Aspire In-Home study, which was considered a small price to pay for the reduced frequency of hypoglycaemia reported with this feature (1053-P).

A cohort of 250 pump users was very satisfied with this technology (most patients were using SAP) and most found CGM useful. Interestingly, very few of 350 pump users found smartphone (<10%) or (especially) web apps (<6%) useful (1739-P). However, in a 12 week uncontrolled study in poorly controlled type 2 diabetes, use of a smartphone-based diabetes care system (Bluetooth connection to a meter, digital food diary and activity monitor) reduced HbA_{1c} by about 0.5%, but the magnitude of improved glycaemic control correlated with the frequency of glucose monitoring (174-OR).

Closing the loop

In a randomised crossover study, 12 pump-treated adolescents with type 1 diabetes completed 7 days of free living under closed loop or SAP conditions (using a bolus calculator for self administration of prandial boluses). Closed loop control was more effective than SAP ($p<0.001$) at increasing the time within glycaemic target range, time in the hypoglycaemic range was low and similar with both devices, daily insulin dose was similar, but there was a small increase in daily basal insulin dose ($p<0.001$) in patients using closed loop (221-OR).

Nineteen children aged 6-11 years at a diabetes camp were treated for 5 days using a bihormonal insulin:glucagon closed loop system and 5 days with an insulin pump with monitoring using CGM (220-OR). Subjects selected their own meals and participated in all camp activities. The closed loop system delivered lower mean glucose values, greater

time within the target glycaemic range and reduced frequency of oral carbohydrate for hypoglycaemia (once in 1.1 versus 1.8 days).

In adults with type 1 diabetes, setting a closed loop system to establish normoglycaemia before wake-up time improved daytime glucose control and reduced the frequency of hypoglycaemia compared with SAP in both outpatients and home settings (224-OR). The Zone-MPC closed loop control system also demonstrated positive results in outpatients, with increased time in range and less time at <70 mg/dL (225-OR). A number of other studies explored different aspects of closed loop control, such as the benefits of using the system overnight only for 2 months (940-P), or the benefit for dual- versus single-hormone closed loop devices in reducing hypoglycaemia risk during exercise (1059-P). Patients were generally impressed with the closed loop, noting that it is "a game changer" (66-LB).

Other devices

Devices intended to improve insulin delivery include InsuPad®, an injection site warming device and Paq®, is a subcutaneous insulin infusion device that delivers pre-programmed basal rates and boluses at the push of a button.

InsuPad® has been shown to improve insulin kinetics and pharmacodynamics in the controlled conditions of clinical trials (1069-P), and more recently it demonstrated similar performance in the 'real world' (1057-P). In type 2 diabetes patients, 12 weeks' use of Paq®, delivering insulin as intended, reduced HbA_{1c} by ~1.7% from the pre-Paq® values when patients were receiving multiple daily injections (1062-P).

Endobarrier® is an implantable (and removable) liner that prevents upper intestinal food absorption. One year of Endobarrier® use in obese patients with poorly controlled type 2 diabetes reduced weight (by about 13 kg) and improved multiple indices of glycaemic control (967-P).

SGLT2 inhibitors – the newest class

The evidence base deepens

The volume of data is increasing for this newest class of oral antidiabetic agents. Weight loss with dapagliflozin is maintained during up to 4 years of treatment (103-OR) and no increased risk of MACE has been seen in a pooled analysis of trials of dapagliflozin for ≤4 years (15-OR, see earlier).

Evidence is now emerging that long-term treatment with a SGLT2 inhibitor may be renoprotective in diabetes (e.g. 107-OR). Dapagliflozin (combined with saxagliptin) appeared to reduce insulin levels by increasing insulin clearance, as shown by increased C-peptide:insulin ratio, in patients with type 2 diabetes (1223-P).

The clinical development of luseogliflozin (e.g. 948-P) and ipragliflozin (e.g. 1203-P, 1236-P) continues, with an appearance from the even newer agents, henagliflozin (1229-P) and ertugliflozin (2605-PO). New, and unnamed, dual SGLT1/SGLT2 inhibitors were described, but with preclinical data only (2073-P, 2610-PO).

Fixed-dose combinations of SGLT2 inhibitors are coming and a number of presentations supported the use in combination of dapagliflozin + saxagliptin, linagliptin + empagliflozin. The use of lower doses in these combinations appears to reduce the risk of genital infections (1208-P).

SGLT2 inhibitors in type 1 diabetes

The insulin independent mechanism of action of SGLT2 inhibitors has led to interest in their use in type 1 diabetes. The EASE-1 trial showed that empagliflozin (2.5mg; 10mg; 25mg) for 28 days in type 1 diabetes reduced HbA_{1c} and body weight and reduced insulin doses (1213-P), and use of CGM showed that addition of empaglifozin reduced glucose exposure and variability (1241-P).

According to a retrospective analysis, the addition of dapagliflozin to liraglutide and insulin in type 1 diabetes reduced HbA_{1c}, plasma glucose and weight; carbohydrate intake was increased but insulin dose was unchanged (130-LB). An algorithm was proposed for adapting insulin doses in dapagliflozin-treated patients with type 1 diabetes, by using observed urinary glucose excretion to estimate the insulin:carbohydrate ratio (1279-P).

Sotagliflozin (LX4211), a dual SGLT1/2 inhibitor which has previously been shown to benefit type 2 diabetes, has now shown promise in the treatment of type 1 diabetes. Sotagliflozin (400mg QD) reduced postprandial hyperglycaemia and HbA_{1c} and mealtime insulin dosage and body weight. CGM throughout the study also showed that patients spent 62% more time within their target glucose range and 25% less time with hyperglycaemia and did not increase the incidence of hypoglycaemia. Mild nausea was the commonest side-effect, all without additional hypoglycaemia.

SGLT2 inhibitors and euglycaemic diabetic ketoacidosis (DKA)

A symposium presentation on glycaemic control in women drew to attention the off-label use of canagliflozin (the first SGLT2 inhibitor to be approved in the USA) in type 1 diabetes with the presentation of seven cases of euglycaemic (blood glucose 90–233 mg/dL 10.6–12.9 mmol/L) DKA in women, aged 22–33 years. Other cases of euglycaemic DKA in type 1 diabetes have been reported with canagliflozin but this was associated with failure of an insulin infusion system (932-P), and in a patient for whom dapagliflozin plus liraglutide was added to insulin (130-LB). In the symposium similar cases were presented for two men and a woman, all with insulin–treated type 2 diabetes who had undergone recent surgery.

It is perhaps noteworthy that glycaemic control improved with a SGLT2 inhibitor while treatment insulin doses were reduced. These agents lower glycaemia via an insulin-independent mechanism, but insulin is necessary for the normal metabolism of glucose and much more. Therefore, assessment for ketones should be undertaken in insulin-requiring euglycaemic patients who present with any symptoms suggestive of DKA. A discussion of euglycaemic DKA by Peters *et al*, featuring the cases described above, has now been published.[3]

Novel antidiabetic mechanisms

Several novel glucose lowering agents are advanced in development. Those not discussed previously are noted below and promising agents in preclinical development are shown in Table 3.

Saroglitazar, a ***dual PPARα/γ activator***, has been approved in India for the treatment of type 2 diabetes patients in whom it has shown improvements in glucose and lipid metabolism (703-P, 704-P, 126-LB). It has also shown benefit in people with non-alcoholic fatty liver disease (NAFLD), improving liver enzymes and indices of glycaemia (712-P). Combination treatment with saroglitazar and exenatide appears promising for the management of NAFLD (134-LB).

A dose-ranging study of ***imeglimin***, a restorer of mitochondrial function which improves insulin secretion and action, in obese type 2 diabetes patients has identified 1500 mg BID as the optimum dose for phase 3 trials. Imeglimin was well tolerated and did not promote hypoglycaemia or weight gain (1169-P).

LEZ763, a ***GPR119 agonist***, increased glucagon ($p<0.05$), active GLP-1 ($p<0.05$), GIP ($p<0.05$) and PYY ($p<0.05$) following a test meal after 4 weeks of treatment in this dose ranging study in type 2 diabetic patients. Postprandial glucose was not significantly decreased (122-LB). Full?

HMS5552, a ***glucokinase activator***

Table 3 Summary of novel compounds with glucose-lowering efficacy in preclinical studies

Agent	Proposed mechanism of action	Abstract
CmpdA	A dual SGLT1/SGLT2 inhibitor	2073-P
Unnamed	A novel dual SGLT1/SGLT2 inhibitor	2610-PO
LGLS120-A	A GPR120 agonist	1284-P
KBP-042	A dual amylin-calcitonin receptor agonist	1098-P
PBI-4547	An antifibrotic compound	552-P
PBI4050	An antifibrotic/inflammatory compound	1166-P
AJS1669	A muscle glycogen synthase activator	2016-P
BTI-320	A glucommanan-based inhibitor of carbohydrate digestion	974-P
MTBL0036	A mitochondrial uncoupler in the liver	1190-P
TP70	A tricyclic pyrone compound with acyl CoA-cholesterol acyltransferase inhibitor activity	1205-P
JWU-A021	A TRPA1 calcium channel activator which stimulates GLP-1 release	112-LB
GMC-252	A conjugate of an anti-inflammatory and an antioxidant (diflunisal + N-acetylcysteine)	2601-PO
CNX-013-B2	A heterodimer selective rexinoid (also has potential to reduce progression of diabetic complications)	120-LB
Unnamed	An insulin degrading enzyme inhibitor	1101-P
X-MetA	An allosteric anti-insulin receptor antibody	1103-P
Unnamed	A monoclonal anti-aP2 antibody (with particular benefit for treating fatty liver disease)	108-LB
2,4- dintrophenol (CRMP)	A controlled-release mitochondrial protonophore; also has potential in NAFLD, NASH and severe lipodystrophy	113LB

targeting both pancreas and liver, has been shown to enhance glucose-stimulated insulin secretion and suppress hepatic glucose production in phase 1 studies in patients with type 2 diabetes. The drug was well tolerated and did not produce any serious or severe adverse events (1165-P, 1167-P).

Three ***glucagon receptor antagonists*** have yielded data which support further development. LGD-6972 has shown promise in non-diabetic subjects (1193-P); and PF-0629187 (1202-P) and LY2786890 (106-LB) both reduced plasma glucose in phase 1 trials in type 2 diabetes patients, producing pharmacokinetic parameters that support once-daily dosing.

A ***vaccine*** against interleukin-1β intended for use in the management of type 2 diabetes has demonstrated glucose-lowering efficacy in a phase 1 trial (1100-P).

The ***ApoA-I Inducer***, RVX-208, increased HDL particle size and reduced both hepatic glucose production and peripheral glucose disposal whilst delaying the appearance of glucose in the circulation of subjects with impaired glucose tolerance (1189-P).

Looking back…and looking ahead

As we look back on this large and hugely varied meeting, it is time for a few final reflections. Perhaps the "positive negative" cardiovascular outcomes with sitagliptin (TECOS) and lixisenatide (ELIXA) will have the greatest impact on how we see the field evolving. Was this the time that many of us realised that these are cardiovascular safety studies, first and foremost, and were never designed to show the way forward to an improved cardiovascular outlook in type 2 diabetes? Will a new generation of trials explore the potential of these novel drugs to prevent adverse cardiovascular outcomes, once the safety-driven needs of the FDA have been met?

Elsewhere, we saw some reassuring data for other incretin-based agents. The absence of new safety concerns with these drugs was certainly welcome, and there are still more outcomes trials to look forward to with the newer agents. Indeed, there is a long list of new incretin-based agents in advanced developments, including agents with a very long duration of action. In addition, we will soon see how the new class of PCSK9 inhibitors impacts on cardiovascular outcomes in at-risk populations, including people with diabetes. These agents have the potential to finally answer the question of just how low should we go with LDL-C?

Another theme has been the steady advance of pharmacotherapy normally associated with type 2 diabetes into type 1 diabetes populations. Incretin drugs and SGLT2 inhibitors potentially bring a range of beneficial effects on glucose control, insulin doses and body weight in this population. But, the unwelcome appearance of euglycaemic DKA will provide a note of caution with regard to the extent of lowering of the insulin dosage when adding-in SGLT2 inhibitors.

Looking further ahead, there are plenty of novel mechanisms making their way through late preclinical development, and into phase 1 and 2 trials. These drugs will provide plenty of interest at future meetings and perhaps the next leaps forward in diabetes pharmacotherapy.

Conflict of interest and disclaimer

The authors have previously provided medical communications/education services to some of the companies whose products are described in this report. No funding has been received for preparation of this report.

This report reflects the authors' personal impressions of the meeting and does not necessarily reflect those of the presenters or the ADA.

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http://dx.doi.org/10.15277/bjdvd.2015.037
Br J Diabetes Vasc Dis 2015;**15**:1-6 online only