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The 2017 annual Oxford Diabetes Symposium was held at Keble College on 20th and 21st July. The event, which is by invitation and focused on senior diabetes specialist clinicians, was organized by Oxford physicians Dr Garry Tan and Dr Jonathan Levy. As usual, the symposium was supported by an unrestricted educational grant from Novo Nordisk (who have recently announced a major collaboration on type 2 diabetes research with the University of Oxford).

News of Dr Levy's impending retirement from full-time clinical medicine generated a warm round of applause from the invited expert audience. Dr Levy's contribution towards the advancement of knowledge in diabetes has been substantial.

Here, I present brief partial summaries of state-of-the-art lectures from world-class investigators currently engaged in cutting-edge cardiometabolic research. The presentations covered in this report address aspects of the interactions that exist between diabetes, metabolism, and cardiovascular disease. Awareness of the potential therapeutic implications of these intersections has emerged with the initial results and further analyses of recent cardiovascular outcome trials (CVOTs) of novel glucose-lowering therapies that have shown benefits on aspects of cardiovascular disease – along with some risks in certain cases – in high-risk patients with type 2 diabetes. Where relevant, some recent updates have also been included.

Professor Cliff Bailey, University of Aston, UK Diabetes medications: delivery mechanisms

Professor Bailey prefaced his review by reminding the audience of the treatment burden of diabetes and related disorders. He then launched into a comprehensive overview of novel aspects of diabetes pharmacotherapy starting with a drug celebrating its 60th anniversary and that remains a cornerstone of therapy. *Metformin*: Compared with immediate-release metformin, metformin XR (extended release) has a lower propensity to cause gastrointestinal side-effects conferred by a dual hydrophobic polymer matrix. Metformin DR (delayed release) involves pH-dependent dissolution. No stomach/duodenal absorption occurs before arrival in the ileum. The lower pharmacokinetic profile of metformin

DR compared with metformin XR reduces systemic exposure while maintaining lower blood lactate concentrations. Intestinal actions of metformin are implicated in the improved potency of metformin DR. On a more general note, fixed-dose combinations provide the metformin component essentially free of acquisition costs. *Glucagon-like peptide 1 (GLP-1) analogs*: Professor Bailey reviewed the technology behind an implantable subcutaneous mini-pump that delivers exenatide (ITCA 650). An osmotic engine drives a plunger releasing exenatide for up to 12 months. Note that the Food and Drug Administration (FDA) recently rejected the product in a complete response letter to the manufacturer (Intarcia). The cardiovascular effects of weekly injectable semaglutide were reported recently in SUSTAIN-6. Oral semaglutide is a novel GLP-1 analog that has shown efficacy in reducing blood glucose in phase 2 clinical trials. *Coformulations*: Fixed-ratio combinations, insulin analogs, and GLP-1 agonists include IdegLira: additive effect of insulin degludec and liraglutide, helps prevent insulin-induced weight gain with lower insulin doses and fewer episodes of hypoglycemia and iGlarlixi (insulin glargine U100 + lixisenatide). Note that peptide stability and solubility are highly pH dependent. Various therapeutic combinations have been explored; for example, pramlintide–metreleptin, which was discontinued in 2011 because of waning effects/higher requirements for metreleptin. *Designer peptides*: This approach seeks to exploit the weight-reducing potential of epitopes in multiagonist single-molecule approaches; for example, chimeric peptides, such as glucagon-GLP-1-GIP (glucose-dependent insulinotropic peptide). *Insulin receptor activators*: Small molecules that mimic insulin action. Sequential binding of insulin on one α/β subunit and then the next results in conformational change in the β subunit with exposure of tyrosine moieties for phosphorylation. Early insulin signaling enhancers with multiple sites of potentiation of insulin signaling in insulin-resistant states; includes non-peptide insulin receptor activators. A small molecular adiponectin receptor agonist (AR1 and AR2 receptors) improves lipid profiles in db/db mice. Other topics covered in Professor Bailey's masterful overview included novel insulin-delivery options; biosimilar insulins including biosimilar insulins glargine

(abasaglar) and biosimilar lispro; high strength (U200 300 400) insulins; very long-acting insulins; ultrafast-acting insulins; inhaled/buccal/oral insulins; smart (glucose-responsive) insulins; transcutaneous patch insulin delivery; devices including smartphone-enabled pen injector devices and insulin pumps; and nasal glucagon.

Professor Rory Holman, University of Oxford, UK

Heart failure in diabetes: the elephant in the room

Professor Holman addressed the increasing awareness of the clinical importance of heart failure in patients with diabetes. He started by reminding the delegates of the wealth of data showing the appreciable (two-fold or more; greater in women) excess risk of heart failure that has been found in observational studies and interventional trials in patients with type 2 diabetes. Heart failure in the context of type 2 diabetes is associated with impaired functional status, renal function, autonomic neuropathy, pulmonary dysfunction, left ventricular diastolic dysfunction, and impaired myocardial metabolism. A first episode of heart failure is associated with an increased risk of diabetes, suggesting a bidirectional association. In terms of iatrogenic heart failure in diabetes, thiazolidinediones may carry a higher risk of heart failure than is generally believed. Professor Holman then reviewed the mixed results of recent CVOTs of various glucose-lowering drugs from the dipeptidyl peptidase-4 inhibitor, GLP-1 receptor agonist and sodium-glucose cotransporter 2 (SGLT-2) inhibitor classes including SAVOR-TIMI 53, EXAMINE, TECOS, ELIXA, EMPA-REG OUTCOME, LEADER, SUSTAIN-6, and CANVAS from the heart failure perspective. Data on heart failure risk (increased by saxagliptin), neutrality (lixisenatide, liraglutide), and benefits (empagliflozin, canagliflozin) were highlighted. The effects of SGLT-2 inhibitors on heart failure in the absence of diabetes are now being explored. Professor Holman also presented relevant recent clinical trial data on other aspects of heart failure therapy – for example, combined angiotensin-neprilysin inhibitors that target both arms of the renin-angiotensin-aldosterone system.

Professor Naveed Sattar, University of Glasgow, UK

The changing face of diabetes complications

Professor Sattar offered the view that there is both ‘good news and bad news in diabetes’. First, there is a higher incidence of diabetes because patients are being kept alive; second, the prevalence of diabetes is also increasing – dietary issues being the main problem – a major public health issue. Diabetes approximately doubles the risk of cardiovascular disease. However, there is appreciable heterogeneity: individual risk varies by duration, absence or presence of renal disease, etc. The controversy on whether diabetes should be considered a coronary heart disease risk equivalent has shifted towards the negative

in recent years. Earlier diagnosis – evidenced by fewer microvascular complications at diagnosis than in previous decades – allied to better glucose control and early use of statins and better control of blood pressure, has reduced the risk of myocardial infarction. Life expectancy is no longer so markedly reduced by diabetes as it was in previous eras. Nonetheless, according to data from the Emerging Risk Factors Collaboration, a 50 year old with diabetes died, on average, 6 years earlier than a counterpart without diabetes, with about 40% of the difference in survival attributable to excess nonvascular deaths. Heart failure and peripheral arterial disease are the most common initial manifestations of cardiovascular disease in type 2 diabetes. Professor Sattar noted that Asian patients tend to be less obese at diagnosis than White counterparts and pointed to evidence of the relevance of differences in adipocyte physiology observed in the GlasVEGAS (Glasgow Visceral and Ectopic Fat With Weight Gain in South AsianS) study. He also noted that risk of type 2 diabetes comes with less weight gain in men than women speculating that perhaps women may have to acquire even more adiposity to overcome their inherent metabolic advantages over men. Younger patients with type 2 diabetes face cardiometabolic risks from the metabolic syndrome – that is, obesity, hypertension, and dyslipidemia with evidence of early emergence of vascular complications.

Professor Steve Bain, University of Swansea, UK

Cardiovascular outcomes in diabetes

Professor Bain reiterated the message that diabetes approximately doubles the risk of vascular disease and briefly reviewed some controversial aspects of the UGDP and PROactive trials along with details of the controversy of the cardiovascular effects of rosiglitazone more recently. The latter issue prompted the requirement to establish cardiovascular safety of new diabetes therapies issued as guidance by the FDA in 2008. This move generated a series of informative large CVOTs of diabetes medications that are transforming the therapeutic landscape. Professor Bain explained the aim of ‘glycemic equipoise’ in safety studies of diabetes drugs – that is, the aim being to minimize glycemic differences between the medication of interest and the comparator treatment groups. Generally, the difference achieved in the mean glycated hemoglobin between the groups has been around 0.2–0.4% (more for SUSTAIN-6, which was associated with a retinopathy safety signal, possibly related to rapid glucose lowering). As new therapies are studied on a background of current standard of care, which incorporates well-established multifactorial risk factor management, diabetes CVOTs are biased against the probability of showing cardiovascular benefit of new therapies. This approach contrasts with standard cardiovascular benefit trials. Professor Bain reviewed relevant aspects of recent diabetes CVOTs, noting that superiority

was not prespecified in SUSTAIN-6; the driver of benefit was a reduction in nonfatal stroke with a nonsignificant reduction in nonfatal myocardial infarction. There was no reduction in cardiovascular deaths during the short duration (2.1 years) of the trial. Professor Bain explained that the complexities of the design of CANVAS reflected a learning experience so shortly after issuance of the 2008 FDA cardiovascular safety guidance, CANVAS being a combination of two studies. Although CANVAS showed no suggestion of a stroke signal (c.f. EMPA-REG OUTCOME), the hazard ratio for lower-extremity amputations was 1.97 (2.03 for major amputations; 29% of the total). Although it is possible that the amputation safety signal could be a class effect of SGLT-2 inhibitors, it was considered unlikely to have been missed in EMPA-REG OUTCOME. Professor Bain speculated about the potential for greater levels of hemoconcentration and peripheral thrombosis in CANVAS, reflecting the greater potency of canagliflozin at the highest dose. Professor Bain also discussed renal function in the context of some of the trials and looked at reports from ongoing and new CVOTs of glucose-lowering therapies.

The neutrality of exenatide in therapy on cardiovascular events in FREEDOM and EXCEL was noted as top-line results that have been presented subsequently in detail at the European Association for the Study of Diabetes conference in Lisbon. DEVOTE was a double-blind, treat-to-target, event-driven CVOT of insulin degludec versus insulin glargine U100. The hazard ratio three-point major adverse cardiovascular events for insulin degludec was noninferior (0.91, 95% confidence interval: 0.78–1.06, $P=0.209$) alongside a statistically significant 37% reduction in adjudicated severe hypoglycemia ($P<0.001$). It was noted that regulatory authorities are also interested in real-world data in addition to data from CVOTs. As for the impact of these CVOTs on clinical diabetes management guidelines, expert groups in some countries have already modified their advice in suggesting the use of glucose-lowering drugs with evidence from CVOTs to reduce the toll from cardiovascular disease.

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Conflicts of interest

There are no conflicts of interest.