PCDS report from the American Diabetes Association's 77th Scientific Sessions

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It is my great pleasure to welcome you to this PCDS report from the American Diabetes Association conference. As primary care clinicians attending the conference, we selected from the huge variety of topics on offer, focusing on those most relevant to day-to-day delivery of diabetes care. There was much to interest and inspire us and we particularly valued the opportunities to discuss and debate ideas and data with primary and secondary care colleagues.

In this report we have distilled out the key take-home messages which we believe have the potential to change practice, both immediately and in the future. Many of the topics, such as the expanding data from cardiovascular outcome trials (CVOTs), impact and management of depression in diabetes, and benefits of diet and physical activity, were of such significant interest that we will be revisiting them with more in-depth coverage in future issues of the journal.

My grateful thanks go to my colleagues Colin Kenny, Nicola Milne, Martin Hadley-Brown and Helen Davies for their hard work and skill in helping bring these messages to you. We hope that within this short conference report every one of you will find something which will encourage you to learn more and to change your practice.

Pam Brown

Cardiovascular outcome trials: What's new?

Canagliflozin is superior to placebo in reducing cardiovascular disease

In the integrated CANVAS (Canagliflozin Cardiovascular Assessment Study)/ CANVAS-R (CANVAS-Renal) cardiovascular outcome trial (CVOT), treatment with canagliflozin 100 mg or 300 mg compared with placebo in those with type 2 diabetes (T2D) at high risk of cardiovascular disease (CVD), resulted in a significant 14% reduction in the primary endpoint, a composite of cardiovascular (CV) death, non-fatal myocardial infarction (MI) and non-fatal stroke (hazard ratio [HR], 0.86 [95% confidence interval (CI), 0.75–0.97]). Hospitalisation for heart failure (HHF) was significantly reduced by 33% (HR, 0.67 [95% CI, 0.52–0.87]), and there was a 40% reduction in the composite renal endpoint (40% reduction in estimated glomerular filtration rate [eGFR], end-stage renal disease or renal death [HR, 0.60 (95% CI, 0.47–0.77)]).

To put this into a practice perspective, for every 1000 patients treated with canagliflozin for 5 years, we could expect 23 fewer patients to develop the major adverse CV events (MACE) of CV death, non-fatal MI or non-fatal stroke, 17 fewer patients would be hospitalised for heart failure (HF) and 16 fewer patients would develop the renal composite if treated with canagliflozin.

The expected increase in genital mycotic infections and urinary infections were seen in those treated with canagliflozin. The previously identified increase in fracture risk with canagliflozin was confirmed, with a 23% increase in low trauma fractures and a 26% increase in all fractures overall, but this was significant only in the CANVAS study population (HR, 1.56 and 1.55, respectively) and not in the CANVAS-R population (HR, 0.76 and 0.86, respectively). The investigators have not yet been able to explain this difference since both populations were similar and treated with the same drug.

The only unexpected adverse reaction was an increased rate of amputations which occurred in 6.3 per 1000 patient years in the canagliflozin treated group versus 3.4 per 1000 patient years with placebo (HR, 1.97 [95% CI, 1.41–2.75]). The European Medicines Agency (EMA) has already issued advice to UK clinicians regarding patient counselling about foot self-care, the importance of presenting early with foot symptoms and when it may be appropriate to stop canagliflozin (EMA, 2017). The Summary of Product Characteristics for all three sodium–glucose co-transporter 2 (SGLT2) inhibitors have also been updated to highlight the possible increased amputation risk across the class until further data are available.

The CANVAS/CANVAS-R integrated study population of 10 142 people had T2D and high CV risk (66% established CVD, 34% risk factors for CVD), with an HbA_{1c} 53–91 mmol/mol (7–10.5%), eGFR >30 mL/min, mean T2D duration 13.5 years, and were either aged >30 years with established CVD or aged 50 years or more with two or more risk factors for CVD. 96% completed the study.

Further information on the renal effects of canagliflozin from the CANVAS programme will be published later in 2017, and at a later date from the canagliflozin renal study, CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation).

Bruce Neal, the principal investigator stated, "I think the cardiovascular benefit is going to be a class effect with SGLT2 inhibitors, but there will be differences

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between the study results depending on the populations recruited". Commenting on the amputation rates, he stated that the effect looks real and is of importance to people with T2D and those who look after them. "Observational studies may be well placed to look at safety issues such as amputation rates and may provide further clarity."

As with other CVOTs, other glucose-lowering drugs were added in the placebo group to keep the HbA_{1c} as similar as possible (glycaemic equipoise), thus removing possible beneficial effects of improved glycaemic control. However, compared with placebo, HbA_{1c}, weight and blood pressure were slightly lower in the canagliflozin-treated group.

Heart failure and death in new users of SGLT2 inhibitors with and without CVD

In the CVD-REAL (The Comparative Effectiveness of Cardiovascular Outcomes) study, initiation of an SGLT2 inhibitor was associated with a significant reduction in death and HF/HHF over the ensuing 8 months compared to use of other oral glucose-lowering drugs, both in people with and without established CVD at initiation (Cavender, 2017).

In those with pre-existing CVD, there was a 31% reduction in HF/HHF (2.2 HF events/100 patient years compared with 3.4/100 patient years) associated with SGLT2 inhibitor initiation versus other oral glucose-lowering drugs (HR, 0.69 [95% CI, 0.59–0.80]), and a 53% mortality rate reduction (1.4 per 100 patient years in those on SGLT2 inhibitors, compared to 3.5 per 100 patient years on other oral glycaemic drugs [HR, 0.47 (95% CI, 0.36–0.61)]). In those without CVD at initiation, mortality was 0.4/100 patient years in those initiated on SGLT2 inhibitors, compared with 0.8% in those on other oral glucose-lowering drugs (HR, 0.54 [95% CI, 0.44–0.66]). Only around 13% of those initiated on SGLT2 inhibitors in this study had established CVD, and in this group, as expected, absolute mortality and HF rates were higher than in those without CVD, resulting in a lower number needed to treat.

This observational, registry-based study of people with T2D newly initiated on SGLT2 inhibitors (canagliflozin 53%, dapagliflozin 42%, empagliflozin 5% total exposure time), propensity matched with people initiated on other oral glucose-lowering drugs, extracted data on more than 300 000 people from registries in five countries, including the Clinical Practice Research Datalink (CPRD) and Health Improvement Network (THIN) in the UK.

Individual country data reflected the varying use of the different drugs in the class and there was no evidence of heterogeneity between the different drugs. "These data suggest that a broad group of patients with T2D, with and without CVD, may benefit from treatment with this class of drugs", according to Matthew Cavender, who presented the data on behalf of the study group. However, he stressed that data from ongoing randomised trials will provide further evidence of individual drugs in different populations, some of which are already published.

These findings build on the previously published data on HHF and all-cause mortality from the same study population (Kosiborod et al, 2017).

Comparable safety of insulin degludec to insulin glargine, with significant reductions in hypoglycaemia

Insulin degludec does not increase CV risk and reduces severe hypoglycaemia by 40% and nocturnal severe hypoglycaemia by 53% compared with insulin glargine 100 units/mL, in those with T2D in the DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events) study, presented at the conference. 7,637 people with T2D who were either >50 years old with established CVD and moderate chronic kidney disease (CKD) or >60 years old with CVD risk factors were randomised to receive either glargine 100 units/mL or degludec insulins. 85% of those recruited had CVD or CKD and the primary endpoint was 3-point MACE. There was no difference in CV events between the insulins, confirming the CV non-inferiority of degludec. This study identified similar hypoglycaemia results (8% per year) to other studies in those with T2D treated with insulin.

Emerging data from the LEADER study

The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) CVOT with liraglutide was first published in 2016 (Marso et al, 2016a), and further analyses of the data were presented at this meeting.

The significant 13% reduction in the primary endpoint (CV death, non-fatal MI or stroke) examined time to first event only. New data explored overall event burden – 735 in the liraglutide-treated group (608 first events) versus 870 events (694 first events) in the placebo group, a similar significant 14% reduction, confirming liraglutide is reducing events, not delaying them.

Severe hypoglycaemia occurred in 2.4% of those treated with liraglutide versus 3.3% in the placebo-treated group (absolute event rates of 1 and 1.5 per 100 patient years respectively), a significant 31% reduction. CV drug or insulin use at baseline, or use of insulin, a sulphonylurea (SU) or thiazolidinedione in the placebo group during the study to maintain glycaemic equipoise, did not influence CV outcomes. Although HbA_{1c}, weight and systolic blood pressure achieved in the liraglutide group were slightly lower compared to the placebo group during the trial, these changes were not deemed responsible for the improved CVD findings.

Those experiencing severe hypoglycaemia were at increased risk of CV events and death compared to those without severe hypoglycaemia, but it remains unclear whether severe hypoglycaemia has a direct effect, is a marker for increased frailty and greater risk of CVD events, or whether it is a combination of both. Although CV death or non-fatal MI or stroke were all more common in the first 7 days after severe hypoglycaemia, risk was still elevated at 1 year. Those suffering severe hypoglycaemia had longer diabetes duration, used more insulin, and had higher rates of HF or CKD, and so might be expected to be at higher risk. Hypoglycaemia and severe hypoglycaemia have a major impact on morbidity, mortality

and quality of life in people with T2D. Even if there is no direct causal relationship between hypoglycaemia and risk of CV events, avoiding hypoglycaemia remains an important goal which should significantly impact patient and clinician therapy choices.

SUSTAIN-6: A plausible explanation for worsening diabetic retinopathy?

Additional information from SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes), a CVOT with semaglutide was also presented at the meeting. Although this trial demonstrated CV benefits with semaglutide, there was also an apparently increased risk of retinopathy in the semaglutide treatment arm compared with placebo. Paradoxically there also appeared to be decreased nephropathy (Marso et al, 2016b). On further analysis of the data, more patients were found to have pre-existing retinopathy in the semaglutide treated group. Possible explanations for the increased rate of progression of retinopathy seen may be poorer initial control and a more rapid decrease in HbA_{1c} in the active treatment arm (Vilsboll, 2017).

Treatment of type 2 diabetes: What's new?

Should we still be prescribing sulphonylureas?

Professor Kamlesh Khunti reviewed the contemporary use of SUs. With approximately 415 million people worldwide living with diabetes, and 75% living in low to middle income countries (International Diabetes Federation, 2015), Professor Khunti argued that it is important that patients have access to affordable, effective therapies. SUs are effective in improving glycaemic control, with a meta-analysis (Hirst et al, 2013) showing that:

- Using an SU as monotherapy reduced HbA_{1c} levels by 16.4 mmol/mol (1.5%) more than placebo
- Adding an SU to other oral antihyperglycaemic therapies reduced HbA_{1c} levels by 17.5 mmol/mol (1.6%)
- Adding an SU to insulin lowered HbA_{1c} by 5.5 mmol/mol (0.5%).

In addition, SUs have also been shown to reduce microvascular complications in people with T2D (UKPDS, 1998), whilst being inexpensive. There are also differences amongst the SUs as a class. For example, risk of hypoglycaemia, in particular severe hypoglycaemia, is lower in the more modern generations of SUs (i.e. gliclazide, glipizide and glimepiride) compared with the older generation SUs.

When thinking about the possible impact of SUs upon weight, no weight gain was observed with SUs in the ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation) study (The ADVANCE Collaborative Group, 2008), whilst in the VADT (Veteran's Affairs Diabetes Trial), people taking an SU actually lost weight (Duckworth et al, 2009). However, it should be borne in mind that subjects in this study were older, and weight loss may have been associated with increasing frailty rather than the SU.

In summary, SUs, when selected and dosed appropriately, have a favourable efficacy and safety profile, and as such may be an affordable treatment choice for people with T2D. Further details regarding appropriate use of SUs in clinical practice are provided in ***Box 1***.

Still more to explore with SGLT2 inhibitors

A number of hot topics relating to the use of SGLT2 inhibitors in clinical practice were discussed at the meeting, including the effect of these drugs on the kidney, diabetic ketoacidosis (DKA), fracture and amputation. Careful identification of appropriate patients and individualisation of treatment were recommended (Weir, 2017).

A useful session reviewed possible causes of fracture in users of SGLT2 inhibitors. The risk was seen mainly with canagliflozin, but only in CANVAS and not in the CANVAS-R study (Neal et al, 2017). The FDA postulated fractures could be caused by early hypotension and falls, small changes in bone density and possible changes in calcium and phosphate (Kwon, 2017). A class effect cannot be ruled out at this stage.

Finally, when thinking about the current and future clinical role of SGLT2 inhibitors, it was advised that the potential benefits of these products (e.g. CV protection, improved glycaemic control, reductions in blood pressure, low risk of hypoglycaemia and weight loss) be balanced with concerns including DKA, hypovolaemia effects, bone fractures, vulvovaginitis and balanitis. Studies such as the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), and the CVD-REAL study (Zinman et al, 2015; Kosiborod et al, 2017), illustrate the potential for using these drugs to reduce mortality and HF in people at high risk of CVD. And looking to the future, other potential (and as yet unlicensed) uses of SGLT2 inhibitors include preventing the progression of diabetic nephropathy, as well as the development of HF, and finally in the management of obesity (Rosenstock, 2017).

Advances in insulin-related therapy

Concentrated insulins are becoming more popular, matching the growing need for people with diabetes to administer higher doses of insulin. These products generally achieve similar levels of glycaemic control compared with conventional insulins with a reduced incidence of nocturnal

Box 1. Using sulphonylureas in clinical practice

- Use the lowest dose of sulphonylurea to achieve target HbA_{1c} to minimise risk of hypoglycaemia
- Use sulphonylureas in a timely manner with early combination therapies demonstrating good long-term outcomes
- Patient education around hypoglycaemia is essential in people taking sulphonylureas, and should be revisited at every review
- Regular review of doses: de-intensify treatment as appropriate and avoid tight glycaemic control in the older adult
- Avoid using long-acting sulphonylureas such as glibenclamide, particularly in the elderly

hypoglycaemia (Heller et al, 2012; Korsatko et al, 2013; Riddle et al, 2014).

In addition to the development of concentrated basal insulins, faster-acting mealtime formulations are in development. For example faster-acting insulin aspart has an earlier onset and higher early exposure than conventional insulin aspart, and a greater early glucose-lowering effect, with similar potency (Heise et al, 2015). Insulin delivery devices such as the InsuPad also have the potential to accelerate the action of insulin (Raz et al, 2015), and developments such as microneedles (Pettis et al, 2011) and patches (Tai et al, 2014) have the potential to improve insulin delivery.

Although barriers to insulin use still exist (e.g. needle phobia, complexity of treatment regimens and cost), advances are also being made. However, recent studies highlighting the problems of delayed insulin initiation (Khunti et al, 2013; Kostev and Rathmann, 2013) suggest that more could still be done, particularly in the area of improving patient education and support.

Inhibition of PCSK9 in people living with diabetes – data from the ODYSSEY studies

In recent studies, alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, reduced low density lipoprotein cholesterol (LDL-C) levels as well as non-high density lipoprotein cholesterol (non-HDL-C) in people with T2D. In the ODYSSEY DM–INSULIN trial, alirocumab significantly reduced LDL-C by 49% in those living with diabetes and receiving insulin therapy compared with placebo and also improved other lipid parameters. In the ODYSSEY DM–DYSLIPIDEMIA trial, alirocumab significantly reduced non-HDL-C by 32.5% in those living with T2D with a mixed dyslipidaemia pattern, compared with usual care.

Lifestyle

New physical activity/exercise guidelines for diabetes

Presenting the updated ADA position statement on physical activity (Colberg et al, 2016), it was stressed that although exercise should be prescribed to all people with diabetes, it needs to be tailored. Aerobic and resistance exercise should be encouraged, along with flexibility and balance activities to prevent stiffness and reduce falls, particularly in the elderly. People should also be encouraged to interrupt sitting/sedentary time with a few minutes of activity every 30 minutes.

In order to optimise glycaemic benefits, exercise should be undertaken at least every 72 hours, but ideally every 48 hours. Although adding high intensity intervals can increase blood sugar reduction, it is important to avoid injury and demotivating people by making exercise feel too hard. Cross training using activities enjoyed by the individual or walking with incremental pedometer step counting are most likely to be continued in the long term.

Physical activity and pre-existing complications

Recommending that people living with diabetes are physically active is an important intervention. However, caution needs to be applied in people with diabetes-related complications. For example, graded treadmill exercise can improve peripheral arterial disease. It should be increased slowly over 6 weeks and then persisted with. People with established diabetic neuropathy can do supervised physical activity on a treadmill, but good footwear and socks are essential. Although physical activity is important to prevent diabetic retinopathy, caution is needed when retinopathy is well established as resistance exercise in particular can increase the risk of retinal haemorrhage.

State of the art on exercise

Presenting the State of the Art lecture on exercise, Bret Goodpaster from Florida reminded delegates that the effects of exercise on insulin sensitivity, insulin signalling and glucose control are complex. Emerging areas of interest and research include fat accumulation in muscle, the importance of exercise after bariatric surgery, and optimisation of mitochondrial function and quantity.

Myosteatosis, the accumulation of fat within muscle, is associated with insulin resistance, accelerated muscle loss (sarcopenia), loss of visceral and subcutaneous fat, increased risk of hip fracture and increased mortality. A 1-year physical activity intervention in the elderly demonstrated that the control group continued to accumulate a further 10–15% intramuscular fat while physical activity prevented further muscle fat accumulation (Goodpaster et al, 2008).

Following bariatric surgery, exercise is important in improving insulin sensitivity, and increasing mitochondrial function but not quantity. Weight loss and exercise have opposite effects on intramuscular lipids – the so-called "athlete paradox" – and cancel each other out.

Other active areas of research focus on muscle mitochondrial content and function. Exercise is known to be beneficial to some conditions thought to be associated with mitochondrial dysfunction. Active people have high mitochondrial content in abdominal subcutaneous fat, but the significance of this and whether other adipose tissue can increase its mitochondrial content in response to exercise is still being investigated.

What is the link between sleep and the development of diabetes?

Recent studies implicate inadequate sleep duration and quality in the development of metabolic disease, with both factors being important for glucose metabolism. In addition, obstructive sleep apnoea (OSA) is more common in people with diabetes (58–86% prevalence) (Resnick et al, 2003; Foster et al, 2009), as is shorter sleep duration (Cappuccio et al, 2010).

A soon to be published meta-analysis presented at the meeting (Knutson, 2017) found that those with a shorter sleep duration have a 45% increased risk of developing obesity and a 28% increased risk of developing T2D. It is already known that those experiencing difficulties falling asleep have a 57% increased risk of developing T2D, and those with problems staying asleep have an 84% increased risk of developing T2D (Cappuccio et al, 2010). Dr Knutson commented that difficulty staying asleep therefore confers a greater

risk of progression to T2D than being inactive (20%), having a family history of the condition (50%), having OSA (57%), or doing shift work (15%).

Studies in people with T1D show that patients tend to have poorer sleep quality but not duration, and those with good sleep quality tend to have a lower HbA_{1c} level. Interestingly, the prevalence of OSA is high in those with T1D despite generally normal BMIs (Meyer et al, 2015).

Quality of sleep rather than sleep duration is most commonly associated with poor glycaemic control and increases the risk of developing T2D. Therefore, healthcare professionals (HCPs) need to ask about sleep and include it in healthy lifestyle messages and behaviours promoted to those at risk of developing or having T2D.

Psychological issues

Why language matters in diabetes

The type of language used by HCPs when speaking to people with diabetes can have a significant impact on their health. Dr Susan Guzman, a clinical and research psychologist at the Behavioural Diabetes Institute in San Diego said, "Language conveys meaning and can reflect bias that will affect outcomes, even when you're not aware of it." Therefore, HCPs play an important role in providing messages which are collaborative and take into account what the person with diabetes is experiencing.

The soon to be published "Joint Consensus Statement on the Use of Language", suggests that words such as "uncontrolled" and "non-adherent" should be avoided when talking to people with diabetes. It goes on to say that describing a person as "diabetic" often makes them feel disrespected, hopeless, and dismissed. Further recommendations from this consensus statement are summarised in ***Box 2***.

Understanding the stigma associated with diabetes

There is a persistent stigmatisation of diabetes. Clinicians should be aware of this and get beyond these negative health beliefs to understand the patient's narrative which, if not addressed, can lead to avoidance, disengagement and distress. People living with diabetes may feel guilty about their condition and those living with T1D feel this more acutely than those with T2D. This stigmatisation may be much worse in developing countries. To help with this, clinicians should change the conversations in diabetes to be more factual, supportive and engaging.

ACTIVE II programme for depression in diabetes

Depression is twice as likely in people with diabetes and results in poorer control, decreased medication adherence, increased severity of complications and increased all-cause mortality. In the ACTIVE II study, 140 people with depression and T2D safe to undertake mild/moderate exercise were randomised to either 10 sessions of cognitive behaviour therapy (CBT), a 12-week exercise programme, CBT and exercise programme, or usual care. Those in the three intervention groups were 5–6 times more likely to have complete depression resolution than those receiving usual care. Those undertaking exercise and CBT also achieved a 0.7% significant reduction in HbA_{1c}. Six- and 12-month reviews are planned (de Groot, 2017).

Complications

Potential renoprotective role of SGLT2 inhibitors and GLP-1 receptor agonists

Emerging evidence suggests that some of the "newer" antihyperglycaemic agents used in T2D may also have renoprotective benefits. For example, SGLT2 inhibitors appear to impact positively on diabetic kidney disease (DKD) by indirectly improving glycaemic control, and reducing insulin levels, weight, blood pressure and uric acid levels. In addition, they exert direct effects on the kidney by reducing glomerular hyperfiltration, oxidative stress and proteinuria. It is not yet known whether these are class effects, and results from further studies are awaited to clarify this. Currently, data from the EMPA-REG OUTCOME trial show that in people with T2D at high CV risk, empagliflozin, when added to standard care, is associated with a slower progression of DKD and lower rates of clinically relevant renal events compared with placebo (Wanner et al, 2016). Renoprotective effects were also seen in the CANVAS/CANVAS-R programme (Neal et al, 2017). However, it should be noted that until further data are published, clinicians should avoid prescribing SGLT2 inhibitors in people with T2D who have CKD stages 4 and 5.

Glucagon-like peptide-1 (GLP-1) receptor agonists are thought to have a direct effect on the kidney by reducing oxidative stress and inflammation levels and enhancing natriuresis. Indirectly they lower blood pressure, weight and HbA_{1c} levels, all of which are beneficial to the kidney. In the LEADER study, a once-daily dose of liraglutide of up to 1.8 mg, administered over a median of 3.8 years, reduced the rate of nephropathy by 22% (Marso et al, 2016a). In addition, late-breaking results from the AWARD 7 study (Tuttle et al, 2017) showed that compared with insulin glargine, people with T2D with moderate to severe DKD treated with dulaglutide had reductions in microalbuminuria and a slower decline in eGFR (both arms in combination with insulin lispro). Similar reductions in HbA_{1c} at 26 weeks were observed in both groups. These results are similar to those observed in the SUSTAIN-6 study, which showed a 36% reduction in microalbuminuria in the semaglutide-treated group compared with placebo (Marso et al, 2016b).

Box 2. Recommendations on HCP's use of language with people with diabetes

Use language that:

- Is neutral and non-judgemental, based on facts, action or physiology/biology
- Is free of stigma in referrals
- Is respectful, inclusive and imparts hope
- Fosters collaboration
- Is person-centred

Clinical innovations in vision

Panretinal photocoagulation has been established for many years as the standard treatment for retinopathy and macular oedema. The exact mechanism of action is largely unknown, but it is thought that cells which survive the thermal stress activate repair pathways. There is a need to establish and assess a laser treatment which minimises unnecessary cell destruction. Results from a 4-month follow-up of patients treated with non-damaging laser therapy showed reduced macular thickness, reduced subfoveal choroidal thickness and improved visual acuity with no unnecessary damage in 100% of participants. Use of non-damaging laser therapy appears to activate an endogenous tissue repair mechanism (Palanker, 2017).

Inflammation is a key component in diabetic macular oedema. Hyperglycaemia leads to chronic inflammation, with an increase in cytokines and chemokines causing retinal capillary damage, which can eventually destroy the blood/retinal barrier, resulting in vascular leakage and oedema. Current treatment of chronic diabetic macular oedema uses anti-vascular endothelial growth factor (VEGF) therapies as VEGF levels are known to increase with severity and duration of retinopathy. However, cytokine levels also increase, and current anti-VEGF treatments such as ranibizumab, afibercept and bevacizumab, despite inhibiting VEGF to control or slow disease progression, do not reduce the levels of other inflammatory cytokines. Studies involving steroid treatment with triamcinolone or dexamethasone implants demonstrate that steroids reduce both VEGF and other inflammatory cytokines, which could be a way forward in treating diabetic macular oedema (Kuppermann, 2017).

Important interventions in diabetic foot care

Important milestones in diabetic foot care have been the development of a robust classification system for the diabetic foot, recognising the importance of debridement, off-loading ulcers and the central role of the multidisciplinary team. An early marker for potential foot ulceration is a hot area on a foot, which may break down subsequently. When a foot ulcer is present, no one antibiotic regimen is better than another, perhaps reflecting the heterogeneous nature of the infections, although antimicrobial dressing can promote healing. In those with T1D, tight glucose control has most impact on neuropathy while in T2D, glycaemic control has less impact than addressing all aspects of metabolic risk. Magnetic resonance imaging in particular has played an important role in understanding underlying pathology in the Charcot foot.

Finding an effective treatment for hypoglycaemia unawareness?

Hypoglycaemia-associated autonomic failure (HAAF), or the experience of repeated episodes of apparently asymptomatic hypoglycaemia (Chico et al, 2003), can impact cognitive function (Hansen et al, 2017) as well as having potentially fatal consequences in people with diabetes (Tanenberg et al, 2010). The condition occurs in up to 27% of people with T1D and 9.2% of people with T2D (Schopman et al, 2010) as a result of an inadequate glucagon response to falling blood glucose levels, imperfect insulin replacement and an attenuated adrenaline response (Dagogo-Jack et al, 1993; Adler et al, 2009). However, HAAF may be reversed in some patients through scrupulous avoidance of treatment-induced hypoglycaemia.

Challenges in translating basic research into therapies for HAAF include how to investigate safe ways to block the effects of hypoglycaemia on the pathways which cause HAAF, and the most appropriate way to test whether an agent can treat the condition and restore awareness. Although the opioid antagonists naloxone and naltrexone have been trialled with mixed results (Vele et al, 2011; Naik et al, 2017), it is considered that the emphasis should be on prevention rather than treatment of the condition.

Heart failure is an important consideration in people with diabetes

Heart failure is more common in people living with diabetes, being 2.4 times more common in males and five times more common in females. HF and diabetes may occur concomitantly and have a bidirectional relationship. Some diabetes drugs can help, whilst others may exacerbate HF, and new therapies for the condition are emerging. A functional classification can help with prognosis in HF, which is worse when diabetes is present. Not all people living with diabetes are equally at risk of HF, with older people, longer duration of diabetes, insulin requiring, poor glycaemic control and existing CVD and nephropathy, all leaving the person with diabetes at higher risk.

Sexual health and male hypogonadism

Sexual dysfunction in men and women can be persistent and recurrent, with approximately twice the risk for these conditions in people with diabetes compared with the population without diabetes. Women with diabetes are twice as likely to report incontinence. These conditions impact quality of life, and those with erectile dysfunction and urinary incontinence are more likely to report poor quality of life.

It can be difficult to make a clear diagnosis of hypogonadism in men, as the condition has considerable overlap with the metabolic syndrome and OSA. Laboratory testing lacks standardisation, and controlled trials have been inconclusive, with some showing harm.

There should be two aspects of diagnosis; firstly, clear symptoms of hypogonadism (i.e. decreased libido, loss of virility, increased visceral obesity, decreased muscle mass and strength, osteopenia, and mood changes and depression) and finally, two low serum testosterone samples taken in the morning.

There is a bidirectional relationship between obesity and low testosterone, with both exercise and weight loss increasing serum testosterone levels. It is of interest that prescriptions for testosterone replacement therapy are increasing in the USA, but so far not in the UK.

Pregnancy

Follow-up data from the HAPO (Hyperglycaemia and Adverse Pregnancy Outcome) study (2008) were presented at

the meeting. Hyperglycaemia in pregnancy (HIP) confers an increased maternal risk of developing glucose metabolism disorders and dyslipidaemia but not an increased risk of hypertension at 8–12-year follow-up. The offspring of mothers with HIP have an increased risk of childhood obesity at 8–12 years' follow-up, which is even greater if maternal obesity is also present.

In another session, early emerging data show that early inadequate glycaemic control in gestational diabetes or pregnancies with pre-existing diabetes before 26 weeks' gestation appears to be a risk factor for autistic spectrum disorder in the offspring (Xiang et al, 2015). Therefore, it is important to improve preconception advice for women around the benefits of weight loss and healthy lifestyles, not only for improved pregnancy outcomes but also for the long-term general well-being of the mother and her children.

Diabetes in later life

Are we overtreating the older adult?

With an ageing population, it is vital that we are effective and appropriate in our management of those older adults with diabetes. However, the elderly are rarely included in randomised controlled trials to help us achieve this.

There is growing international consensus from both the American Diabetes Association (ADA) and International Diabetes Federation (IDF) that diabetes management decisions and targets should be related to frailty index scoring with HbA_{1c} values in the range 53–64 mmol/mol (7–8%; Palta et al, 2017). Currently 50% of patients with complex poor health and diabetes have an HbA_{1c} of <53 mmol/mol (7%), with half of these taking SUs, and in patients with a life expectancy of <5 years many have an HbA_{1c} <42 mmol/mol (6%) and take antidiabetes therapies including insulin (Lipska et al, 2015).

Avoidance of hypoglycaemia in the elderly is especially important as cognitive decline can contribute to reduced awareness of hypoglycaemia and recurrent hypoglycaemia increases the risk of cognitive decline. So what are the targets? The ADA recommends a target of <58 mmol/mol (7.5%) in the healthy older person, <64 mmol/mol (8%) in the complex older person, and <70 mmol/mol (8.5%) in the very complex older person (ADA, 2016). Further recommendations for the older adult are shown in ***Box 3***.

Cognitive decline in people with diabetes

A number of strategies were proposed for use in people with diabetes and cognitive decline. HCPs should consider which medications are prescribed for people in later life with diabetes, particularly since they are much more vulnerable to hypoglycaemia-induced cognitive impairment, and less resilient to recover from an episode. People living with diabetes in later life are also at greater risk for polypharmacy, hypoglycaemia, cognitive impairment, urinary incontinence, falls, persistent pain and depression. Therefore, careful de-intensification of hyperglycaemia medication may be important. It is useful to obtain a complete list of all medication, including over-the-counter medications, and to assess the overall risk of drug-induced harm, adjust for risks and benefits, and consider active de-prescribing of any unnecessary medication.

Individualising therapy

HCPs often underestimate the impact of polypharmacy and hypoglycaemia on individuals with T2D, whilst overestimating the benefits of tight glycaemic control. This can result in the oldest and most unwell patients being overtreated. The heterogeneity of treatment effect means that not all patients will benefit from interventions that are judged effective in a clinical trial. Therefore, baseline risk assessment is vital to ensure that treatments are likely to provide demonstrable benefits to the patients who are prescribed them. For example, it can be deduced from UKPDS (UK Prospective Diabetes Study) that a fairly long life expectancy is needed to experience the benefits of intensive glycaemic control on CVD (Holman et al, 2008), meaning that older patients may receive less benefit.

Treatment choice in special populations should also be considered. For example, those with T2D with CVD may benefit more from therapies such as empagliflozin or liraglutide, whereas those with non-alcoholic fatty liver disease, especially young males, may benefit from being prescribed pioglitazone.

Finally, there appear to be numerous phenotypes within those with T2D. To truly individualise diabetes therapy, further research into identifying these subtypes is needed. Until then, HCPs must continue to work with patients using collaborative decision-making tools to ensure the best individual fit for therapies.

Harnessing the power of the digital age in diabetes

Although there is a huge potential for digital data to transform the care of people with diabetes, many challenges remain because while digital tools abound (e.g. there are over 1000 apps available for diabetes alone), few studies have assessed their impact on patient outcomes. In addition, as patients become more knowledgeable because of these new tools, HCPs need to be better acquainted with what is available so that treatment decision-making becomes more of a partnership. On a positive note, organisations such the ADA are now recognising and credentialling apps, but some HCPs still question the value of technology, particularly when consultation time is limited and workloads are high.

Box 3. Recommendations on care in the older adult

- Glycaemic targets should be negotiated taking into account frailty status rather than age
- Hypoglycaemia is a major problem in the elderly: remember cognitive assessment and education to include family and carers
- Newer agents offer the promise of better HbA_{1c} control without the risk of hypoglycaemia and may transform how we manage this age group. More research is required
- Try to keep treatment regimens as simple as possible

So what are the opportunities for digital medicine?

- Electronic health records can be used to help improve glycaemic control (Rushakoff et al, 2017)
- Telemedicine can aid the early detection and treatment of retinopathy (Daskivich et al, 2017)
- Behavioural treatment approaches using the internet have been shown to outperform conventional educational approaches also offered via the internet (Tate et al, 2001).

Advances in digital technology in diabetes now mean that HCPs are confronted with a "tsunami of digital data". It is important to realise that helpful digital data for the HCP may not make sense to the patient. Furthermore, any digital data must be stored securely using encrypted devices to reduce the risk of data being compromised. A particular challenge faced in this area is that patient expectations often do not match the current capabilities of available technology. When choosing a particular technology for a particular patient, it should be remembered that people with diabetes are individuals and there is no "one size fits all". Finally, diabetes data devices need to be more than just "cool", they need to have built-in quality assurance, and have a safe but useful design in order to minimise risk to users.

Should continuous glucose monitoring be used in type 2 diabetes?

Although continuous glucose monitoring (CGM) may be useful for some people with T2D, the challenge remains in identifying the right patients, according to a debate featuring Dr Jeremy Pettus and Dr William Polonsky.

For people with T2D on intensive insulin therapy, recent data show that CGM improves HbA_{1c} and reduces glycaemic variability in those using multiple daily injections (Ruedy et al, 2017). Although there are some concerns about people with T2D being able to learn how to use CGM, seeing changes in blood glucose in real-time can empower and educate patients (Pettus et al, 2015). However, evidence is lacking on the impact of CGM in reducing hypoglycaemia.

When using CGM in people with T2D on basal insulin, it was highlighted that people make use of their results, eating fewer calories, losing weight, and exercising more (Yoo et al, 2008). CGM also has the potential to detect previously unrecognised episodes of hypoglycaemia and assist with basal insulin titration. However, treatment satisfaction may be lower with real-time CGM compared with internet-based blood glucose monitoring (Tang et al, 2014).

Finally, what about CGM use for those on oral agents? This approach provides the opportunity for patients to become and stay engaged with their treatment (Polonsky and Fisher, 2013), and HbA_{1c} reductions are sustained for longer when CGM is used compared with no CGM (Vigersky et al, 2012). However, time constraints often make it easier for a clinician to write a prescription rather than teach patients how to use CGM. It was felt that for those on oral therapy, the priority should be to overcome clinical inertia and improve medication adherence rather than using CGM.

In closing, although it was agreed that CGM has the potential to benefit the disengaged, those with severe hypoglycaemia or poor glycaemic control, more evidence of benefit is needed for its use in people with T2D. ■

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