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56th EASD Annual Meeting

Content

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1. Ertugliflozin offers some kidney protection

Despite earlier reports that the sodium-glucose transport protein 2 (SGLT2) inhibitor ertugliflozin did not live up to expectations for kidney disease outcomes, an analysis by Prof. David Cherney (University of Toronto, Canada) provides evidence that kidney disease outcomes with ertugliflozin were similar to those seen with other SGLT2 inhibitors.

The VERTIS CV study (NCT01986881) compared the SGLT2 inhibitor ertugliflozin (n=5,499) with placebo (n=2,747). The primary endpoint was a composite of kidney outcomes, including renal death, need for dialysis or transplant, or a doubling of serum creatinine reflecting a drop of at least 50% in estimated glomerular filtration rate (eGFR). Although the composite outcome showed a trend towards significant benefit, there was only a nominal 19% reduction of primary outcome events with ertugliflozin (HR 0.81; 95.8% CI 0.63-1.04; P=0.08) [1].

At the EASD 2020, Prof. Cherney presented several exploratory analyses [2], which were published in the journal *Circulation* [3]. He pointed out that applying a lower threshold for serum creatinine resulted in a sustained 40% or greater reduction in eGFR instead of a sustained doubling of serum creatinine, with consequent reductions in chronic kidney dialysis, transplant, or renal death. Adding this threshold in a post-hoc analysis showed a clinical benefit reaching statistical significance for the patients receiving ertugliflozin (HR 0.66; 95% CI 0.50-0.88; P<0.01). "This is in line with what has been observed with the other 3 SGLT2 inhibitor drugs", Prof. Cherney said. He concluded that the results of the VERTIS CV trial provided evidence supporting the beneficial effects of this class of SGLT2 inhibitor on cardiovascular and renal outcomes. Ertugliflozin reduced the risk of the exploratory composite renal outcome of a sustained 40% decline in eGFR, chronic renal replacement therapy, or renal death. The relative risk reduction for the kidney composite was similar across all stages of chronic kidney disease (CKD), level of urine albumin-to-creatinine ratio (UACR), and type of kidney disease: improving global outcomes (KDIGO)-CKD risk category regardless of how CKD was defined. Ertugliflozin significantly reduced UACR in patients with albuminuria at baseline and preserved kidney function, especially in patients with microalbuminuria who are at greatest risk for CKD progression. Unfortunately, the routine use of UACR testing in patients with diabetes in general practice remains low, and UACR testing is also not part of standard care in cardiology practice. The eGFR declined acutely with ertugliflozin and the reduction was sustained over time when compared with placebo.

1. Pratley RE, et al. Results of the eValuation of ERTugliflozinEffIcacy and Safety CardioVascular Outcomes Trial (VERTIS-CV). ADA 2020.
2. Cherney DZ. Late-breaking presentation on renal outcomes. EASD 2020. Session: VERTIS CV outcome.
3. Cherney DZI, et al. Circulation. 2020 Nov 13.

2. DAPA-CKD trial shows extensive benefits of dapagliflozin

Treatment with dapagliflozin produced positive outcomes in patients with kidney disease both with and without type 2 diabetes. The number needed to treat (NNT) was much lower compared with established therapies to prevent a sustained decrease in estimated glomerular filtration rate (eGFR) of ≥50%, end stage renal disease (ESRD), or death from renal or cardiovascular (CV) causes.

The purpose of the DAPA-CKD trial (NCT03036150) was to assess whether dapagliflozin reduced the risk of renal and cardiovascular (CV) events in patients with chronic kidney disease (CKD) with or without type 2 diabetes, compared with placebo [1]. Patients received standard care, including maximum doses of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). The primary endpoint was a composite of a sustained decrease in eGFR (≥50%), ESRD, and death from renal or CV causes.

The trial was stopped early in March 2020, because of overwhelming efficacy based on 408 primary events (60% of planned events). Baseline characteristics of patients were well balanced between both treatment arms. A total of 4,289 patients completed the study, and over a median of 2.4 years, a primary outcome event occurred in 9.2% of patients in the dapagliflozin group compared with 14.5% of patients in the placebo group (HR 0.61; 95% CI 0.51-0.72; P<0.001). The NNT to prevent 1 primary outcome event was 19 (95% CI 15-27). "This NNT is much lower than what was previously seen with ACE inhibitors and ARBs", Prof. Hiddo Heerspink (University of Groningen, the Netherlands) said. Dapagliflozin treatment resulted in the desired outcome of a sustained decline in eGFR (≥50%), or death from renal causes (HR 0.56; 95% CI 0.45-0.68; P<0.001). For end-stage renal disease only, the HR was 0.66 (95% CI 0.49-0.90; P=0.0072). The HR for the composite of death from CV or hospitalisation for heart failure was 0.71 (95% CI 0.55-0.92; P=0.0089). All-cause mortality was seen in 4.7% of patients in the dapagliflozin group versus 6.8% in the placebo group (HR 0.69; 95% CI 0.53-0.88; P=0.0035). The effects of dapagliflozin were similar both with and without type 2 diabetes. The safety of dapagliflozin was confirmed, with a similar proportion of patients in the dapagliflozin and placebo group experiencing a serious adverse event.

1. Heerspink HJL. Results of the DAPA-CKD trial. EASD 2020. Session: DAPA-CKD trial.

3. Empagliflozin significantly reduces CV and renal risk

Data from the EMPEROR-Reduced trial (NCT03057977) showed that empagliflozin reduces the risk of cardiovascular (CV) death or hospitalisation for heart failure (HF) in patients with HF and a reduced ejection fraction (HFrEF).

This trial was designed to evaluate the effects of 10 mg empagliflozin once daily compared with placebo in patients with HFreEF, with or without diabetes, who were receiving treatment for HF [1,2]. The primary endpoint was the composite of CV death or hospitalisation for HF. The first secondary endpoint was total (first and recurrent) HF hospitalisation and the second secondary endpoint was the slope of decline in glomerular filtration rate (GFR) over time. A total of 3,730 patients with HF and a left ventricular ejection fraction of 40% or less, with or without diabetes, were randomised to 10 mg empagliflozin once daily or placebo. Median follow-up was 16 months. "It is noteworthy, that these patients were sicker and were more high risk than patients included in other studies such as DAPA-HF", Dr Milton Packer (Baylor University Medical Center, Dallas, USA) said [3].

The primary endpoint occurred in 361 patients in the empagliflozin group (15.8/100 patient-years) and 462 patients in the placebo group (21.0/100 patient-years; HR 0.75; 95% CI 0.65-0.86; P<0.0001). Empagliflozin reduced the total number of hospitalisations for heart failure (HR 0.70; 95% CI 0.58-0.85; P<0.001). Regarding the second secondary endpoint, there was a difference in slope of 1.7 mL/min/1.73m^2/year favouring the empagliflozin arm (95% CI 1.1-2.4; P<0.0001). In 966 patients, eGFR was reassessed at the end of the trial, 23-45 days after withdrawal of double-blind therapy, and over 16 months. The eGFR decreased by -4.2 mL/min/1.73m^2 in the placebo group, and -0.9 mL/min/1.73m^2 in the empagliflozin group (P<0.001). Adverse renal events occurred in 30 patients in the empagliflozin group and in 58 patients in the placebo group (HR 0.50; 95% CI 0.32-0.77; P<0.01), which translates into a 50% risk reduction.

1. Packer M, et al. N Engl J Med 2020; 383:1413-1424.
2. Packer M, et al. Eur J Heart Fail. 2019;21:1270–1278.
3. Packer M. Primary results. EASD 2020. Session: Empagliflozin for the treatment of chronic heart failure and a reduced ejection fraction in patients with and without diabetes: new results of the EMPEROR-Reduced trial.

4. Poor prognosis for T2D patients on loop diuretics in addition to SGLT2 inhibitor

Type 2 diabetes (T2D) patients with cardiovascular disease being treated with a sodium-glucose transport protein 2 (SGLT2) inhibitor have poorer outcomes if they also use loop diuretics. The poor prognosis also holds true for T2 diabetics who have not been diagnosed with heart failure (HF).

An analysis of the EMPA-REG OUTCOME trial (NCT01131676) compared T2D patients without HF who received loop diuretics in addition to the SGLT2 inhibitor empagliflozin (n=755) with T2D patients without HF and without loop diuretics (n=5,559), as well as T2D patients with HF taking both drugs (n=706) [1].

The results, presented by Prof. Pierpaolo Pellicori (University of Glasgow, United Kingdom), showed no significant interaction between loop diuretic use and HF for all endpoints studied. The baseline patient characteristics did differ significantly for some measures; patients using loop diuretics were older, had a higher body mass index, had worse renal function, were more likely to have had a myocardial infarction, and were more likely to have been diagnosed with diabetes 10 years earlier or longer. Regarding medicine use, the group on took significantly more beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers. Patients using loop diuretics in the absence of HF had intermediate outcomes between patients with and without HF, thus indicating that taking a loop diuretic is a marker for worse prognosis. Prof. Pellicori suggested that undiagnosed or unreported HF in this cohort may have been prevalent, because only 31% of patients taking a loop diuretic were diagnosed with HF.

1. Pellicori P, et al. Use of loop diuretics and outcomes in patients with type 2 diabetes: findings from the EMPA-REG OUTCOME trial. EASD 2020. Abstract #933.

5. Once daily oral treatment with glucokinase activator TTP399 reduced HbA1c in patients with type 1 diabetes

Findings from the Simplici-T1 trial (NCT03335371) suggest that adding the novel hepatoselective glucokinase activator TTP399 to insulin reduced HbA1c by 0.32% at 12 weeks in type 1 diabetics compared with placebo + insulin.

The Simplici-T1 study was the first to evaluate the activation of glucokinase in patients with type 1 diabetes receiving a daily oral

dose of TTP399 as an adjunct to insulin therapy [1]. The primary endpoint of the randomised, double-blind study was a change in HbA1c at week 12.

This study was conducted in 2 parts under the same protocol to evaluate the safety and efficacy of TTP399 in adults with type 1 diabetes. After several weeks of insulin optimisation and placebo run-in, daily dosing with TTP399 was continued for 12 weeks. The 19 patients in part 1 received insulin pump therapy and glucose was continuously monitored. In part 2, 85 patients used an insulin pump or multiple daily insulin injections. Two statistical approaches were used to evaluate the effects of daily 800 mg TTP399 in this second group.

The study achieved its primary endpoint at week 12; HbA1c was reduced by 0.21% in the group receiving TTP399, whereas the placebo group experienced a mean 0.11% increase in HbA1c (P=0.03). A secondary estimand analysis confirmed that patients in the TTP399 arm achieved a placebo-subtracted HbA1c reduction of 0.32% (P=0.001). Treatment-emergent adverse events did not differ between the arms, not even when stratified by system organ class. No diabetic ketoacidosis occurred in either treatment group and no reports of severe hypoglycaemia were reported in the TTP399 arm. Overall, the safety profile was favourable.

1. Valcarce C, et al. The Simplici-T1 trial: activation of glucokinase by TTP399 improves glycaemic control in patients with type 1 diabetes. EASD 2020. Abstract #50.

6. High risk of vascular dementia in patients with T2D

Patients with type 2 diabetes (T2D) have a 36% higher risk of developing vascular dementia, mainly thought to be due to cardiovascular (CV) risk factors.

Presented by Dr Carlos Celis-Morales (University of Glasgow, Scotland), this conclusion was derived by accessing the Swedish National Diabetes Register, holding data on 378,299 T2D patients and 1,886,022 age- and sex-matched controls to assess dementia risk in diabetic patients [1]. The mean follow-up time was 7 years, and during that period 10,143 (2.7%) individuals who had diabetes developed dementia as well as 46,479 (2.5%) of the controls. The average age of the subjects was 64 years.

Patients with T2D had an 8% increased risk for developing non-vascular dementia (HR 1.08; 95% CI, 1.04-1.12), which was small but significant, and an 8% reduced risk for Alzheimer's disease (HR 0.92; 95% CI, 0.87-0.98). However, the risk of developing vascular dementia was increased by 36% (HR 1.36; 95% CI 1.03-1.09). When stratified by HbA1c levels, researchers found that people who had HbA1c >10.1% had a 93% increase in the risk of vascular dementia compared to those with HbA1c <7%. The risk of non-vascular dementia increased by 67% and that of Alzheimer's disease-associated dementia by 34%. It was found that CV factors as a whole accounted for 40% of the association between diabetes and dementia.

The greatest individual effects were caused by high blood pressure, existing CV disease, duration of T2D, and body mass index. These findings suggest that high-risk individuals could be identified and specific interventions, dietary regimens, or treatments could be used to reduce the risk of dementia in T2D patients.

1. Celis-Morales C, et al. Glycated hemoglobin, type 2 diabetes and the links to dementia and its major subtypes: findings from the Swedish National Diabetes Register. EASD 2020. Abstract #6.

7. HbA1c reduction with GLP-1RA leads to lower risk of CV events in cardiovascular outcome trials

The reduction of cardiovascular (CV) events in CV outcome trials (CVOTs) of glucagon-like peptide-1 receptor agonist (GLP-1RA) can be explained by a decrease in HbA1c.

Sodium-glucose transport protein 2 inhibitors and GLP-1RA have not only shown glycaemic benefits in several trials, but also significant positive effects on CV risk. However, variability in outcomes of better glycaemic control with GLP-1RA has cast some doubt over whether improved glycaemic control mediated CV risk reduction with these agents.

Dr Mart Roosimaa (University of Tartu, Estonia) and colleagues performed a meta-analysis to determine whether better glycaemic control was responsible for the GLP-1RA-mediated reduction in CV risk [1]. HbA1c levels were used as an indicator of glycaemic control, and for the primary outcome of absolute CV risk, the number of patients at risk was extracted for both GLP-1RA and placebo groups at multiple time points from each published GLP-1RA trial. The cumulative glycaemic exposure was calculated separately for the placebo and GLP-1RA groups in each trial and correlated with observed absolute CV risk. Differential glycaemic exposure between the GLP-1RA and placebo group was calculated for each trial and correlated with the published hazard ratio (HR).

A linear correlation between increased HbA1c and CV risk with both GLP-1RA and placebo was observed. The placebo group appeared to have lower absolute risk for the same glycaemic exposure. However, this

difference disappeared after correction for patient age. There was a strong correlation between the difference in glycaemic exposure of the GLP-1RA group compared with the placebo group and the reported HR. The 95% confidence intervals of the HRs from all trials supported the hypothesis that the risk reduction could be attributed to differences in HbA1c. Lowering the HbA1c by 1% decreased CV risk by 30%; this relationship was consistent within the placebo and the GLP-1RA groups and between groups.

1. Roosimaa M & Jõgis A. Reduction of cardiovascular events by GLP-1 receptor agonists is explained by HbA1c reduction. EASD 2020. Abstract #147.

8. Diabetes still goes unnoticed, resulting in delayed diagnosis

A British study of more than 200,000 blood samples from people not diagnosed with diabetes showed that HbA1c screening could have identified 1% of cases of undiagnosed diabetes in people aged 40-69 years. These individuals were only clinically diagnosed with diabetes 2.3 years later on average, thus highlighting a substantial delay in time to diagnosis.

The UK Biobank (UKBB) is a cohort of about 500,000 participants aged 40-69 years at recruitment, with primary care records (clinical codes and prescription data) available for 44% of participants. Dr Katie Young (University of Exeter Medical School, United Kingdom), presented the study which included participants without a diagnosis of diabetes at recruitment and had no indications of diabetes in their primary care records prior to recruitment (clinical codes for diabetes, HbA1c measurements ≥48 mmol/mol, or prescription for glucose-lowering medication) [1]. For these subjects, the time to receive a clinical diagnosis was determined from their primary care records and defined as the first occurrence of a diagnostic code for diabetes, an HbA1c ≥48 mmol/mol, or a prescription for glucose-lowering medication.

Of the 201,465 UKBB participants with primary care records available, no prior diagnosis of diabetes, and HbA1c measured at recruitment, 2,022 (1.0%) had undiagnosed diabetes by HbA1c screening. People who had undiagnosed diabetes on screening were older (61 vs 58 years), more likely to be obese (body mass index 31.0 vs 26.6 kg/m^2), and were more frequently male (60% vs 45%) than those without diabetes. It took an average of 2.3 years following UKBB recruitment for these patients to be diagnosed with diabetes; 23% still had not been diagnosed at 5 years follow-up.

The availability of this screening data and primary care records on a large cohort of individuals offers a unique opportunity to study the impact of a delay in diagnosis on the risk of developing future complications, the researchers added.

1. Young KG, et al. HbA1c screening in 195,460 'non-diabetic' individuals (40-69 years) identifies 1.1% with undiagnosed diabetes 2 years before clinical diagnosis. EASD 2020. Abstract #331.

9. Shared pathways for COVID-19 and diabetes?

The idea that COVID-19 and diabetes have shared pathways stems from the fact that medications used to treat diabetes often include agents that modulate the expression and activity of angiotensin converting enzyme 2 (ACE2), a key player in SARS-CoV-2 infectivity. Despite new insights, the effects of possible shared pathways remain unclear [1].

ACE2 is the principal receptor through which SARS-CoV-2 enters cells, and the cellular protease, TMPRSS2, enables this entry through priming of the spike protein. In addition, no entry of SARS-CoV-2 has been observed in the absence of dipeptidyl peptidase-4 (DPP-4), as DPP-4 is permissive for entry of the virus.

Regarding DDP-4 inhibitors, there is no clear evidence in patients with COVID-19 and type 2 diabetes that these agents are beneficial. Data has shown that they can reduce inflammation, but a recent analysis of the TECOS trial in which patients were treated with sitagliptin, showed no change in the inflammatory biomarkers, CRP, IL-6, and TNF-α. The use of metformin in the TECOS trial, however, significantly reduced inflammation. In people with COVID-19 who are using metformin, an increased risk was seen for ketoacidosis, although this did not affect mortality.

Observational data also suggested that people taking statins may experience improved COVID-19 outcomes in the hospital. Diabetics taking insulin had a higher risk of morbidity and mortality from the virus, but this may result from comorbidities associated with diabetes.

The question remains as to whether SARS-CoV-2 can infect insulin-producing beta cells causing insulin deficiency and onset of type 1 diabetes. ACE2 and TMPRSS2 are expressed on endothelial cells in the ducts of the pancreas and CoV-2 may attack them. It was concluded that in patients with COVID-19 and type 2 diabetes, optimising glycaemic control was most important.

1. Drucker DJ. COVID-19 and type 2 diabetes: Do shared pathways have therapeutic implications? EASD 2020. Session: COVID-19 and diabetes.

10. Patients with RA have higher risk of developing diabetes

The inflammatory pathways involved in the pathogenesis of diabetes mellitus (DM) also play an important role in rheumatoid arthritis (RA). Therefore, it comes as no surprise that RA is associated with an increased risk of DM.

Given that inflammation is a key factor in the onset and progression of DM and that RA is an inflammatory autoimmune disease, an association between the two conditions seems probable. A systematic review and meta-analysis were conducted to investigate the relation between RA and the incidence of DM [1].

Dr Zixing Tian (University of Manchester, United Kingdom) and colleagues presented the results of their comprehensive search up to March 10, 2020 in Medline, Embase, and the Web of Science core collection to identify cohort studies comparing DM incidence in people with RA to that in the general population. This resulted in 3,667 articles from which 47 studies were identified after screening. Of those, 5 journal articles and 2 conference abstracts comprising a total of 1,629,854 patients were included in this meta-analysis. All studies were retrospective and all but one hospital study were population-based.

RA was associated with a higher risk of DM (pooled relative risk 1.23; 95% CI 1.07-1.40). In a sensitivity analysis, excluding the hospital study did not materially change the result (pooled relative risk 1.23; 95% CI 1.06-1.42). A funnel plot showed potential publication bias which was proven by Egger's test (-3.15, P<0.01) but not by Begg's test (-0.05, P=1.00).

The researchers asserted that intensive screening and management of DM risk factors should be considered in people with RA. Drugs that reduce systemic inflammation may be effective in lowering the incidence of DM and possibly RA as well through targeting more than one pathway at a time.

1. Tian Z, et al. The relation between rheumatoid arthritis and diabetes incidence: a systematic review and meta-analysis. EASD 2020. Abstract #271.

11. Once-weekly insulin is a promising treatment option

The once-weekly basal insulin analogue, icodec, showed comparable efficacy and safety to once-daily insulin glargine U100 in a phase 2 study (NCT03751657). Patients with type 2 diabetes who need basal insulin could potentially have a simpler, once-weekly treatment regimen without compromising blood sugar control and safety.

The investigational drug, insulin icodec, is a long-acting basal insulin analogue with a half-life of approximately 1 week. After injection, insulin icodec binds strongly but reversibly to albumin, resulting in a slow and steady release of active icodec that lowers blood sugar throughout the week. As it is a concentrated formulation, icodec's injection volume is equivalent to that of daily glargine U100.

Dr Julio Rosenstock (University of Texas Southwestern, USA) and colleagues conducted a 26-week, randomised, double-blind, double-dummy, phase 2 trial to investigate the efficacy and safety of once-weekly insulin icodec compared with once-daily insulin glargine U100 in patients who had not previously received long-term insulin treatment and whose type 2 diabetes was inadequately controlled (HbA1c, 7.0-9.5%) by metformin with or without a dipeptidyl peptidase-4 inhibitor [1]. The results were published in *the New England Journal of Medicine* as well [2]. The primary endpoint of the study was a change in HbA1c from baseline to week 26. Safety, including hypoglycaemia and insulin-related adverse events, was also evaluated.

A total of 247 participants were randomly assigned to receive icodec (n=125) or glargine (n=122). Baseline characteristics were similar between the 2 arms. The results showed that the mean change from baseline in the HbA1c level was similar between the 2 arms (-1.33% for icodec vs -1.15% for glargine, P=0.08). The secondary endpoint, change in fasting plasma glucose level from baseline to week 26, decreased by 57.74 mg/dL and 53.86 mg/dL for the icodec and glargine groups, respectively (difference -3.9; 95% CI -11.9 to 4.2). Regarding hypoglycaemia, the icodec group had 0.53 events per patient-year, and the glargine group 0.46 events per patient-year (estimated rate ratio 1.09; 95% CI 0.45 to 2.65). Insulin-related adverse events did not differ between the groups, and the rates of hypersensitivity and injection-site reactions were both low. Overall, most adverse reactions were mild, and no serious events related to the trial drugs were reported.

1. Rosenstock J, et al. Once-weekly basal insulin icodec offers comparable efficacy and safety vs. once-daily insulin glargine U100 in insulin naïve patients with type 2 diabetes inadequately controls on OADs. EASD 2020. Abstract #56.
2. Rosenstock J, et al. N Engl J Med. 2020 Nov 26;383(22):2107-2116.

12. Non-invasive monitoring by measuring glycated albumin in tears

Tears may offer a new opportunity for monitoring blood glucose in diabetic patients. It has been shown that measuring glycated albumin (GA) in tears is feasible and that the GA in tears accurately reflects the levels of GA in blood.

GA is a biomarker which corresponds to the average level of blood glucose over 2 weeks. HbA1c reflects changes over a longer period of time (2 to 3 months), so GA may be a better biomarker for detecting earlier changes in blood glucose. This prompted Japanese researchers to determine the feasibility of measuring the level of GA in tears of 100 patients; the findings were presented by Dr Masakazu Aihara (University of Tokyo, Japan) [1].

Tear and blood samples were collected from the participants at the same time. GA in tear samples was measured by liquid chromatography and mass spectrometry, whilst an enzyme method was used to assay the level of GA in blood. After multiple regression analysis, it was shown that the correlation between GA in tears and in blood was maintained, even when researchers adjusted for age, gender, nephropathy stage, and obesity ($r=0.722$; $P<0.001$).

These findings open up new possibilities to non-invasively monitor patients' blood glucose levels. Researchers are attempting to improve the method by which tear samples are collected and to reduce the volume of tears required for analysis. The current method involves collecting tears with a dropper, and 100 µL of tear fluid is needed to accurately measure GA concentration. Other studies are being done to test this method for monitoring the effect of glucose-lowering treatments.

1. Aihara M, et al. Development of noninvasive diabetes monitoring method using tear samples. EASD 2020. Abstract #644.

13. More exercise means less risk of all-cause mortality amongst T2D patients

Physical activity and exercise is important for long-term survival in patients with type 2 diabetes. In fact, a study of more than 4,500 patients over a 15-year period revealed that increased exercise was linked to a 25-32% reduction in risk of all-cause mortality in this population.

A Taiwanese study, presented by Dr Yun-Ju Lai (Taichung Veterans General Hospital, Nantou, Taiwan), used data from the National Health Interview Survey (NHIS) and the National Health Insurance research databases to examine the association between exercise capacity and all-cause mortality [1]. In total, 4,859 patients with type 2 diabetes were selected. Of these, 49.2% were male with a mean age of 59.5 years.

Using univariate Cox regression analysis, it was found that patients who had a greater exercise capacity also had a significantly decreased risk of all-cause mortality compared with patients who did not exercise at all. If patients did moderate exercise (≤800 kcal/week), the HR was 0.83 (95% CI 0.71-0.97). For those maintaining a more strenuous exercise regimen (>800 kcal/week), the HR was 0.77 (95% CI 0.67-0.89). The researchers then adjusted outcomes for potential confounders using multivariate Cox regression analysis. This resulted in a significantly decreased risk of all-cause mortality for patients with a higher exercise capacity versus those with poor exercise habits, for both moderate exercise (HR 0.75; 95% CI 0.62-0.91) and for more intense exercise (HR 0.68; 95% CI 0.57-0.81). A sensitivity analysis which excluded mortality in the first and second year in the study period was also done and showed that people with a greater capacity for exercise had a significantly decreased risk of all-cause mortality.

1. Lai Y-J. Association between exercise capacity and all-cause mortality in people with type 2 diabetes. EASD 2020. Abstract #267.

14. Intermittent fasting: consuming fewer calories but in a different way

Intermittent fasting has become quite common in recent years. What is it and how is it done? Does it really lead to weight loss? A quick insight into intermittent fasting was given at EASD 2020 by Prof. Krista Varady (University of Illinois, Chicago, USA).

Intermittent fasting is an umbrella term for 3 types of dieting. First, there is alternate day fasting where 1 day you restrict your consumption to about 500 kcal and the next you eat normally. Second is the 5:2 diet, which means 1 or 2 days of fasting followed by 6 or 5 days of normal eating. On fast days, only about 50 kcal are allowed.

The third type of intermittent fasting involves eating only during a certain time period each day, usually a 4- to 10-hour window. During that time, people can eat whatever they like, but outside the window, they only consume water or zero-calorie drinks.

Tests of the alternate day fasting regimen resulted in a 10-15 pound weight loss in 3

months. The time-restricted eating method also results in weight loss, but only 5-10 pounds in 3 months. Time-restricted eating is easier to follow, however, because it does not require counting calories.

A study of time-restricted feeding (8-hour window) in obese individuals showed an average 3% weight loss over 3 months, high (80%) self-reported adherence, and unintentional calorie restriction of around 350 kcal/day. Under this diet, systolic blood pressure decreased, but there was no change in plasma lipids or glucoregulatory factors.

Shorter feeding windows (4-6 hours) resulted in similar outcomes, but with higher unintentional calorie restriction (550 kcal/day) and 3% weight loss in 2 months. Intermittent fasting should not be attempted by pregnant women, people who have binge eating disorders, shift workers, and those given to frequent snacking.

Those who wish to try intermittent fasting should be advised that the first 10 days can be rough, with headache being the most common complaint. Consuming 50 grams of protein on a fast day helps to reduce hunger.

1. Varady KA. Clinical application of intermittent fasting. EASD 2020. Session: We are what we do not eat.

15. Timing of mealtime insulin can affect quality of life

Bolus insulin dosing still poses challenges to most people with type 1 diabetes (T1D). A majority of patients would prefer to administer insulin immediately prior to or following a meal; this timing is thought to improve their quality of life.

A multinational study assessed attitudes, behaviours, and the overall impact of pre-meal (15-20 minutes) bolus insulin dosing on adults with T1D (n=1,401), parents of children with T1D (n=350), and physicians (n=960) [1].

Of the adults with T1D, 46% were male with a mean age of 43 years and a mean duration of T1D of 19 years. Most (72%) administered their bolus insulin by injection, and 28% used an insulin pump. Continuous glucose monitoring was used by 43%.

The mean age of the children was 10 years with a mean T1D duration of 4 years, 64% was male. Of the children, 74% administered their bolus insulin by injection and 26% used an insulin pump, with 58% using continuous glucose monitoring.

A vast majority (96%) of both adults with T1D and parents of children with T1D understood the importance of administering bolus insulin accurately, but only 35% of adults and 47% of parents felt very confident in accurately estimating the amount of insulin required, and 91% of adults and 96% of parents experienced difficulties with pre-meal insulin dosing.

Almost all physicians (99.6%) reported that they believed their patients with T1D found pre-meal bolus insulin dosing challenging. Both T1D adults (82%) and parents (93%) felt that administering insulin 15-20 minutes before a meal had a negative impact on quality of life, while 73% of adults and 67% of parents preferred bolus insulin administration either immediately before (42% adults, 44% parents) or after (31% adults, 23% parents) a meal.

1. Lane W, et al. The burden of mealtime insulin dosing in adults and children with type 1 diabetes. EASD 2020. Abstract #694.