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European Association for the Study of Diabetes (EASD) congress 2022

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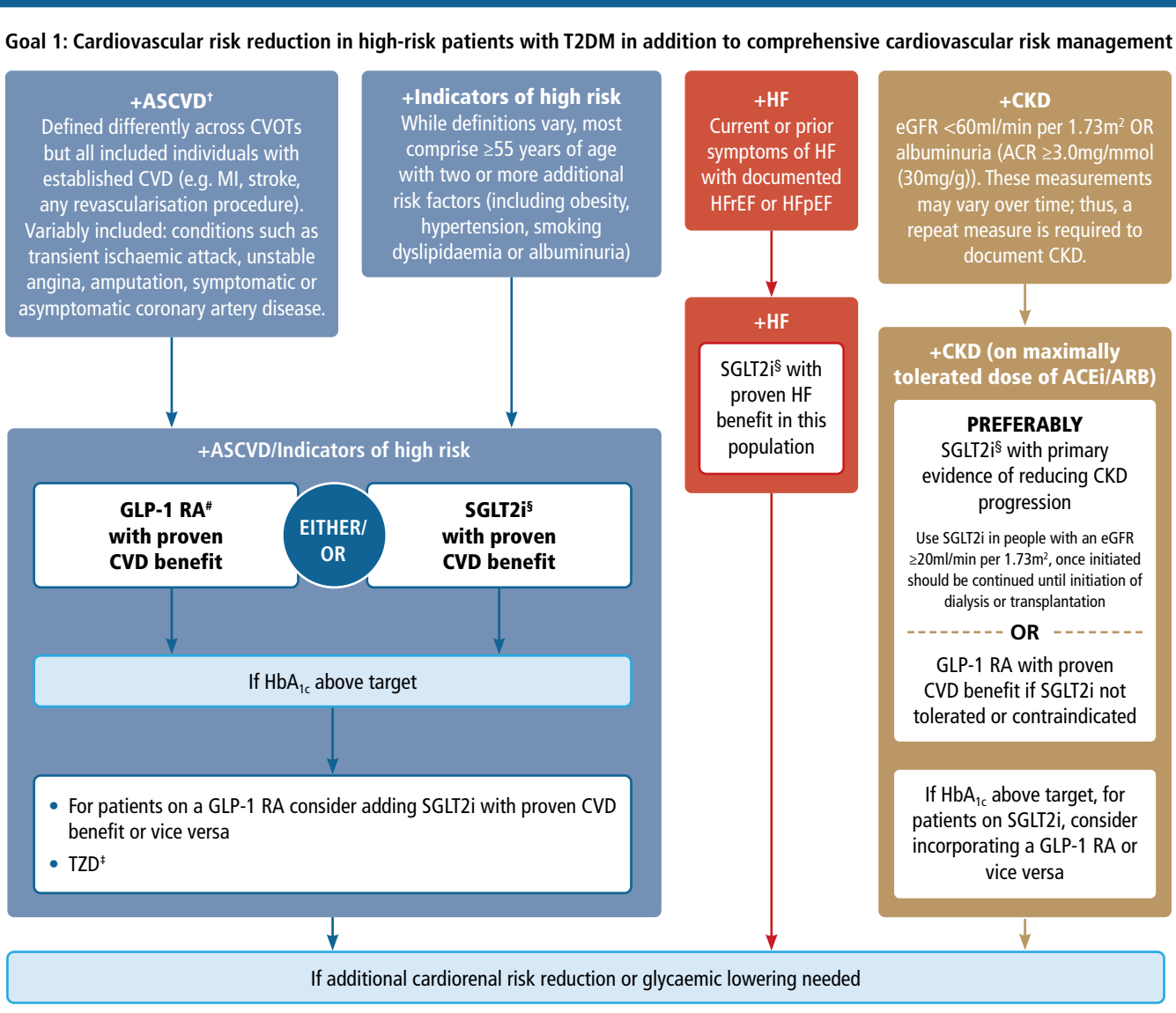
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2022 ADA/EASD consensus update on hyperglycaemia in type 2 diabetes

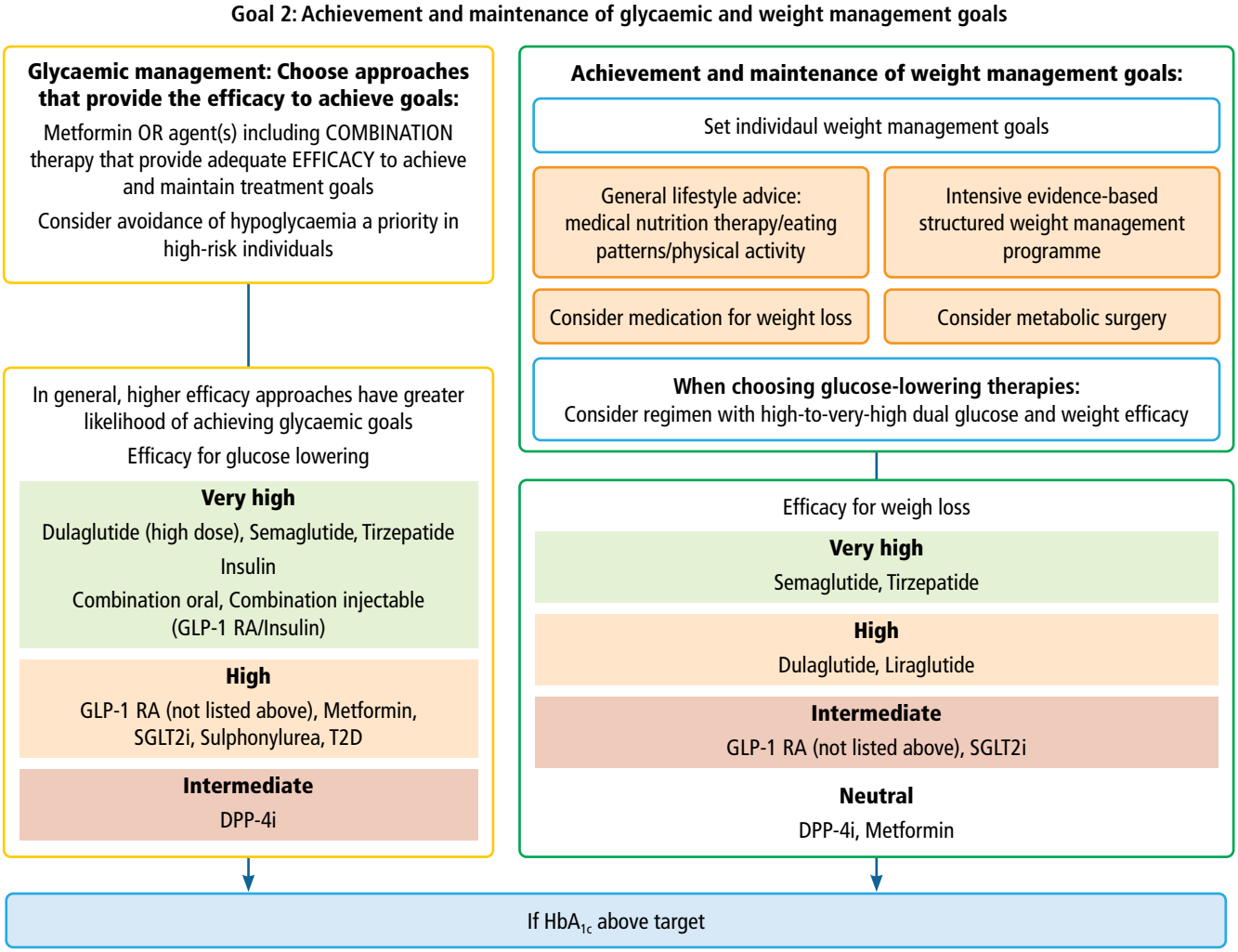
This 2022 consensus update from the American Diabetes Association (ADA) and the EASD[1] includes a treatment algorithm with an important new focus on weight loss that uses new evidence from recent randomised controlled trials (RCTs) of glucose-lowering medications to support its recommended treatment approaches for reducing cardiorenal risk in high-risk type 2 diabetes mellitus (T2DM) patients (Figure 1). The updated treatment algorithm has been simplified in respect of risk reduction strategies, with a separate clinical focus on atherosclerotic cardiovascular disease (ASCVD), heart failure (HF) and chronic kidney disease (CKD); also included is guidance on other established comprehensive cardiovascular risk management strategies, e.g. for lipids and blood pressure (BP).

Figure 1. ADA/EASD recommendations for the use of glucose-lowering medications for cardiovascular risk reduction in the management of T2DM[1]



* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. ‡ Low-dose T2D may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

Figure 2. ADA/EASD recommendations on the use of glucose-lowering medications to achieve and maintain glycaemic targets and weight in the management of T2DM[1]



A second major, but equally ranked, goal is to achieve and maintain glycaemic targets and weight management (Figure 2).

As with previous consensus reports, significant attention is given to the individual's involvement in their own diabetes care and includes factors such as their home and financial circumstances and how they feel about the different possible side effects of medications and the selection of medication.

Updated dietary guidelines – treatment and prevention of T2DM

The Diabetes and Nutrition Study Group (DNSG) recently updated its guidelines for the treatment and prevention of T2DM, and these will be published in the coming months. New recommendations include advice relating to dietary patterns, environmental sustainability, food processing, patient support and remission of T2DM.

The four components of weight management in diabetes are to prevent weight gain, to achieve weight loss, the maintenance of weight loss and to minimise cardiometabolic risks. Those who are overweight or obese and at increased risk of T2DM and those who have T2DM should adopt an intensive lifestyle intervention involving an energy-restricted diet and increased physical activity. It is important to note that diet compositions for weight

loss induction are not necessarily the same as those for weight maintenance.

In general, the DNSG recommendations include a range of foods and different dietary patterns suitable for weight management and the prevention or remission of T2DM (Table 1). Key points include the following:

- Very low-energy diets are difficult to sustain, and step-down approaches are advocated for those patients with severe obesity
- Very low-carbohydrate intakes, such as with ketogenic diets, are not recommended
- Foods naturally high in fibre should be encouraged; fibre-enriched foods and supplements should be considered if sufficient intake cannot be obtained from diet alone
- Intake of free or added sugars should be <10% of total energy intake
- Dietary fats should come mainly from plant-based foods high in monounsaturated and polyunsaturated fats; saturated and trans-fat intakes should contribute <10% and <1% of total energy, respectively
- Protein recommendations are partly dependent on weight status, age and kidney function.

Table 1. DNSG recommendations: foods and dietary patterns

Minimally processed whole grains and whole grain foods	Improve glycaemic control, cardiovascular risk factors and body weight
Whole vegetables and fruit	Improve glycaemic control and other cardiometabolic risk factors
Legumes	Improve glycaemic control and other cardiometabolic risk factors
Nuts and seeds	Improve glycaemic control and other cardiometabolic risk factors
Mediterranean dietary pattern	Improve glycaemic control and other cardiometabolic risk factors
Nordic dietary pattern	Improve adiposity and other cardiometabolic risk factors
Vegetarian dietary pattern	Improve glycaemic control and other cardiometabolic risk factors
No recommendations were issued for the Portfolio or DASH dietary patterns	

Diet and all-cause mortality in T2DM – what is the current evidence?

Investigating how dietary factors may influence the progression of diabetes, Janett Barbaresko (Germany) presented the findings of a systematic review and meta-analysis of 97 prospective observational studies. This comprehensive overview of dietary intake and all-cause mortality among people with T2DM demonstrated high-certainty evidence of a reduced risk with the higher consumption of whole grain (RR, risk ratio 0.84), fibre (RR 0.86), fish (RR 0.95) and omega-3 polyunsaturated fatty acids (RR 0.87). A low certainty of evidence of reduced risk was associated with vegetable consumption (0.88) and plant protein intake (0.91). Higher consumption of eggs (RR 1.05) and cholesterol intake (RR 1.19) were positively associated with all-cause mortality in T2DM, although the certainty of evidence was low. This review is important because although several dietary guidelines with varying recommendations are available, these are largely based on the general population and an evidence-base for specific nutrients and foods to prevent T2DM-related outcomes is lacking.[2]

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Lipids – New research brings us closer to understanding residual cardiovascular risk in statin-treated patients

In a session entitled 'Juggling with lipids to find new targets for managing diabetes and comorbidities', three presentations looked at the role of ceramides in diabetes, obesity and coronary artery disease (CAD). Ceramides are the so-called 'waxy lipids' found in the cell membrane; they are the products of the 'mopping up' process of dealing with excessive fatty acids from the diet and other sources such as the liver. Ceramides are increased in adipose dysfunction and inflammation (obesity), insulin resistance, β-cell failure (diabetes) and non-alcoholic fatty liver disease (NAFLD). Furthermore, ceramides contribute to the development of CAD, diabetic kidney disease (DKD) and non-alcoholic steatohepatitis (NASH).

While these effects of ceramides have been known for some 10 years, this EASD congress presented an update of current work with a look to the future. The main points are:

- Blocking the increase in ceramides with a DES-1 inhibitor (dihydroceramide desatuase-1) has been shown in laboratory experiments to reduce hepatic steatosis, hypertriglyceridaemia and glucose intolerance.
- A first-in-class ceramide inhibitor (CNT2130) is being developed as a potential therapy for triglyceride reduction, improved insulin sensitivity, reduced fatty liver disease and improved kidney function
- Diet influences the levels of plasma ceramides and saturated fats increase levels of these waxy lipids, with the greatest increase in liver fat and insulin resistance
- A ceramide test (CERT) has been developed and is available through the Mayo Medical Laboratories accompanied by a CERT2 risk score to assess risk in both primary and secondary prevention. This test is a better predictor of cardiovascular death than low-density lipoprotein cholesterol (LDL-c) in stable coronary heart disease. This is probably because the mechanisms that lead to cardiovascular events may very well be different from those which drive the decades-long atherogenic process (e.g. LDL-c).
- The levels of 'monster' ceramides, particular types of waxy lipids associated with cardiovascular events, are reduced by statin therapy, metformin, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), aerobic exercise and healthy diets.
- A recent publication[3] has shown that specific ceramides are associated with an increased three-year risk of a major adverse cardiovascular event (MACE) after carotid endarterectomy undertaken to reduce risk of a future stroke in patients with extracranial carotid artery stenosis.

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Does exercise matter? Effects on β-cell function in T2DM

Of interest were two studies on the effects of exercise on β-cell function in patients with T2DM. The DOSE-EX study compared the effects on β-cell function, insulin secretion and insulin sensitivity of 16 weeks of standard care, or dietary intervention, or dietary intervention with exercise three times weekly, or dietary intervention with exercise six times weekly.[4] Exercise, both aerobic and resistance training, as an adjunct to diet therapy improved β-cell function more than standard care or diet alone in participants with T2DM, although there was no significant difference between moderate and high-volume exercise. Mark Lyngbaek (Denmark) concluded that the improvement in β-cell function was mainly mediated by improved insulin sensitivity, because adding

exercise to the dietary intervention did not increase glucose- or meal-stimulated insulin secretion beyond dietary weight loss alone. He is of the view that exercise three times weekly may be sufficient for a beneficial effect on β-cell function.

Maria Petersen (Denmark) presented a study on the effects of high-intensity interval training (HIIT), combining rowing and cycling, on the β-cell function of obese men with T2DM compared with glucose-tolerant men who were obese or lean. It was found that HIIT markedly improved (>200%) β-cell function adjusted for insulin sensitivity to the degree seen in controls at baseline; β-cell function was still severely impaired, however, suggesting that β-cell dysfunction is less reversible than insulin sensitivity. To a minor extent, an improvement in β-cell function was also observed in the glucose-tolerant lean and obese controls after 16 weeks.

win FACT GLP-1 RAs – from here to eternity

This session explored the extension of the use of GLP-1 RAs across different age groups, as well as our increased understanding of their value in obese and overweight adults.

Dulaglutide in children and adolescents

David Cox (Eli Lilly) presented the results of the AWARD-PEDS study on behalf of Silva Arshanian, lead researcher, who was not able to attend the EASD congress. This efficacy and safety trial of dulaglutide (0.75mg or 1.5mg) in children with T2DM aged 10-18 years (body mass index, BMI >85th percentile) recruited 154 participants who were treated for 26 weeks; thereafter all participants, including the control group, continued with dulaglutide therapy to 52 weeks. Fifteen percent of the cohort were African Americans and the study was conducted in nine countries. At the time of entry into the study, all participants had been treated with metformin or with metformin and basal insulin; baseline HbA_{1c} was 8.1%.

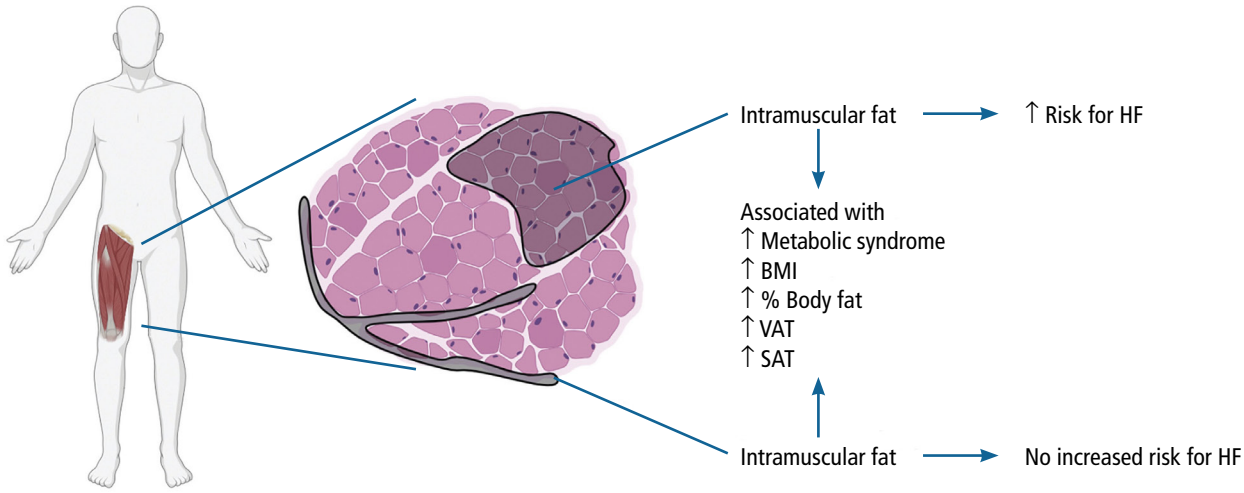
At 26 weeks in the pooled dulaglutide-treated arm, HbA_{1c} was reduced by 0.7%; fasting plasma glucose (FPG) was also reduced and 50% of the dulaglutide-treated participants reached the target HbA_{1c} of <7%. The overall safety profile in youth was consistent with that of dulaglutide treatment in adults.

Effect of GLP-1 RAs on muscle fat infiltration relates to the HF effects of these agents

Ambarish Pandey (United States) presented the results of a study investigating the relationship between intramuscular fat and intermuscular fat using computed tomography (CT) thigh muscle fat assessments.[5] This CT study showed that intramuscular fat deposition but not that of intermuscular fat is related to a higher risk of developing HF (Figure 3). There were 485 HF events among community-dwelling older adults during the follow-up of 12.2 years, and multivariable adjustment showed that the association of intramuscular fat deposition remained significant even after additional adjustment for BMI, visceral fat and muscle strength.

Investigating whether weight-reducing agents can reduce intramuscular fat using liraglutide, a GLP-1 RA, a study among non-diabetic overweight and obese adults has shown that visceral adipose tissue showed an 11% reduction over 40 weeks; a 3% average reduction in muscle fat infiltration (MFI) was observed. Among individuals with high MFI, GLP-1 RA therapy led to a 30% reduction in MFI. This is an interesting study assessing the mechanism of the beneficial effect of GLP-1 RAs on HF.

Figure 3. Skeletal muscle fat and the risk of HF[5]



New once-daily oral small-molecule GLP-1 RA, PF-07081232

Adding to the choices of molecules in the GLP-1 RA class, Clare Buckeridge (United States) presented the positive results of a phase 1 study of a new oral GLP-1 RA (PF-07081232), which showed robust and dose-dependent reductions in glucose levels and HbA_{1c} accompanied by weight loss over a 4–6-week period.

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Heterogenous response to anti-obesity medication not of concern with newer agents – The SURMOUNT programme

Carel du Toit (Ireland) described the rationale for the SURMOUNT chronic weight management programme, using the opportunity to highlight current principles underlying obesity therapy. He stressed that:

- Eating less and moving more is a weight-loss strategy, not an obesity therapy
- Two in 10 obese patients will respond to lifestyle therapy
- The treatment of obesity, even with new third-generation therapies such as tirzepatide, cannot rely on one silver bullet; multiple therapeutic approaches are needed
- In obesity treatment, health gain is as important as weight loss
- Successful weight loss in obesity treatment has to increase satiety and reduce hunger as a central nervous system intervention.

The SURMOUNT clinical trial programme

The SURMOUNT clinical development programme consists of the typical clinical trial series required for regulatory approval but has now also launched a cardiovascular outcome trial (CVOT) in obese patients without diabetes. The trial will recruit 15 000 patients in both a primary prevention arm involving high-risk obese patients and a secondary prevention arm involving patients ≥40 years of age with established cardiovascular disease (CVD). The study protocol will be published soon.

SURMOUNT 1 obesity results – Striking response to tirzepatide treatment

The efficacy and safety data of the SURMOUNT 1 trial were presented by Aria Jastreboff (United States). This double-blind, randomised, controlled study involved 2 500 obese adult patients (BMI

≥30kg/m^2 or ≥27kg/m^2) with hypertension, dyslipidaemia, obstructive sleep apnoea or CVD. Diabetic patients were excluded. The study period was 72 weeks with a further add-on of two years for patients with prediabetes (results not yet available). Tirzepatide was given subcutaneously once-weekly in three different doses: 5mg, 10mg and 15mg. A categorical absolute weight loss of >20% was achieved with the 10mg and 15mg doses of tirzepatide (Figure 4).[6]

Figure 4. SURMOUNT 1 - Weight reduction over 72 weeks (absolute change)[6]

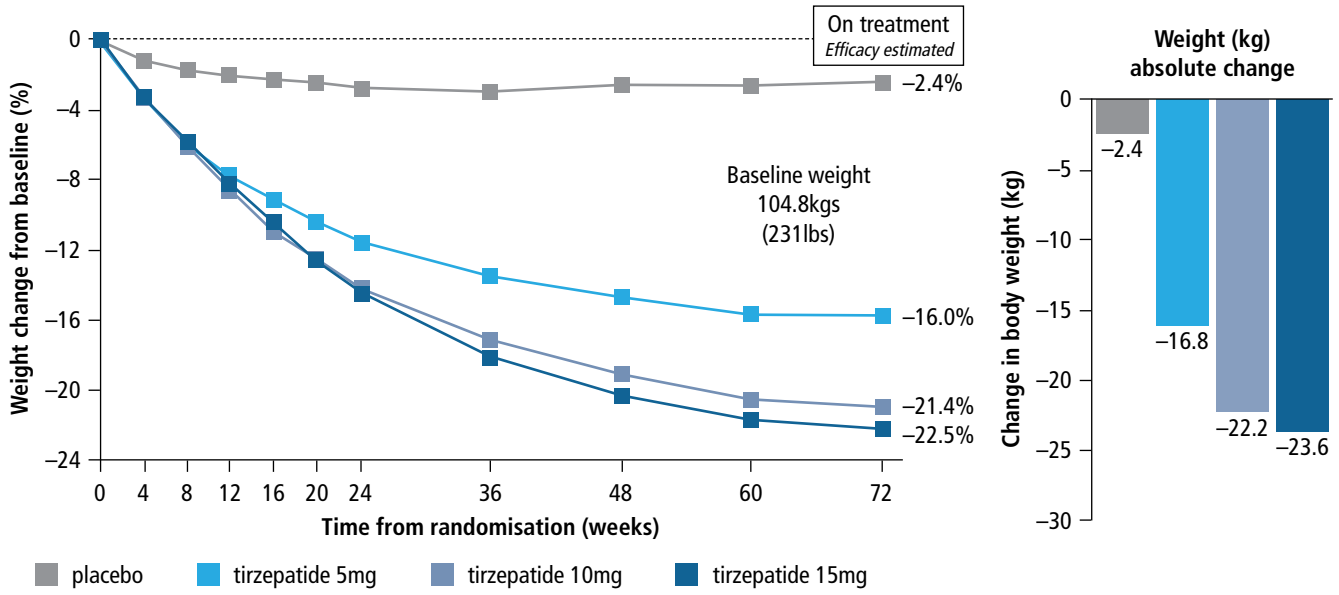
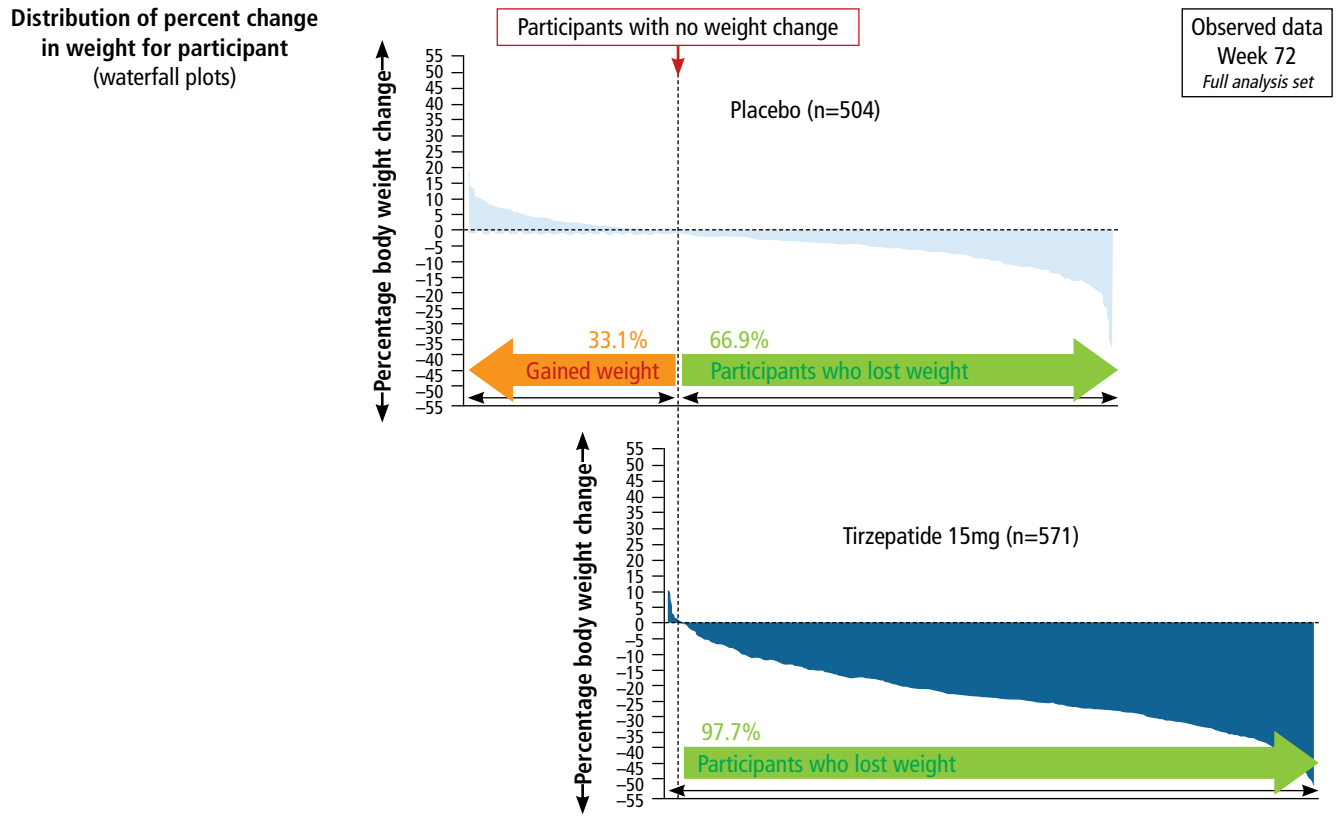


Figure 5. Overcoming challenges in obesity medicine - The SURMOUNT 1 clinical development programme



Science cannot yet predict who will respond to anti-obesity agents, given the heterogenous nature of obesity, but this matters less with tirzepatide as 97.5% of treated participants lost weight using the 15mg dose compared to 67% on placebo and lifestyle intervention involving dietitian-guided balanced meals with a deficit of 500 calories per day and 150 minutes of physical activity (Figure 5). The efficacy and safety results of SURMOUNT 1 are summarised in Table 2.

Table 2. SURMOUNT 1 summary - Efficacy and safety results with tirzepatide

- All three doses demonstrated clinically meaningful and sustained body weight reduction
- Up to 57% of participants achieved a ≥20% weight reduction on tirzepatide
- Fat mass to lean mass ratio improved in all treated patients, with visceral fat mass showing a 40% reduction as determined in a subset of 160 patients drawn from pooled tirzepatide dosing
- Lean body mass was not sacrificed, and increased on treatment
- HbA_{1c} decreased by 0.5% from a baseline of 5.6%, lipid and BP profiles improved
- The most frequently reported adverse events were gastrointestinal, mild to moderate and transient, and occurring primarily during dose escalation
- Patient assessment of all domains (physical functioning, general health, vitality, social functioning) showed significant improvement.

Luc van Gaal (Belgium), a doyen on the role of overweight and obesity in the development of chronic disease, noted that the level of weight loss achieved by tirzepatide was unprecedented and may well lead to regulatory agencies increasing the bar for new weight loss agents from the current 5%. "The nature of the fat loss, particularly the reduction in visceral fat, is important in terms of achieving better cardiovascular outcomes." He concluded that today's pharmacotherapy will help to motivate adherence to ongoing lifestyle change.

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Merging a glucocentric and a cardiorenal metabolic focus is a priority for primary care clinicians in T2DM

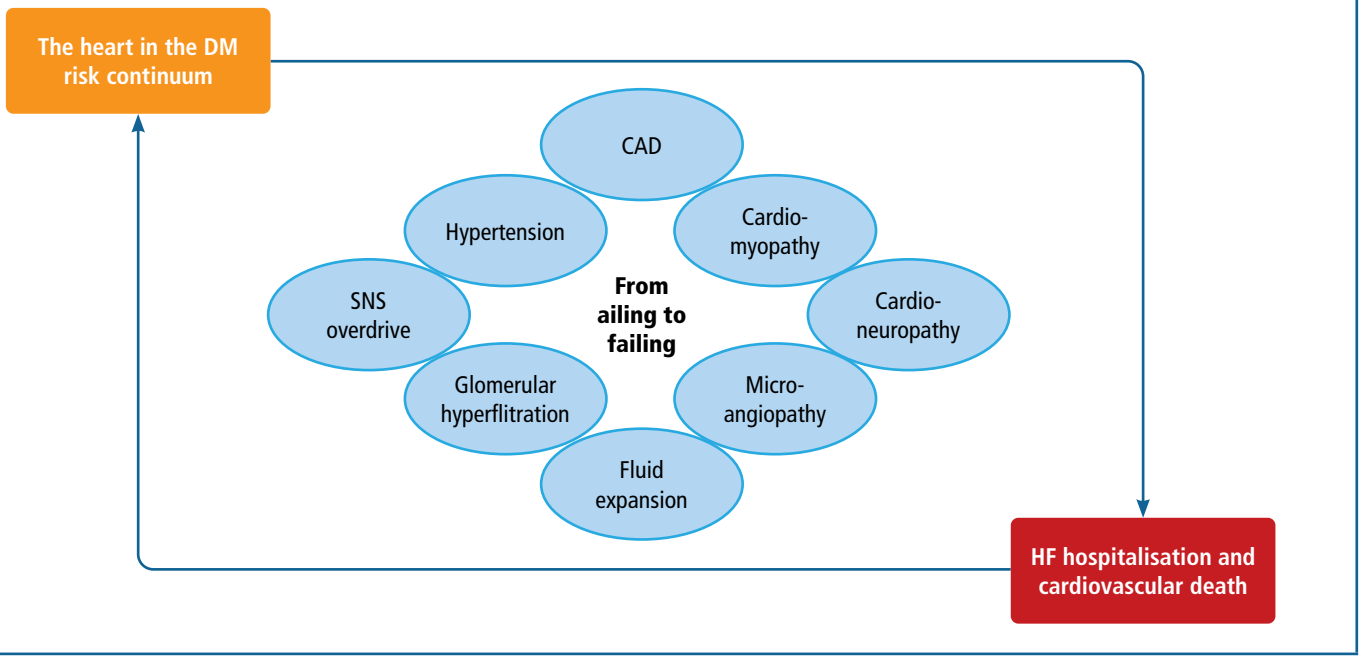
Eberhard Standl (Germany) chaired the session on the cardiorenal metabolic interplay in T2DM. He is of the view that it is vital, as clinicians, that we understand that studies have shown that >30% of patients already have microalbuminuria at diagnosis of their T2DM. Furthermore, over time, one in two T2DM patients will develop CKD and three in 10 patients will develop HF.

The Ominous Octet of risk factors for HF is driven by cardiac and CVD lipo-/glucotoxicity, cardiac fuel overload and renal glucotoxicity (Figure 6). The Ominous Octet for DKD is driven primarily by hypoxaemia, deranged tubuloglomerular feedback, hyperglycaemia, obesity and hypertension.

The benefits of intensive glucose control with regard to microvascular outcomes are well known and implemented by clinicians worldwide. We now need every doctor to know how to use cardiorenal-beneficial agents, the GLP-1 RAs and the sodium-glucose cotransporter-2 (SGLT-2) inhibitors, in the same way in order to prevent the development of DKD and HF. The primary prevention role of GLP-1 RAs, as seen in REWIND with dulaglutide, supports useful early intervention in T2DM. "Clinicians need to merge their glucocentric focus with a cardiorenal metabolic focus to achieve better outcomes for their patients."

Clinicians need to merge their glucocentric focus with a cardiorenal metabolic focus to achieve better outcomes for their patients

Figure 6. HF in diabetes - the OMINOUS Octet



win FACT **SGLT-2 inhibitors in the spotlight**

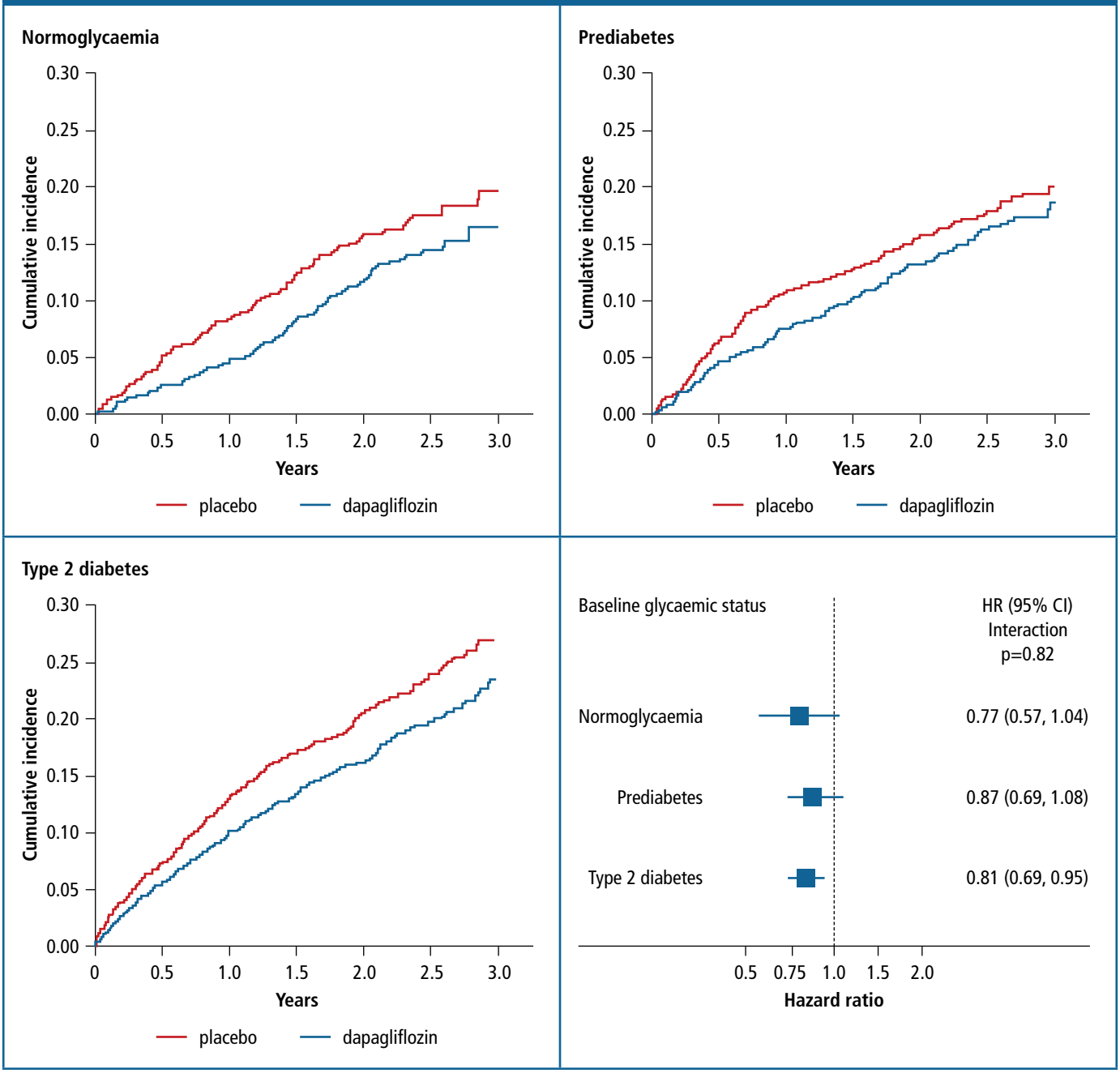
DELIVER – Effects of glycaemic status on HFpEF outcomes

Principal investigators presented outcomes across glycaemic categories of the DELIVER trial of dapagliflozin versus placebo in 6 263 HF patients with mildly reduced (>40%) or preserved ejection fraction (HFmrEF, HFpEF).[7] Compared with placebo, the composite of hospitalisation for HF and cardiovascular death was decreased by 18% in the cohort, of whom one-fifth were normoglycaemic (no history of diabetes and HbA_{1c} <5.7%) and the majority prediabetic (no history of diabetes and HbA_{1c} 5.7% to <6.5%) or diabetic (history of use of a glucose-lowering agent and HbA_{1c} ≥6.5%). In general, cardiovascular event rates increased with worsening glycaemic status. For dapagliflozin-treated patients who had T2DM at enrolment, the primary endpoint was decreased by 19% compared with 23% in those patients who were not diabetic at baseline; of interest, patients with prediabetes demonstrated a 13% risk reduction (Figure 7).

In the T2DM dapagliflozin-treated subgroup, a similar treatment effect was observed across duration of diabetes and baseline HbA_{1c}, irrespective of baseline use of biguanides, insulin and DPP-4 inhibitors. For those patients using GLP-1 RAs at baseline, there was a risk reduction of 54% compared with 17% in those not using GLP-1 RAs at baseline. Of particular interest, there was a significant 50% risk reduction in patients with baseline sulphonylurea use compared with 6% for those not using sulphonylureas. Silvio Inzucchi (United States) mused: "We have no idea what this means."

Summarising, Mikhail Kosiborod (United States) remarked that in HF, SGLT-2 inhibitors are the first foundational therapy demonstrated to reduce cardiovascular death and hospitalisations for HF across the range of ejection fraction, age, glycaemia, kidney function, background therapies and clinical setting (in-hospital or ambulatory), while demonstrating a favourable safety profile.

Figure 7. DELIVER: Worsening HF and cardiovascular death by glycaemic status in HFmrEF/HFpEF patients treated with dapagliflozin versus placebo



Effects of SGLT-2 inhibition on subcutaneous and epicardial adipose tissue metabolism

A study has demonstrated that treatment with SGLT-2 inhibitors elicits different metabolic responses in subcutaneous adipose tissue (SAT) and epicardial adipose tissue (EAT) in patients with severe HF with reduced EF (HFrEF) scheduled for heart transplantation or mechanical support implantation, including patients with T2DM. Metabolomic analysis of SAT and EAT was performed on samples obtained during surgery. Milos Mraz (Czech Republic) outlined the study's conclusions with regard to the different metabolic responses elicited by SGLT-2 inhibitor treatment:

- SAT showed a marked increase in ketone bodies and a corresponding decrease of ketogenic triacylglycerols with medium-chain fatty acids; this is suggestive of the enhanced ketogenesis typically associated with SGLT-2 inhibitor use.
- EAT showed an increased amount of long-chain triacylglycerols, suggesting a

cardioprotective function of SGLT-2 inhibition through preservation of EAT lipid content.
- Both SAT and EAT had high levels of sphingolipids, especially sphingomyelins and ceramides, and ether-linked lipid species. The exact role of increased sphingolipids remains to be elucidated.

win FACT Type 1 diabetes - The future is personalised choice and new technologies

Richard Bergenstal (United States) expressed the view that this is an exciting time for type 1 diabetes mellitus (T1DM) patients and their clinicians. "There are so many innovative devices and technologies emerging that it is proving difficult for healthcare providers to keep up with all the new continuous glucose monitoring (CGM) devices and related automated insulin delivery systems."

It was stressed that while CGM is the greatest advance in T1DM since insulin, the provision of simple interpretative data to the clinician's rooms is needed so that the results can be available on the patient's records as easily as other laboratory results are.

Dr Bergenstal noted: "CMG's provision of time-in-range for the patient is 'the space that I am safe in'; for the clinician, it provides better, more informative data than an $HbA_{1c.}$ reading." Jeremy Pettus (United States) pointed out that he likes to start with CGM and move as quickly as he can to a hybrid closed-loop insulin delivery system for his patients.

"CMG's provision of time-in-range for the patient is 'the space that I am safe in'; for the clinician, it provides better, more informative data than an HbA_{1c} reading" - Dr Bergenstal

The future of T1DM care – immunotherapy

Immunotherapy technology has the potential to shift the paradigm of T1DM management into the future (Table 3).[8] "While much of this therapy is still investigational, the promise of slowing progression in T1DM is beginning to emerge," Dr Pettus noted.

Table 3. Advances beyond immunotherapy may have the potential to shift the paradigm of T1DM management in the future

β-cell preservation	β-cell replacement	β-cell regeneration
• Phase 2 trial indicated anti-CD3 monoclonal antibody, **teplizumab**, initiated in stage 2 T1DM*, was shown to delay progression to clinical T1DM • Efforts to conduct population screening for genetic susceptibility at birth and **attempt primary prevention** before antibody appearance	• Whole pancreas or isolated islet transplantation • Potential use of pluripotent stem cells to provide cells for transplantation • Need for protection against **alloimmune rejection** and, potentially, against **autoimmune recurrence**	• A potential way to improve function and **potentially reverse T1DM** • Approaches to regeneration have been used in animal models, human studies have not yet been successful

All approaches are investigational.
*Defined as those with both autoantibodies and dysglycaemia as evidence of decline

Adjunct therapies in T1DM

For patients with T1DM, current therapies address insulin deficiency but do not target other aspects of metabolic dysfunction such as insulin resistance and hyperglucagonaemia. Considering that <30% of people with T1DM achieve adequate glycaemic control, many are not satisfied with their current treatment options and are willing to consider other therapies in addition to insulin, despite off-label status, and place pressure on their clinicians to prescribe adjunct therapies. Current evidence for GLP-1 RAs and SGLT-2 inhibitors as adjunct therapies in T1DM were discussed, as were the advantages of a combination therapy approach.

GLP-1 RAs as adjunct therapy in T1DM

The use of GLP-1 RAs with insulin in the patient with T1DM remains off-label. Jerry Greenfield (Australia) summarised the evidence base suggesting that there is a cardiovascular benefit when GLP-1 RAs are used with insulin for the patient with T1DM.

Data from the MAG1C trial of exenatide in T1DM demonstrated that even though there was no significant difference in glycaemic control compared with placebo at 26 weeks, there was a 4.4kg weight loss in the exenatide arm and daily insulin use was decreased by 9U.[9] At 26 weeks, liraglutide added to insulin therapy reduced HbA_{1c} levels, total insulin dose and body weight in ADJUNCT ONE and TWO; dose-dependent increases in symptomatic hypoglycaemia and hyperglycaemia with ketosis were observed.[10,11]

There was a clear and early separation of weight curves between the treatment and placebo arms in the MAG1C and ADJUNCT studies; weight loss was driven entirely by decreased fat mass and decreased visceral adiposity was observed. The real-world STEMT1 trial is ongoing, investigating the effect of once-weekly semaglutide on weight loss and metabolic control in people with T1DM.

The benefits of GLP-1 RAs on glycaemia, weight and total daily insulin dose may justify their use in select T1DM patients, although these benefits remain to be proven in randomised placebo-controlled CVOTs. It is recommended that clinicians measure stimulated C-peptide prior to initiating GLP-1 RA therapy in T1DM in order to predict glycaemic response and the risk of diabetic ketoacidosis (DKA).

SGLT-2 inhibitors as adjunct therapy in T1DM

Parth Narendran (United Kingdom) observed that although SGLT-2 inhibitor therapy remains unlicensed for use in T1DM, there is evidence of improved glucose control over and above currently available approaches to glucose sensing and insulin delivery. SGLT-2 inhibitor trials in T1DM are summarised in Table 4.

Investigation of SGLT-2 inhibitor therapy in T1DM patients using closed-loop therapy has demonstrated a tightening of glucose range.[12] Post hoc analysis of the InTandem trials of sotagliflozin in T1DM demonstrated a 7% reduction in estimated cardiovascular risk between baseline and 24 weeks, and post hoc analysis of the DEPICT trials demonstrates an improved albumin:creatinine ratio, suggesting that the renal benefits of dapagliflozin observed with T2DM may also apply to T1DM.

AstraZeneca, in light of the known risk of DKA, withdrew dapagliflozin after it had been licenced for use in T1DM although real-world evidence of ~13 000 T1DM patients currently using dapagliflozin does not signal an increased risk of DKA.[13]

Table 4. Key outcomes of SGLT-2 inhibitor trials in T1DM

	DEPICT Dapagliflozin	InTandem Sotagliflozin	EASE Empagliflozin
HbA_{1c} reduction *An HbA_{1c} reduction of 0.5% is considered clinically meaningful in terms of cardiovascular outcomes*	0.4-0.5%	0.5%	0.2-0.5%
Daily insulin reduction	10%	9%	9%
Body weight reduction	3kg	3kg	3kg
Systolic BP reduction	3-6mmHg	3-5mmHg	2-3mmHg
Symptomatic hypoglycaemia	Not significant	Not significant	Not significant
Genitourinary infection	4x	5x	3-4x
DKA	Not significant	3x	3-4x

Combination therapy in T1DM

The rationale for using SGLT-2 inhibitors and GLP-1 RAs as combined therapy together with insulin in T1DM arises from the synergistic effects of their different mechanisms of action to improve glycaemic control and it is possible that this combined therapy may reduce ketogenesis as glucagon levels are stabilised. Other potential benefits of combination (triple) therapy include a further reduced dependency on insulin and therefore a reduced risk of hypoglycaemia, further weight and BP reductions to improve cardiometabolic outcomes, a cardiorenal protective effect and an improved overall quality of life. Outcomes of the ongoing TTT-1 study of insulin plus semaglutide plus dapagliflozin in T1DM are eagerly awaited.

win FACT **CVD mechanisms in T2DM – Something new?**

Biomarkers of cardiovascular events and mortality in newly diagnosed T2DM

The relationship between C-reactive protein (CRP), low-grade inflammation and increased risk of cardiovascular events and mortality has been demonstrated in the general population and it has also been related to an increased risk of MACE in diabetes patients with previous myocardial infarction (MI) or multivessel coronary diseases; however, it is not related to all-cause mortality in these patients.

A study was undertaken in Denmark to assess the relationship between CRP and the risk of cardiovascular events and all-cause mortality in individuals with recent-onset T2DM and without a history of cardiovascular events. It was shown that high C-peptide, as a proxy of insulin resistance, is a better marker of increased cardiovascular risk while high CRP is a better predictor of all-cause mortality than future cardiovascular disease. This emphasises that it is important to target insulin resistance and high C-peptide levels in newly diagnosed diabetes patients in order to reduce the risk of cardiovascular events.

It is important to target insulin resistance and high C-peptide levels in newly diagnosed diabetes patients in order to reduce the risk of cardiovascular events

Exploring the mechanisms of SGLT-2 inhibitor effects on HF

An interesting small but innovative ***in vitro*** study of empagliflozin-treated patients looked at potential mechanisms of HF reduction: plasma biomarkers of HF progression, parameters of cardiac remodelling – using echocardiography; left ventricular end-diastolic diameter (LVEDD), collagen accumulation in septum diameter and posterior wall diameter - and effects on downstream mediators of inflammation.

Presented by Asmae Elrakaybi (Germany), these unpublished new data showed that empagliflozin did not alter HF progression biomarkers. However, in patients with high EF, empagliflozin significantly reduced KIM-1 (a biomarker of renal tubular injury), improved cardiac remodelling parameters (reduced posterior wall diameter, and LVEDD at lower EF levels) regardless of EF, but did not affect inflammatory protein expression.

This study provides data to support the concept that SGLT-2 inhibitors attenuate adverse cardiac remodelling and preserve renal tubular integrity. No evidence of anti-inflammatory effects was observed.

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GLP-1 RA beneficial effects on MACE reduction across T2DM patients with a spectrum of kidney function and damage

A post hoc analysis of patients treated within the semaglutide trials, SUSTAIN 6 and PIONEER 6, affirmed that the risk of MACE was greater for participants with impaired kidney function than for those with normal kidney function and that this GLP-1 RA showed consistent reductions in the risk of MACE across all estimated glomerular filtration rates (eGFR <45ml/min/1.73m^2 to ≥60 ml/min/1.73m^2) and urine albumin-creatinine ratio (UACR <30 to >300) subgroups.

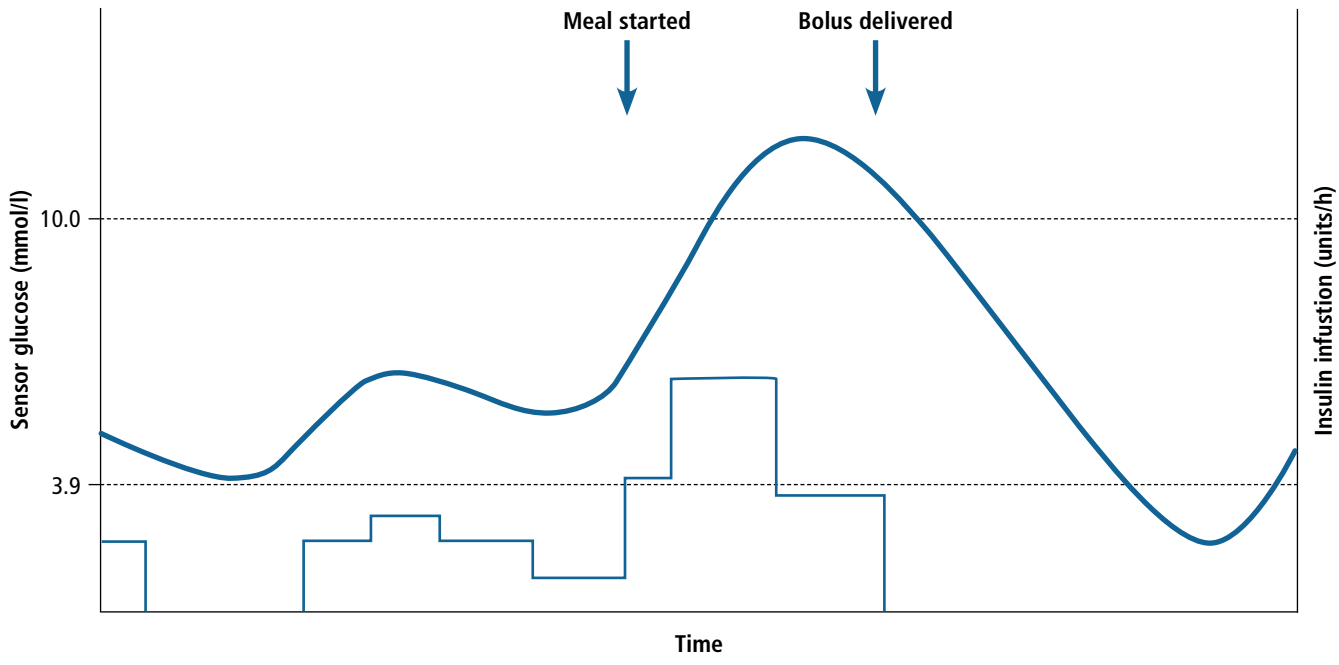
These data affirm the value of GLP-1 RAs in providing cardiovascular benefits in high-risk T2DM patients across a broad spectrum of kidney function and damage.

win FACT **Insulin therapy – Simple, simpler, safest**

Even with advanced glucose-control technologies, mistimed insulin boluses are common

Giovanni Annuzzi (Italy) presented a two-week CGM evaluation of the impact of delayed prandial boluses on glucose control in patients using advanced technologies. Delayed insulin boluses were very common, one out of five meals, and contributed to worsening blood glucose control (Figure 8).[14] Fear of hypoglycaemia was positively associated with the number of delayed boluses and this aspect should not be neglected by healthcare professionals who may focus primarily on carbohydrate-counting (or miscounting) as the main cause of high postprandial glucose levels.

Figure 8. Impact of post-meal bolusing on sensor glucose concentration during hybrid closed-loop insulin delivery



The thick blue line represents sensor glucose. The thin black line represents algorithm-driven insulin delivery. Horizontal dashed lines reflect target glucose range.

Starting NPH dose at night? Some useful evidence

Several guidelines recommend a starting basal insulin dose of up to 0.2U/kg body weight, although the current SEMDSA guidelines advise starting basal insulin at a dose of 10U at night. Bernado Mertes (Germany) provoked a great deal of discussion of his study of 1 006 patients put on basal insulin after oral treatment failure. Patients were on metformin mainly and using a total of 1.2 oral agents, a quite homogenous group compared to a more heterogeneous group treated with new oral agents.

Glucose levels were monitored and all patients receiving ≥12U were asked to measure levels at 22h00, 02h00 and 07h00 for two consecutive nights. If nocturnal blood sugar levels dropped, the insulin dose was reduced. The average NPH dosing after correction in 7% of patients was 9.8±2.7U, corresponding to 0.11±0.03U/kg body weight. No symptomatic or severe hypoglycaemia occurred with this effective bedtime dose of NPH 0.11U/kg, which was sufficient to maintain control for three years.

InRange RCT of two second-generation basal insulins (glargine 300U/ml vs degludec 100U/ml) in T1DM

The primary objective of this trial was to demonstrate noninferiority of GLA-300 to IDeg-100 with regard to glycaemic control as measured by time-in-range (TIR) and variability using blinded CGM in adult T1DM patients. These results were presented at the annual ADA conference three months before (doi.10.2337/db22-105-LB).

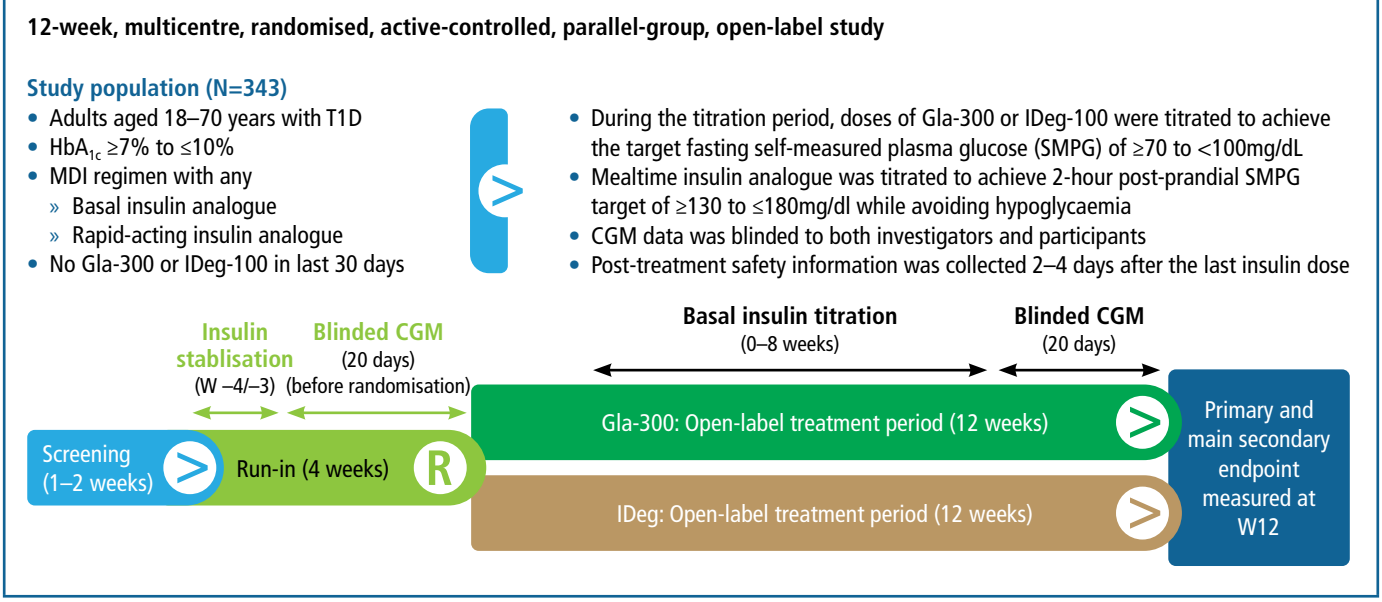
The study design is summarised in Figure 9. The participants and healthcare providers were not blinded as to which insulin the patient was receiving. A blinded 20-day CGM was performed at the start and end of the study. The primary endpoint was %TIR ≥70 and blood glucose <10mmol/l, with secondary efficacy endpoints (HbA_{1c} and time-above-range at study end) and safety endpoints.

The baseline characteristics were comparable; there was no difference between the primary endpoint and secondary endpoint of glucose variability (glucose total coefficient of variation) at the end of the study. "Clinicians now clearly have a choice of two efficient second-generation basal insulins," Tadej Battelino (Slovenia) noted.

Importantly, when using CGM-derived anytime hypoglycaemia measures, there were no differences between the two insulins but the CGM data provided rates three- to five-fold higher than self-monitored plasma glucose rates. Regulatory agencies should look more closely at using this standard in future. There were no additional safety concerns with either basal insulin beyond those already known.

It was noted that the titration phase during which insulin glargine was shown to cause less hypoglycaemia was not included in this evaluation; the investigators regarded it as 'a dynamic phase' and thought it was therefore fair that it be excluded.

Figure 9. InRange study design



win FACT

Use TIR to open the conversation about patient issues

In a practical networking session, Tadej Battelino (Slovenia) and Samuel Seidy (United Kingdom) discussed the barriers to fuller use of CGM and the associated parameter, TIR. Assessing the EASD audience's view of the use of CGM in T2DM patients on insulin therapy, 30% of attendees felt that the use of CGM is 'too complex for people with T2DM'.

Professor Battelino contested this view, noting that CGM is really easy to read and understand with its 'safe' green and red 'danger' colour-coding. The most valuable aspect of TIR, however, is its use as a conversational tool and introduction to discussions on what really matters to a particular patient (What bothers him/her the most? What can he/she do with the clinician to help) and not as a past record of failure. "While the target may be to be in-range for 70% of the time in T1DM patients, this may be too high for a T2DM patient," Professor Seidy noted.

It was pointed out that the glucose management indicator (GMI) derived from CGM data correlates quite well with an average HbA_{1c} and can be used in an immediate clinical discussion, with no need to wait for an HbA_{1c} reading. The discussion concluded with clinicians being encouraged to use TIR as a communication tool with patients and as an opening to conversations, rather than as a barrier.

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The Soli Simplify study of switching from multiple insulin injections to a fixed combination of degludec and liraglutide in T2DM

This real-world study presented by Martinka Emil (Slovakia) showed that switching from basal-bolus to IGlarLixi (to Soliqua) was effective, safe and a less demanding treatment for the T2DM patient; furthermore, it led to improvement in all glucose control measures and reduction of body weight, BP and lipid profiles.

win FACT Precision medicine in diabetes

Biomedicine is generating large amounts of data that can be of benefit to researchers, clinicians and patients. Using machine-learning to gain insights from biomedical data requires attention to the type and scale of the data, the purpose of the data and whom the data is intended to support. Different aspects of precision medicine in T2DM were considered by Paul Franks (Sweden), Robert Wagner (Denmark) and Phong Nguyen (Denmark).

Precision medicine can be viewed as part of the evolution of medicine, rather than a revolution of medicine. Precision medicine seeks to reduce error in health recommendations and medical decision-making; this involves intelligent analysis of data to refine the characterisation of disease and optimise its prediction, prevention, diagnosis, treatment or prognosis. Precision medicine should be safer and more efficacious, accessible, equitable and economically viable than contemporary medicine. A consensus report from the ADA and EASD on precision medicine in diabetes has been published.[15]

Because preventive interventions such as promotion of a healthy diet, physical activity and weight loss are non-specific, these interventions are assumed to be equally beneficial for all individuals at high risk of disease. However, data from the PREDICT and LookAHEAD trials showed that intensive lifestyle intervention, with or without metformin, was not effective for all patients with T2DM, underscoring the need for interventions individualised to the specific patient. A machine-learning approach compared the clinical effects of a personalised postprandial-targeting (PPT) diet versus a Mediterranean (MED) diet in prediabetes and found that a PPT diet improved glycaemic control significantly more than a MED diet.[16]

Other applications of precision medicine include polygenic risk scores, which explain ~8% of phenotypic variants and have some value in identifying high-risk individuals from birth. Studies of T2DM genetic loci reflect clustering archetypes of different patterns of dysfunction across aetiological processes,[17] although the majority of data are currently based on people of European descent. An evaluation of genetic risk scores derived from data on African American individuals has been found to enhance polygenic prediction of lipid traits in sub-Saharan Africa as

compared to European and multiancestry scores, although prediction varied greatly between South African Zulu and Ugandan cohorts. Differences in genetic and environmental factors between these population groups might lead to the poor transferability of genetic risk scores within sub-Saharan Africa.[18]

win FACT South Africans build a community for diabetic amputees

Salih Hendricks (South Africa) shared his story of the 'phenomenal power of peer support' that emerged when he created a social media community for diabetic amputees during the COVID-19 lockdown. The comforting realisation that he was not alone in his daily challenges and the support he derived from this amputee community led him to wonder about how diabetic amputees without access to technology or who are illiterate were coping, and if there was any community support available to them.

He has since established a Diabetic Amputee Peer Advocacy group that utilises 'smoke-signal' media, whereby advocates go into different communities armed with information pamphlets and print-outs, with the aim of educating the community and sharing the challenges and experiences faced by diabetic amputees on a day-to-day basis. Further to this, he feels that peer support collaboration within the multidisciplinary healthcare team is an effective approach to the overall management of the diabetic amputee.

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