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GLP-1 Summit – Key learnings about the added benefits of GLP-1 in diabetes

Professor Rayaz Malik
Professor of Medicine
Weill Cornell Medicine
Qatar

Dr Ahmed Riaz Motara
Cardiologist
The Heart Wellness Centre
Johannesburg

Dr Sundeep Ruder
Clinical Endocrinologist
Life Fourways Hospital
Johannesburg

Introduction

Type 2 diabetes mellitus (T2DM) is the leading cause of blindness, end-stage renal disease and non-traumatic lower extremity amputations in working-age adults. Risk of stroke is increased 1.2- to 1.8-fold compared to the general population and most importantly, 75% of diabetes patients die from cardiovascular events.[1] In fact, compared with the general population, patients with T2DM have twice the risk of cardiovascular disease (CVD). Approximately one-third of those with T2DM have CVD, which often occurs even in the years before diagnosis.[2] Not only does T2DM share common risk factors with CVD, but direct effects of hyperglycaemia also contribute to vascular damage - arterial stiffness, endothelial dysfunction, oxidative stress, platelet activation, inflammation, metabolic syndrome and metabolic dysfunction.[1]

Early incretin research described the antidiabetogenic properties of glucagon-like peptide-1 (GLP-1) with its major physiological effects on the brain as a satiety hormone; on the stomach, where it reduces gastric motility, thereby delaying gastric emptying; and on the pancreas, where insulin secretion is augmented and glucagon secretion is lowered. Further research shows that beyond reduction of hyperglycaemia in the T2DM patient, evidence of the cardioprotective role of GLP-1 receptor agonists (GLP-1 RAs) is accumulating.

LEARNING OBJECTIVES

You will learn:

- How GLP-1 RAs as used for glycaemic control in T2DM work
- The latest data on the cardioprotective effects of GLP-1 RAs
- The importance of weight management in both T2DM and cardiovascular risk
- To interpret updated guidelines in response to recent cardiovascular outcomes trials (CVOTs), in your management of T2DM patients at high or very high cardiovascular risk.

What is the mechanism of action of different GLP-1 RAs?

Impairment of GLP-1 action has physiological effects on other tissues and organs, as revealed by loss of function studies (Figure 1, Table 1).[3]

Even though the different GLP-1 RAs all target the same receptor, the structural variations between the individual compounds have important implications for mode of action. The key mechanism of action of the short-acting compounds, lixisenatide and exenatide, with a half-life of approximately 3.5 hours, is a delay in gastric emptying. A subsequent delay in intestinal glucose absorption results in lowered postprandial insulin secretion. These agents have little effect on fasting glucose or glucose concentrations between meals.

The long-acting GLP-1 RAs permanently activate the GLP-1 receptors for a full 24 hours; longer in the case of once-weekly semaglutide.

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Long-acting GLP-1 RAs also have structural differences: dulaglutide and albiglutide (discontinued) have very large molecules coupled to the GLP-1, exenatide-LAR (long-acting release) contains microspheres, and liraglutide and oral semaglutide have a fatty acid side chain. The predominant effects of long-acting GLP-1 RAs are on fasting glucose levels, mediated through insulinotropic and glucagonostatic actions. They do not inhibit gastric emptying.[4]

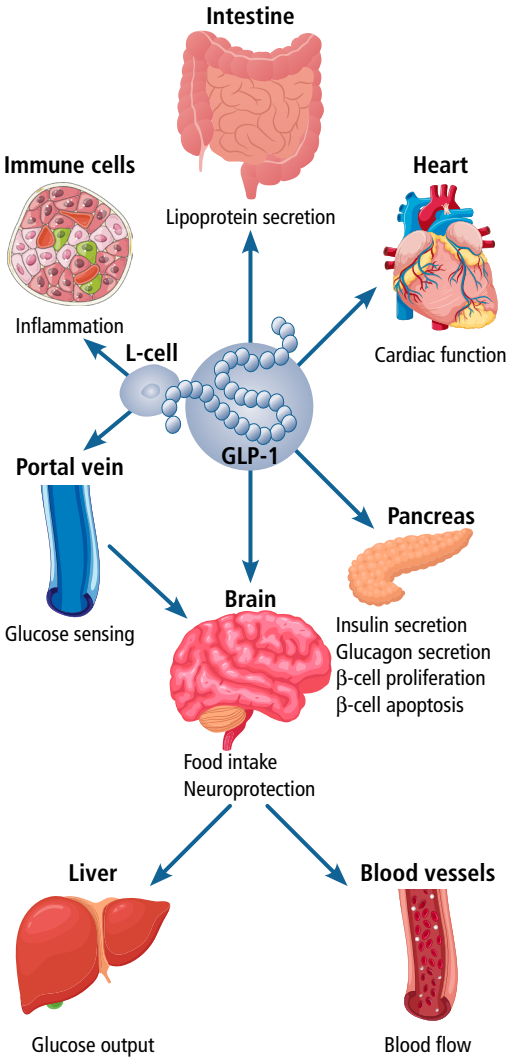

Figure 1. The effects of GLP-1 on organs and tissues[3]

Table 1. The physiological actions of endogenous GLP-1[3]

Physiology	Impairment of GLP-1 action
Fasting glucose	Increased
Glucose-dependent insulin secretion	Decreased
Glucagon secretion	Increased
β-cell signal transduction	Abnormal
β-cell apoptosis	Increased
β-cell proliferation	Decreased
Islet size	Decreased
Food intake	Increased
Energy expenditure	Increased
Locomotion	Increased
Body weight	Increased
Portal glucose sensing	Decreased
Postprandial lipid metabolism	Decreased
CNS control of blood flow	Decreased
Cardiovascular function	Decreased
CNS stress response	Increased
Susceptibility to neural injury	Increased
Immune system	Decreased
Gastric emptying	Normal
Susceptibility to pancreatitis	Normal

The cardiovascular benefits of GLP-1 RA therapy

GLP-1 RAs reduce cardiovascular events through multiple mechanisms, the combination of which probably explains the cardioprotective effects of GLP-1 RA therapy.

Key GLP-1 RA cardiovascular outcomes trials (CVOTs)

The LEADER study of T2DM patients with high cardiovascular risk had time-to-event of death from cardiovascular causes, non-fatal myocardial infarction (MI) or non-fatal stroke as a primary endpoint.[5] Compared to placebo, a 22% reduction in cardiovascular mortality was observed in the liraglutide arm.

Similarly, clear evidence of cardiovascular protection comes from the SUSTAIN-6 trial using once weekly semaglutide compared to placebo, showing a 26% reduction in the combined cardiovascular endpoints. This was driven primarily by a reduction of 26% in non-fatal MI and an almost 40% reduction in

non-fatal stroke events. There was no statistical significance in respect to cardiovascular death, possibly due to the short two-year duration of this study.[6]

Meta-analysis of seven completed and published CVOTs[7] show great heterogeneity among GLP-1 RAs with regard to MACE. Data from a combined total of 56 004 participants come from the ELIXA (lixisenatide), LEADER, SUSTAIN-6, EXSCEL (exenatide-LAR), Harmony Outcomes (albiglutide), REWIND (dulaglutide) and PIONEER-6 (oral semaglutide) trials. There was an overall 12% reduction in MACE with the GLP-1 analogues, with a risk reduction of 12% for cardiovascular death, 9% for MI and 16% for stroke. ELIXA and EXSCEL missed the endpoints of cardiovascular death, fatal or non-fatal MI, and fatal or non-fatal stroke.

What are the effects of GLP-1 RAs on cardiovascular risk factors?

Randomised controlled trial (RCT) data associate GLP-1 RAs with reductions in HbA_{1c} (0.8-1.5%), body weight (3-4kg), systolic blood pressure (2.0-8.0mmHg) and modest but consistent reductions in LDL cholesterol. GLP-1 RAs also lower postprandial triglycerides.[4,8]

Further evidence of the beneficial effects of GLP-1 RAs on cardiovascular risk factors was seen in various real-world studies with liraglutide showing a reduction in both HbA_{1c} (0.8-1.5%) and body weight (2.5-5.5kg), consistent with the outcomes of liraglutide RCTs. Real-world data on oral semaglutide show that after 3-12 months of treatment, HbA_{1c} was reduced by 1.3% across all T2DM patients, 2.0% in GLP-1 RA-naïve patients and 2.9% in GLP-1 RA-naïve patients with baseline HbA_{1c} >9%. Of the high-risk group of patients, 30-40% attained HbA_{1c} <7%.[9]

Tight glycaemic control is crucial to the prognosis of cardiovascular mortality in patients with T2DM, particularly those of a young age.[10] Long-acting GLP-1 RAs reduce HbA_{1c} and body weight more effectively than insulin[11] and are associated with a reduced risk of hypoglycaemia compared to insulin.[12]

GLP-1 has acute effects on vascular function, notably a significant improvement in endothelial function, and is associated with a reduction in markers of inflammation and oxidative stress

What are the effects of GLP-1 RAs on blood vessels?

GLP-1 has acute effects on vascular function, notably a significant improvement in endothelial function, and is associated with a reduction in markers of inflammation and oxidative stress.[13] A significant reduction in intima media thickness of the carotid artery, suggesting improvement in atherosclerosis, has been observed after 18 months of liraglutide treatment in T2DM patients.[14] Indicators of plaque stability have also been shown to improve with incretin therapy.[15]

Data from the LEADER study[16] show that in 10 000 T2DM patients, treatment with liraglutide was associated with a 35% lower risk of diabetic ulcer-associated amputations compared with placebo, consistent with an improvement in peripheral arterial disease and a general reduction in atherosclerosis.

What are the other potential cardioprotective effects of GLP-1 RAs?

Peripheral inflammation is recognised as an independent risk factor for atherosclerosis, with anti-inflammatory drugs such as canakinumab being associated with a reduction in cardiovascular events. In the context of peripheral inflammation as a therapeutic target for cardiovascular protection, GLP-1 reduces levels of inflammatory cytokines such as TNF-α, IL-6 and IL-1β, increases adiponectin and reduces markers of macrophage activation.[17]

It has also been demonstrated that GLP-1 has a modest diuretic and natriuretic effect; although not as pronounced as with SGLT-2 inhibitors, it is still significant. Liraglutide has demonstrated an increase in urinary sodium excretion.[18]

Inhibition of platelet function and the prevention of thrombus formation by GLP-1 RAs represent potential mechanisms for reduced atherothrombotic events, potentially contributing to a reduction in MI and stroke events.[19]

Current evidence - GLP-1 RA adverse events

The gastrointestinal side effects of nausea (20-25%), vomiting (8-9%) and diarrhoea (10-15%) are common at initiation with GLP-1 analogues but are typically transient in nature. The incidence of nausea is higher with the short-acting GLP-1 RAs.[20]

Meta-analysis of acute pancreatitis in phase III trials and CVOTs shows a lower absolute number of events with GLP-1 analogues than with placebo[21] and although there are anecdotal reports of pancreatitis with GLP-1 RAs, there is no evidence of an increased incidence from clinical trials and real-world registries.

The LEADER and SUSTAIN-6 trials show a small increase in the number of retinopathy events, with statistical significance for semaglutide but not for liraglutide. The mechanism behind this is not known, but it is thought that the early significant reduction of HbA_{1c} by oral semaglutide may contribute to worsening of pre-existing diabetic retinopathy. There was no evidence of oral semaglutide inducing retinopathy in those not previously affected by the condition.[5,6]

Defining the problem of weight in T2DM

The complications of obesity

There are numerous medical complications of obesity that overlap with those of diabetic patients (Figure 2). Obesity is a risk factor for T2DM and 85-90% of T2DM patients are overweight or obese. Some studies suggest that waist circumference, waist-to-hip ratio or direct measures of visceral adiposity are associated with risk for T2DM as well as certain cancers (e.g. colon), independently of body mass index (BMI).[22]

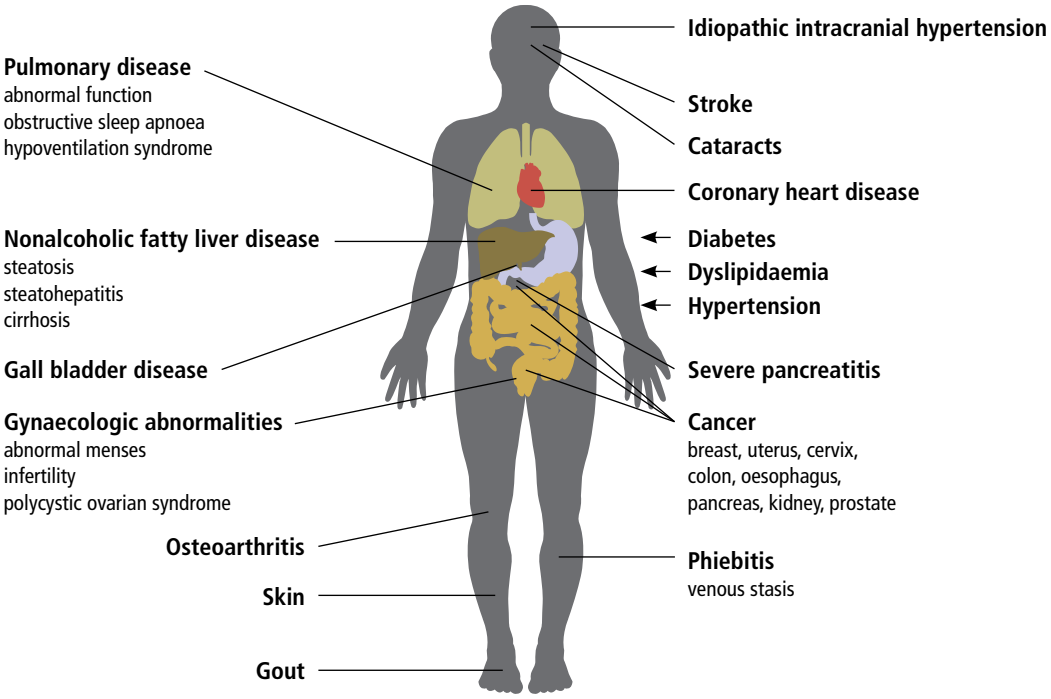

Figure 2. Medical complications associated with obesity

Weight gain is problematic in T2DM as it can be a barrier to intensifying treatment. Approximately 50% of patients are very anxious about their weight and fear of the cosmetic effects of weight gain may outweigh their fear of long-term complications. Further negative psychosocial and behavioural variables are also associated with weight gain (Table 2).

Weight gain increases the cardiovascular risk factors of hyperlipidaemia and hypertension. A five-unit increment in BMI can increase coronary heart disease mortality by 30%, and is associated with increased risk of stroke (11%), CVD (13%) and total mortality (27%).[23,24]

Table 2. Psychosocial and behavioural variables associated with weight change

Domains	Variable	Description	Weight gain	Weight loss
Cognitive	Dichotomous thinking	The tendency to think in terms of polar opposites, such as "good or bad" or "black or white"	✓	
	Conscientiousness	The degree that a person controls, regulates, and directs impulses		✓
	Vigilance	Devoted attentiveness or watchfulness		✓
Psychological	Dissatisfaction with weight achieved	Concern about weight or shape	✓	
	Adverse childhood experiences	All types of abuse, negelect, and other potentially traumatic experiences that occur to people under the age of 18	✓	
	Self-efficacy	An individual's belief in his or her capacity to execute behaviours necessary to produce specific performance attainments		✓
	Self-regulation	Controlling one's behaviour, emotions, and thoughts in the pursuit of long-term goals		✓
Personality	Novelty seeking	Personality trait associated with impulsive decision-making, extravagance in approach to reward cues, quick loss of temper, and avoidance of frustration	✓	
	Lower persistence	Ability to follow a course of action in spite of difficulty or opposition	✓	
	Lower self-directiveness	Ability to regulate and adapt behaviour to the demands of a situation in order to achieve personally chosen goals and values	✓	
Behavioural	Adherence	Sticking to a course of action		✓
	Self-monitoring	Observing and evaluating one's behaviour		✓
	Dietary restraint	Limiting the overall amount of food eaten, what foods are eaten, or both	✓	

Strategies that lead to weight loss, including use of diabetes medications associated with weight loss, may improve medication adherence

Dr Ruder considers the following to be important in the assessment of weight:

- One-third of patients have normal BMI with high body fat, usually due to sarcopenia
- Remember that there are ethnic differences in waist circumference markers
- Visceral fat distribution has been shown to elevate the risk of atherosclerosis and mortality, independently of BMI and waist circumference. DEXA scanning may be useful but is not used routinely
- The SARC-F questionnaire and hand grip tests for middle-aged and elderly patients are useful tools for measuring sarcopenia.

What are the benefits of weight loss in T2DM?

Data from the Finnish Diabetes Prevention Study on those with pre-diabetes showed that an intensive dietary and exercise programme decreased the overall risk of diabetes by 58%. Similar results were obtained in the Diabetes Prevention Program, where moderate weight loss through lifestyle intervention reduced the incidence of diabetes by 58%, while metformin alone reduced it only by 31%. A weight loss of 1kg in the first year was associated with 3-4 months of prolonged survival, whereas a 10kg weight loss was associated with a restoration and increase in life expectancy of 35%.[25]

Benefits of weight loss in established diabetes were indicated by the American Cancer Society Cancer Prevention Study I,

where weight loss >10kg reduced cancer mortality by 25%. The Look AHEAD study indicated that a 5-10% weight loss is associated with improved overall fitness, reduced HbA_{1c}, improved cardiovascular risk factors, reduced number of medications used, reduced number of depression symptoms and reduced severity or remission of obstructive sleep apnoea.[25]

Conclusions from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD)[26] were that T2DM respondents with weight loss had significantly better medication adherence and were less likely to be on treatment regimens that increase weight than T2DM respondents with weight gain. These findings suggest that strategies that lead to weight loss, including use of diabetes medications associated with weight loss, may improve medication adherence.

SEMDSA 2017[27] recommendations for achieving and maintaining weight loss goals are listed in Table 3. Dietary therapy and calorie reduction (low-fat, low-carbohydrate diet, Mediterranean diet, very-low-carbohydrate diet) are integral to other individualised considerations such as which form of exercise and behavioural therapy is appropriate for the patient.

Table 3. T2DM and weight - SEMDSA 2017 recommendations[27]

The BMI and and waist circumference of all patients with T2DM must be recorded at every visit	C
Modest weight loss (5-10%) in overweight and obese individuals improves glycaemic control and cardiovascular risk factors	A
For obese or overweight patients with T2DM who are willing, an intensive lifestyle intervention focusing on diet, physical activity, and behavioural therapy should be available to support >5% weight loss over 6 months. Successful programmes require high frequency contact (weekly for 6 months and at least monthly thereafter for those who achieve their goals). Behavioural therapy can/should be offered in groups	A
The primary focus of the dietary intervention for weight loss should be on caloric restriction (aim for >500 to 750kcal deficit/day) irrespective of macronutrient composition, which is less important	A
Very low calorie diets must not be prescribed in the primary health care setting	C
For achieving and maintaining weight loss goals, encourage individuals to engage in at least 4 hours of moderate intensity exercise (e.g. brisk walking, dancing, gardening) per week	
Orlistat is the only weight-loss medication approved in South Africa and can be used as an adjunct to intensive lifestyle interventions in selected patients (BMI ≥27kg/m^2) with diabetes or BMI ≥30kg/m^2 with IGT	A
When choosing medications for the management of diabetes and comorbid conditions, always consider the potential effects on weight in obese patients. If weight gain from other glucose therapies is problematic consider switching to drugs with a neutral or beneficial effect on weight (metformin, DPP-4 inhibitors, alpha-glucosidase inhibitors, GLP-1 agonists and SGLT-2 inhibitors)	C
Batriatric surgery is a treatment option for obesity and diabetes in patients whose BMI ≥35kg/m^2 and in selected patients with a BMI ≥30kg/m^2 when glucose levels are not controlled despite the best efforts with medications and lifestyle modification	B

Professor Malik believes that current evidence firmly challenges previously held beliefs that metformin should be first-line therapy for all T2DM patients

Is there a role for GLP-1 RAs in weight management?

GLP-1 RAs are associated with lower body weight, as well as less visceral adipose tissue, subcutaneous adipose tissue and a smaller waist circumference.[28]

Which clinical guidelines are appropriate for *this* patient?

In response to recent CVOTs in the diabetes field, national and international guidelines reflect a move towards a more individualised approach to managing cardiovascular risk in the T2DM patient.

The current 2018 ADA/EASD consensus and 2019 update[29] categorises T2DM patients as those with or without CVD. For patients at very high cardiovascular risk, the ADA/EASD recommend second-line GLP-1 RAs or SGLT-2 inhibitors after metformin, which remains first line for all T2DM patients:

- If an atherosclerotic condition

predominates, GLP-1 RAs are the recommended treatment
- If heart failure predominates, or if there is an eGFR 30-60ml/min with proteinuria, an SGLT-2 inhibitor is preferred.

Professor Malik believes that current evidence firmly challenges previously held beliefs that metformin should be first-line therapy for all T2DM patients, with meta-analysis of all-cause mortality showing that intensive glucose-lowering (ACCORD trial HbA_{1c} 6.4%) with metformin, sulphonylureas, thiazide diuretics or insulin causes more harm, or no benefit for all-cause mortality.[30]

The European Society of Cardiology (ESC) has categorised cardiovascular risk in T2DM patients as moderate, high or very high. Metformin, together with lifestyle intervention, remains a recommended first-line glucose-lowering medication for T2DM based on efficacy, safety, tolerability, extensive clinical experience and low cost. Whereas 2013 ESC guidelines recommended metformin as first-line therapy in patients with diabetes, the 2019 recommendations specify that metformin be considered in overweight patients with T2DM without CVD and at moderate cardiovascular risk.[31]

Professor Malik is supportive of key new additions to the 2019 ESC guidelines, which include recommendations for GLP-1 RA or SGLT-2 inhibitor treatment as first-line therapy, before metformin in patients with T2DM and CVD, or those at very high/high risk of CVD, as outlined in Table 4.[31]

Diabetes is no longer about treating the HbA_{1c}; a multifactorial approach is needed. Look at the newer classes of drugs and their effects on cardiovascular benefit and then individualise the therapy

Table 4. 2019 ESC recommendations for glucose-lowering treatment of T2DM patients with CVD, or at very high/high cardiovascular risk[31]

Empagliflozin, canagliflozin or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high cardiovascular risk, to reduce cardiovascular events
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death
Liraglutide, semaglutide or dulaglutide are recommended in patients with T2DM and CVD, or very high/high cardiovascular risk, to reduce cardiovascular events
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high cardiovascular risk, to reduce the risk of death
Saxagliptin is not recommended in patients with T2DM and a high risk of heart failure

Dr Motara emphasises that at the practical primary care level, lifestyle modification and psychosocial support are fundamental to managing T2DM patients, as well as individualising the overall therapeutic approach. Age at diagnosis, duration of diabetes and extent of blood sugar control are crucial to quantifying cardiovascular risk and selecting appropriate therapy. He recommends that treatment should cover as many pathophysiological risk factors as possible, with anti-inflammatory treatment now a standard approach in the management of T2DM. He considers blood pressure control to be one of the most important interventions in T2DM for lowering risk of ischaemic heart disease and stroke.

"Diabetes is no longer about treating the HbA_{1c}; a multifactorial approach is needed. Look at the newer classes of drugs and their effects on cardiovascular benefit and then individualise the therapy," he concluded.

KEY LEARNINGS

- GLP-1 RAs reduce cardiovascular events through a combination of mechanisms
- GLP-1 RAs are associated with a reduction in cardiovascular death, fatal and non-fatal MI, and fatal and non-fatal stroke
- GLP-1 analogues are associated with reductions in HbA_{1c}, body weight, systolic blood pressure and postprandial triglycerides
- Other cardioprotective effects of GLP-1 RAs are seen in the heart, blood vessels and kidneys
- Obesity is a risk factor for T2DM and CVD, as well as many other medical complaints and complications
- The ADA/EASD and the ESC have different risk stratifications and recommendations for the first-line management of T2DM patients with CVD, or at high/very high cardiovascular risk.

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