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Simplicity and control – cardiometabolic effects of GLP-1 receptor agonists in type 2 diabetes

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Introduction

The diabetes pandemic is undoubtedly out of control; the projected diabetes prevalence for the year 2025 increased from 333 million in 2003 to 500 million in 2019. In South Africa, the age-adjusted prevalence of diabetes has increased more than three-fold since 2009, to 12.7% in 2019. Monitoring and screening for complications is poor in South Africa and complications are also not being managed, irrespective of access to the private or public healthcare sectors.[1-3]

Despite compelling indications for the use of the glucagon-like peptide 1 receptor agonist (GLP-1RA) and the sodium-glucose cotransporter-2 inhibitor (SGLT2i) classes (Figure 1), these important interventions are not funded in the South African public sector and are not included in the formularies of any medical schemes. Therapeutic inertia is evident across Africa; prospective observational data indicate that with a mean HbA_{1c} of 8.6%, the time from diagnosis to initiating a second-line glucose-lowering regimen is 6.9 years; by this stage, 14.5% of patients already have microvascular complications and 9.1% exhibit macrovascular complications.[3,4]

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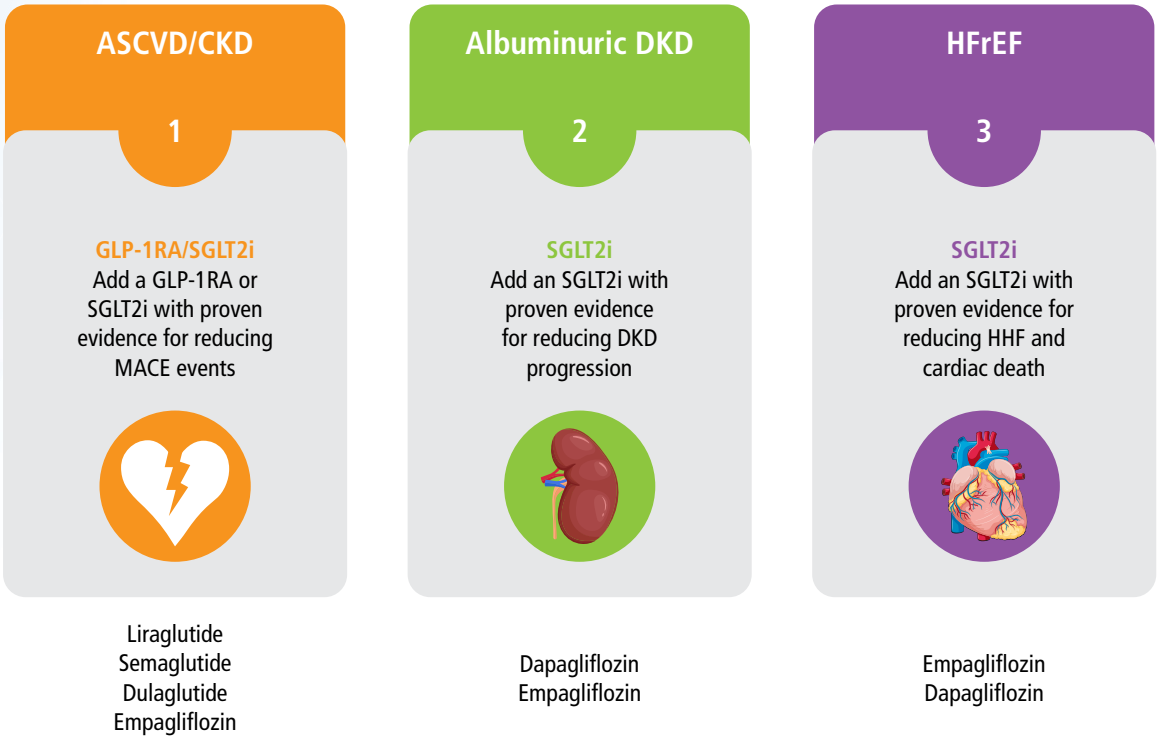


ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; DKD: diabetic kidney disease; HFrEF: heart failure with reduced ejection fraction; MACE: major adverse cardiovascular events

Figure 1. Morbidity and mortality benefit of GLP-1RA and SGLT2i therapy in type 2 diabetes mellitus (T2DM)

An alternative view of diabetes as a cardiometabolic disease arises from the high rates of cardiovascular disease that often occur independently of glycaemic control

Diabetes is a cardiometabolic disorder

Diabetes has historically been viewed as a metabolic disorder where the primary goal is to achieve optimal glucose control. An alternative view of diabetes as a cardiometabolic disorder arises from the high rates of cardiovascular disease that often occur independently of glycaemic control, with the primary goal of care then being the prevention and management of microvascular and macrovascular complications. Professor Ntsekhe maintains, "Atherosclerotic cardiovascular disease (ASCVD), particularly stroke, myocardial infarction (MI) and peripheral vascular disease (PVD), and heart failure are the main cause of mortality in T2DM and are a major cause of morbidity and disability-adjusted life years (DALYs)." The absolute risk of ASCVD in each individual is dependent on multiple variables:

- Age
- Gender
- Hypertension
- Lipid profile
- Smoking
- Duration of diabetes
- Presence of microvascular complications
- Use of specific risk-lowering medications.[5,6]

What is the prevalence of cardiovascular disease among patients with T2DM?

Cardiovascular disease affects ~32% of all people with T2DM and accounts for approximately half of all deaths, with coronary artery disease and stroke being the major contributors.[7] Much discussion has recently centred on the predominant manifestation of cardiovascular disease (ischaemic heart disease vs PVD vs stroke vs heart failure), as this has potential implications for prevention and treatment.

Data from the Caliber Program in the United Kingdom compared cumulative disease incidences in a cohort of 1.9 million people with T2DM but free of cardiovascular disease at entry. In this group, coronary heart disease (acute coronary syndrome, unstable angina pectoris, angina pectoris) was responsible for 42% of morbidity and 24% of cardiovascular deaths after a median follow-up of 5.5 years.[8]

ASCVD prevention and cardiovascular disease risk reduction

"Multifactorial risk factor control (Table 1) forms the foundation for clinical care for patients with diabetes," reminds Professor Ntsekhe. He says, "Of the glucose-lowering drug classes, the GLP-1RAs and SGLT2is have proven cardiovascular disease benefit and the majority of international guidelines recommend early introduction (second-line) of these agents in patients who are at high risk or have established cardiovascular disease."[5]

The safety and efficacy of semaglutide, a GLP-1 analogue that has an extended half-life of approximately one week, was tested in patients with T2DM in the SUSTAIN 6 randomised controlled trial.[9] Once-weekly semaglutide added to standard care over 104 weeks found a relative risk reduction of 26% for the primary outcome, a composite of cardiovascular death, non-fatal MI or non-fatal stroke, compared to standard care alone.[9,10]

Of note, the average duration of diabetes in this cohort was longer than 13 years and more than 80% of the cohort had established cardiovascular disease, CKD or both; use of antihypertensives, statins and antiplatelet agents was high. Once-weekly semaglutide added to standard care was also associated with improved control of glucose, weight and blood pressure.[9]

Table 1. Risk factor control for patients with diabetes[5]

- ✓ Tight glycaemic control
- ✓ Tight blood pressure control
- ✓ Tight lipid control
- ✓ Statins ± aspirin
- ✓ Smoking cessation
- ✓ Exercise
- ✓ Weight loss
- ✓ Diet

GLP-1RAs and SGLT2is have proven cardiovascular disease benefit and the majority of international guidelines recommend early introduction (second-line) of these agents in patients who are at high risk or have established cardiovascular disease

What is the role of baseline cardiovascular disease risk in patient selection for semaglutide therapy?

Post hoc analysis stratified by gender, age (younger or older than 65 years) and baseline cardiovascular risk profile in the SUSTAIN 6 trial showed that once-weekly semaglutide versus placebo reduced the risk of MACE in all subjects.[10]

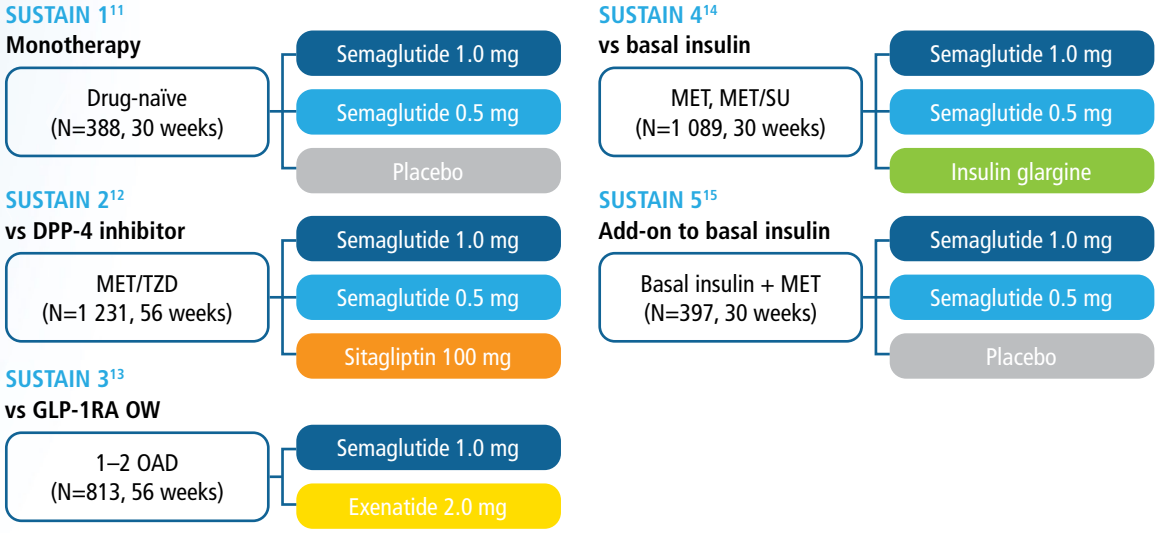
Simplicity and control using GLP-1 therapy – updates from the SUSTAIN clinical programme

The SUSTAIN clinical programme compared semaglutide against placebo as well as various other treatments for T2DM (Figure 2); key inclusion and exclusion criteria of the SUSTAIN 1-5 trials are described in Table 2.[11-15] Baseline characteristics of patients included an average HbA_{1c} of 8.1-8.4% and body weight, body mass index and age were similar across the groups. Duration of diabetes differed between the groups, ranging from an average of 4.2-13.3 years, depending on the study.

Table 2. Key inclusion and exclusion criteria of the SUSTAIN 1-5 trials[11-15]

Inclusion criteria	Exclusion criteria
✓ Males or females aged ≥ 18 years	✗ History of chronic or idiopathic acute pancreatitis
✓ Diagnosed with T2DM	✗ History/family history of MTC/MEN2
✓ HbA_{1c} ≥ 7% or ≤ 10.5% depending on comparator	✗ Calcitonin level ≥ 50 ng/l
	✗ Acute coronary or cerebrovascular event within 90 days before randomisation
	✗ NYHA class IV heart failure
	✗ Known proliferative retinopathy or maculopathy requiring acute treatment

MTC: medullary thyroid cancer; MEN2: multiple endocrine neoplasia type 2



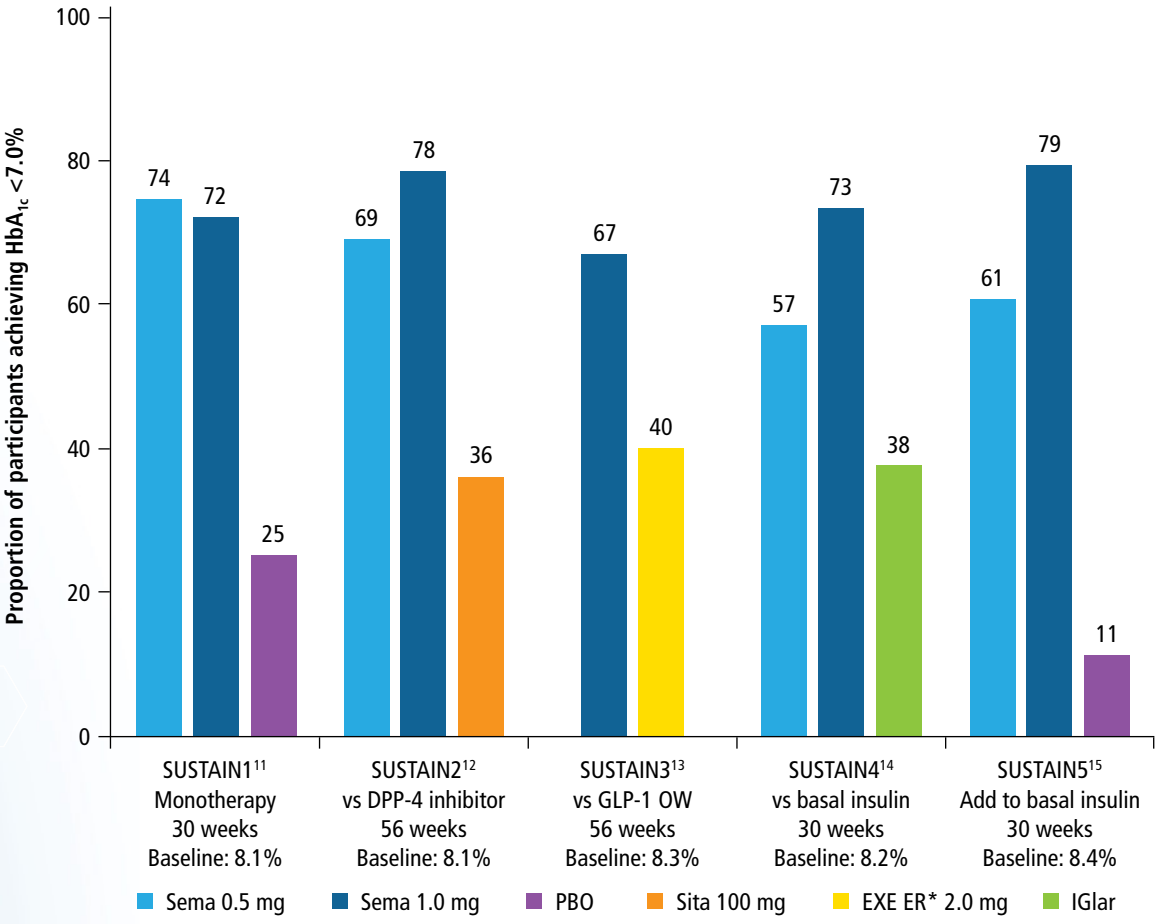
MET: metformin; TZD: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; GLP-1RA: glucagon-like peptide-1 receptor agonists; OW: once weekly; OAD: oral antidiabetic drug; SU: sulphonylurea

Figure 2. The SUSTAIN 1-5 clinical programme

Semaglutide, both the 0.5 mg and 1 mg doses, showed greater improvements in HbA_{1c} control than the comparators used across the five SUSTAIN studies

Change in HbA_{1c}

One manner of assessing how well T2DM patients respond to a treatment is through measuring the change in HbA_{1c} from baseline. Semaglutide, both the 0.5 mg and 1mg doses, showed greater improvements in HbA_{1c} control than the comparators used across the five SUSTAIN studies. Semaglutide also outperformed all the comparators, including exenatide ER and basal insulin, in terms of the proportion of participants who achieved an HbA_{1c} < 7% (Figure 3).[11-15]



*Exenatide Extended Release is not available in South Africa. Please refer to local professional information for products that are registered by the local Regulatory Authority.

Figure 3. Proportion of participants who achieved an HbA_{1c} < 7% - SUSTAIN 1-5[11-15]

Fasting glucose and self-measured plasma glucose

Change in fasting plasma glucose from baseline was significantly improved (up to 2.8 mmol/l) across the SUSTAIN 1-5 studies, as was reduction in postprandial glucose increments, with both doses of semaglutide showing superiority over each comparator.[11-15]

Weight management

Dr Kok indicated that "there was a significant improvement in body weight across the SUSTAIN studies; a 5-6 kg weight loss, up to 56 weeks, was achieved in the semaglutide arms, which showed superiority over the comparator in each study. More participants achieved ≥ 5% weight loss using semaglutide versus comparators; 66% of patients using 1mg semaglutide in SUSTAIN 5 achieved this outcome."[11-15]

Among participants achieving an HbA_{1c} reduction of ≥ 1%, ≥ 5% weight loss and ≥ 5 mmHg reduction in systolic blood pressure, the semaglutide arms outperformed each comparator

Blood pressure control

Change in systolic blood pressure from baseline was greater with both the 0.5 mg and 1 mg doses of semaglutide than with each comparator.[11-15]

Post hoc analysis – combined outcomes

Among participants achieving an HbA_{1c} reduction of ≥ 1%, ≥ 5% weight loss and ≥ 5 mmHg reduction in systolic blood pressure, the semaglutide arms outperformed each comparator across SUSTAIN 1-5 and SUSTAIN 7 (Figure 4), with the semaglutide 1mg arms showing the greatest proportion of participants who achieved the combined outcome.[16]

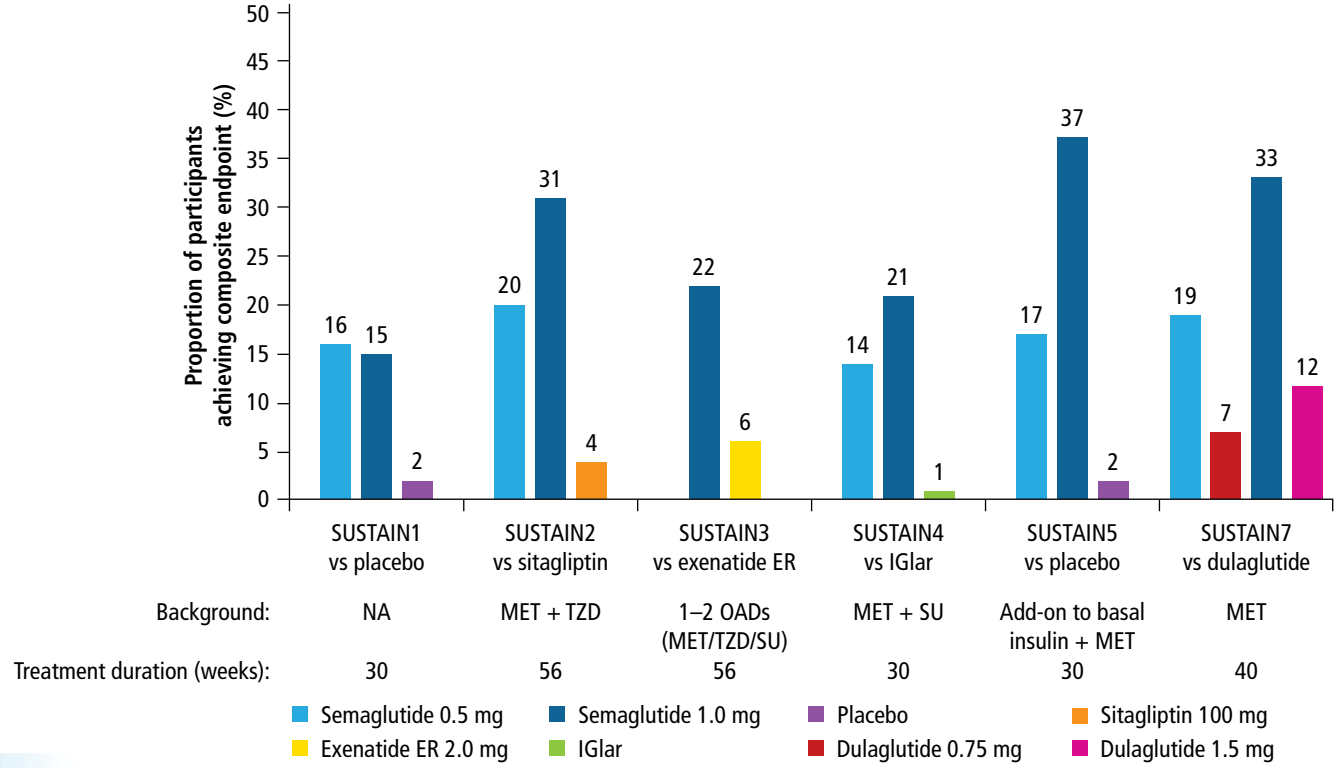
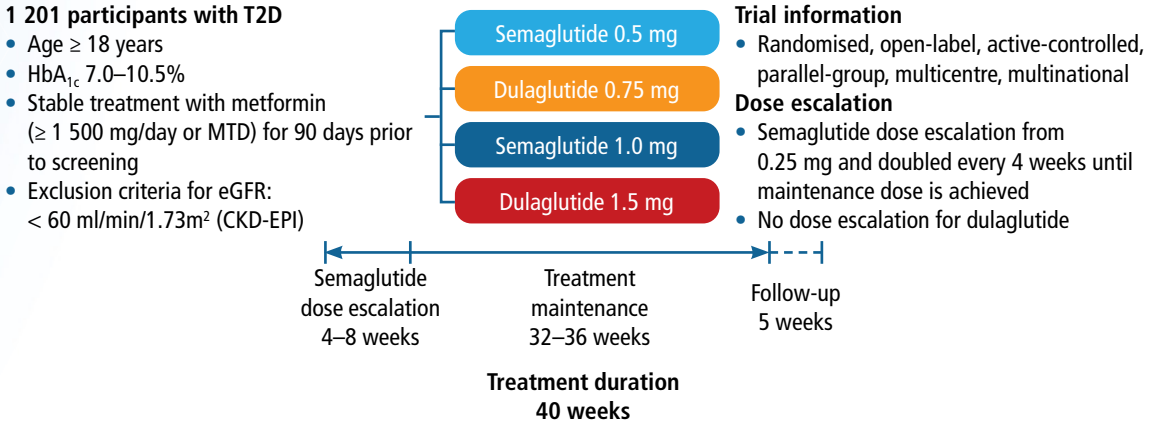


Figure 4. Participants achieving ≥ 1% HbA_{1c} reduction, ≥ 5% weight loss and ≥ 5 mmHg reduction in systolic blood pressure – SUSTAIN 1-5 and 7[16]

SUSTAIN 7

The trial design and key outcomes of SUSTAIN 7, comparing 0.5 mg and 1 mg semaglutide against 0.75 mg and 1.5 mg dulaglutide, are represented in Figure 5.[17]



Primary endpoint
- Change from baseline to week 40 in HbA_{1c}

Confirmatory secondary endpoint
- Change from baseline to week 40 in body weight

Other pre-specified secondary efficacy endpoints
- Change from baseline to week 40 in:
  - Fasting plasma glucose and seven-point SMBG
  - Mean and postprandial increment in blood glucose
  - BMI, waist circumference and blood pressure
  - Fasting blood lipids
  - Patient-reported outcomes

Figure 5. Trial design and key outcomes of SUSTAIN 7[17]

In terms of the composite endpoint of HbA_{1c} < 7% without severe or symptomatic hypoglycaemia and no weight gain, semaglutide in both dosages outperformed dulaglutide with statistical significance

In terms of HbA_{1c} reduction, both doses of semaglutide outperformed the comparator over the 40-week period, showing statistical significance. Glycaemic targets were achieved with both dosages of each agent; the semaglutide doses achieved statistical significance for superiority over the dulaglutide doses, even for HbA_{1c} < 6.5%.[18]

Fasting plasma glucose improvement and body weight were better for the semaglutide dosages than the dulaglutide dosages, with change from baseline being statistically significant for the semaglutide arms. In terms of weight loss responses, semaglutide outperformed dulaglutide for ≥ 5% and ≥ 10% weight loss, with statistical significance (Figure 6).[17]

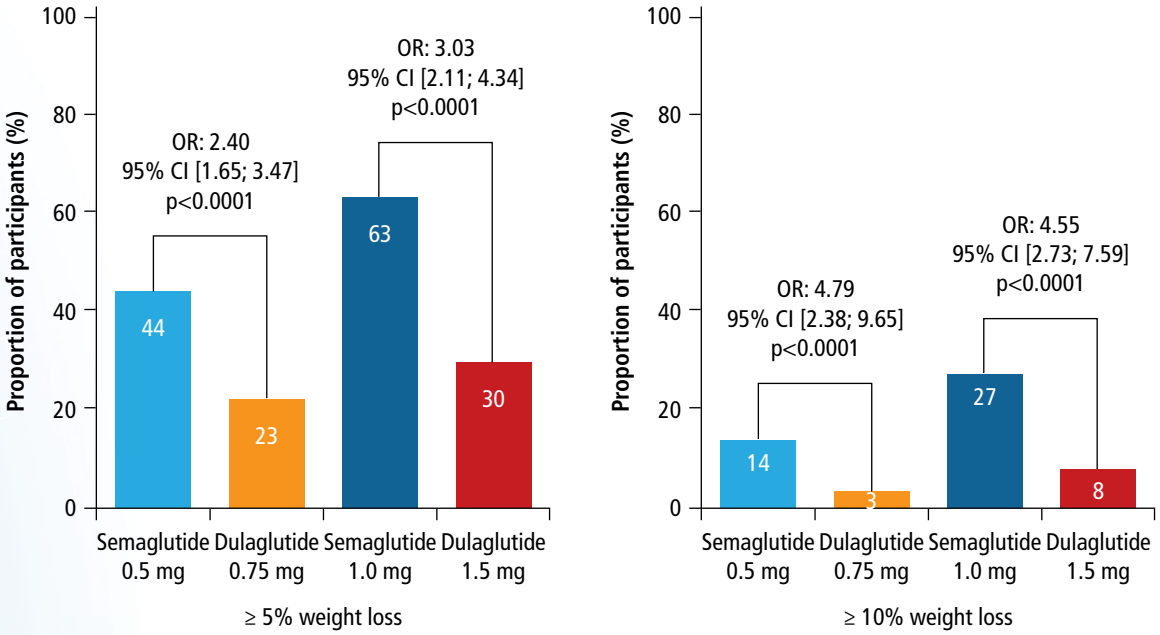


Figure 6. Weight loss responses – SUSTAIN 7[17]

In terms of the composite endpoint of HbA_{1c} < 7% without severe or symptomatic hypoglycaemia and no weight gain, semaglutide in both dosages outperformed dulaglutide with statistical significance.[17]

Cardiovascular mode of action of GLP-1RAs

Numerous studies have, over recent years, shown benefit from the use of GLP-1RAs for primary cardiovascular outcomes and the individual components thereof in patients with T2DM (Figure 7).[10,18-21] These finding have led to changes in the guidelines used for the management of patients with T2DM.

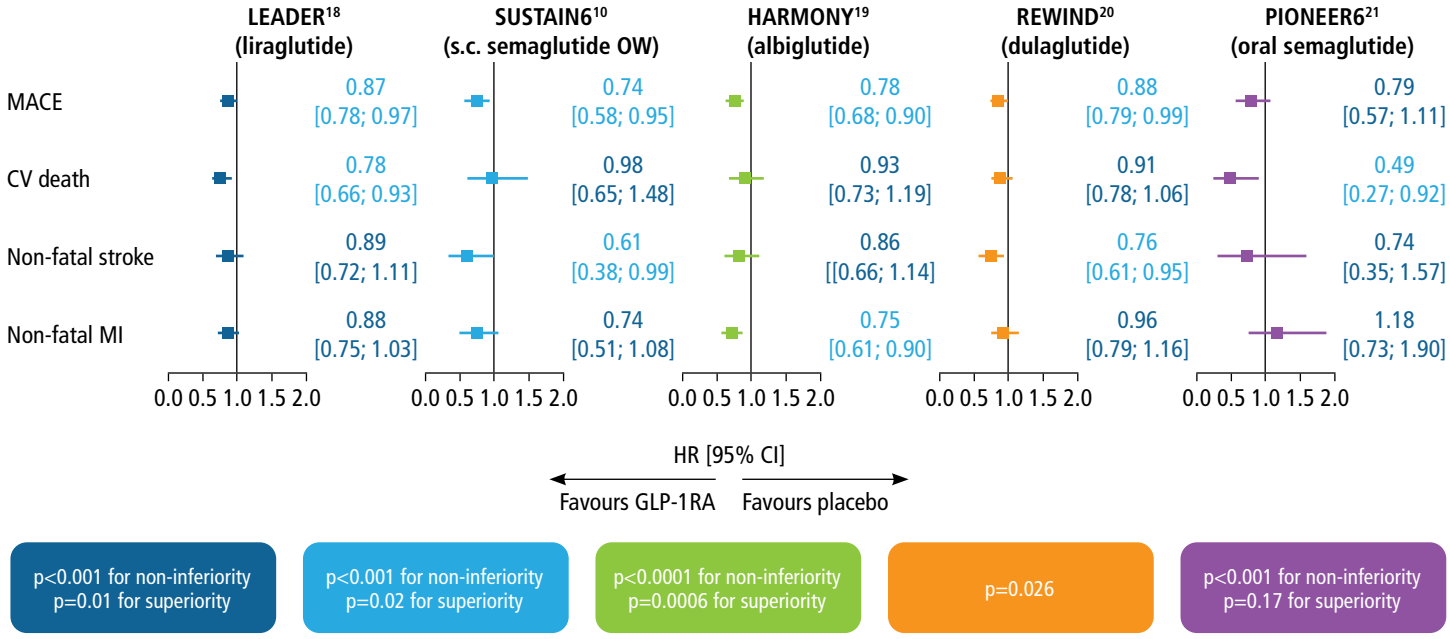


Figure 7. Cardiovascular outcomes trials for GLP-1 analogues – primary outcomes and individual components[10,18-21]

Numerous studies have, over recent years, shown benefit from the use of GLP-1RAs for primary cardiovascular outcomes and the individual components thereof in patients with T2DM

Effect of GLP-1RAs on cardiovascular risk factors

The overview of Professor Montanya is that "GLP-1RAs have shown proven benefit for all classic cardiovascular risk factors such as blood pressure, blood lipids, glycaemia and body weight."

Systolic blood pressure

Systolic blood pressure often decreases with GLP-1RA therapy; many head-to-head trials have compared different GLP-1RAs against each other, with the majority of trials showing a 2-5 mmHg reduction in blood pressure. In general, the long-acting GLP-1RAs show greater efficacy in reducing systolic blood pressure than the short-acting GLP-1RAs.[22]

Heart rate

Initial concerns regarding the slight increase in heart rate (1-3 beats per minute) that was observed with GLP-1RA use, more likely to occur with the long-acting agents, has been shown not to be relevant in terms of cardiovascular risk.[22]

Lipids

GLP-1RAs confer very modest improvements in lipids; reductions in total cholesterol range from 0.1-0.3 mmol/l, with larger reductions occurring with the long-acting versus short-acting GLP-1RAs.[22]

Body weight

It is well established that GLP-1RA therapy is effective in reducing body weight; those GLP-1RAs that have more difficulty crossing the blood-brain barrier (albiglutide, dulaglutide) are less effective in reducing body weight.[22]

GLP-1 effects on atherosclerosis and inflammation

Data from animal models have shown liraglutide to inhibit progression of early, low-burden atherosclerotic lesion development in ApoE$^{-/-}$ mice through the inhibition of lipid deposition, with a reduction in intima:media ratio. Liraglutide has also been found to reduce aortic plaque lesion area independent of body weight and cholesterol in ApoE$^{-/-}$ mice; it is suggested that an anti-inflammatory effect from GLP-1RA therapy may confer this benefit. Semaglutide has been shown to significantly downregulate genes related to the process of atherosclerosis in LDLr$^{-/-}$ mice, including those genes related to cholesterol metabolism, leukocyte recruitment, leukocyte adhesion and extravasation, and extracellular matrix protein turnover. Of particular importance is the significant reduction in expression of the osteopontin gene, as this is considered to be a potential biomarker for the progression of atherosclerotic disease in humans and osteopontin levels are predictive of cardiovascular disease in T2DM.[23,24]

Incretin therapy improves indicators of atherosclerotic plaque stability in patients with T2DM, showing increased expression of genes with beneficial effects for inflammation, oxidative stress and collagen content.[23,,24] There is also evidence that T2DM patients using liraglutide show reduced carotid intima media thickness, with significant reductions still evident 18 months after cessation of treatment.[25]

GLP-1 effects on endothelial dysfunction

Endothelial dysfunction creates an atherogenic environment giving rise to abnormal blood flow, smooth muscle growth, increased endothelial permeability, impaired coagulation, leukocyte adhesion and vascular inflammation.[26] There are data that infusions of native GLP-1 acutely modify endothelial function in healthy humans; observational data arising from patients with T2DM indicate that exenatide improves arterial dilation.[27]

GLP-1RAs have shown proven benefit for all classic cardiovascular risk factors such as blood pressure, blood lipids, glycaemia and body weight

GLP-1 effects on the heart

A study has shown that liraglutide improves infarct size in T2DM patients with ST-segment elevation MI.[28]

Key learnings

- The burden of cardiovascular disease in patients with T2DM is high, with ASCVD predominating as the main manifestation
- It is important to view T2DM as a cardiometabolic disorder rather than a disorder of dysglycaemia
- Early use of once-weekly semaglutide provides an opportunity to improve cardiovascular disease outcomes beyond traditional risk factor control
- Superiority in glycaemic control and body weight loss has been confirmed for both doses of semaglutide versus comparators in SUSTAIN 1-5
- Superiority in glycaemic control and body weight loss has been confirmed for both doses of semaglutide versus comparators in SUSTAIN 7
- Over-and-above conferring benefit in terms of cardiovascular risk factors, there is evidence that GLP-1RAs have beneficial effects in terms of protection against atherosclerosis and vascular inflammation, improvements in endothelial function and direct cardiac effects when used as therapy in the T2DM patient.

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