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Diabetes

Clinical issues and answers

GLP-1 RAs and cardiovascular protection for your type 2 diabetes patient

Professor Ntobeko Ntusi
Chair and Head: Department of Medicine
Division of Cardiology, University of Cape Town and Groote Schuur Hospital
Hatter Institute for Cardiovascular Research in Africa, University of Cape Town

Dr Zaheer Bayat
Endocrinologist
Bryanston

Learning objectives

You will learn:

- Current evidence on the cardiovascular protection benefits of GLP-1 RA therapy
- In daily clinical practice, the T2DM patient's cardiovascular risk should be addressed as early as possible.

Introduction

This report deals with commonly encountered clinical issues arising from the expanding use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in everyday practice. South African cardiologists and endocrinologists present the evidence for the expanded use of these antidiabetic agents and suggest how they can be used most effectively in selected type 2 diabetes mellitus (T2DM) patients.

Clinicians are alert to the fact that the cardiovascular complications of diabetes are severe, leading to increased morbidity, mortality and a significant reduction in the lifespan of their diabetic patients. The lifespan of patients who develop T2DM is reduced by an average of six years, but once they experience a cardiovascular event, such as a myocardial infarction (MI), the average years of life lost increase to 12 or more.

Diabetes is the leading cause of death (2016 statistics) in South African women, whereas in men it ranks sixth, with cardiovascular disease being the second most important cause of death in men.[1] During a recent South African virtual meeting, sponsored by NovoNordisk, leading cardiologists and endocrinologists evaluated the clinical issues and the expanding role of GLP-1 RAs in protecting T2DM patients from cardiovascular disease (Figure 1).

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This report was made possible by an unrestricted educational grant from **Novo Nordisk**. The content of the report is independent of the sponsor.

	Rank	Male %	Rank	Female %
Tuberculosis	1	7.6	5	5.2
Other forms of heart disease	2	4.6	3	5.8
HIV disease	3	4.6	6	5.0
Influenza and pneumonia	4	4.2	7	4.4
Cerebrovascular disease	5	4.0	2	6.2
Diabetes mellitus	6	4.0	1	7.2
Other viral diseases	7	3.4	8	3.9
Chronic lower respiratory diseases	8	3.3	...	...
Hypertensive diseases	9	3.2	4	5.8
Ischaemic heart diseases	10	3.1	9	2.5
Malignant neoplasms of female genital organs	...	...	10	2.5

Figure 1. Leading underlying causes of death by sex in 2016

ISSUE Should clinicians be managing cardiovascular risk in their patients more aggressively?

In my view, the greatest benefit for patients lies in the early use of GLP-1 RAs; they have been shown to slow down the development of cardiovascular disease

Professor Ntusi: "In my view, the greatest benefit for patients lies in the early use of GLP-1 RAs; they have been shown to slow down the development of cardiovascular disease."

A review of cardiovascular outcome trials provides an evidence base for the selection of patients who will benefit most from GLP-1 RA therapy. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes (LEADER) trial of T2DM patients at high cardiovascular risk was the first trial of GLP-1 RAs to show reduction of major adverse cardiovascular events as measured in terms of three-point MACE comprising cardiovascular death, non-fatal MI and non-fatal stroke.[2] It is important to note that the 9 000 patients recruited for and included in LEADER had T2DM and were either over the age of 50 years with established cardiovascular disease (coronary heart disease, stroke, peripheral vascular disease, chronic kidney disease (CKD) stage ≥3, or heart failure NYHA class II or III), or over the age of 60 years at high cardiovascular risk (with microalbuminuria/proteinuria, hypertension, left ventricular (LV) hypertrophy, LV systolic or diastolic dysfunction, or an ankle-brachial index of <0.9). The final cohort consisted of 80% of patients with established cardiovascular disease, CKD stage ≥3, or both. The mean duration of diabetes was 12.8 years and the mean HbA_{1c} was 8.7%. The median follow-up was 3.8 years and the median daily dose of liraglutide was 1.78mg. Type 1 diabetic patients and previous users of GLP-1 RAs or dipeptidyl peptidase-4 (DPP-4) inhibitors or rapid-acting insulin were excluded.

The key findings of LEADER were:

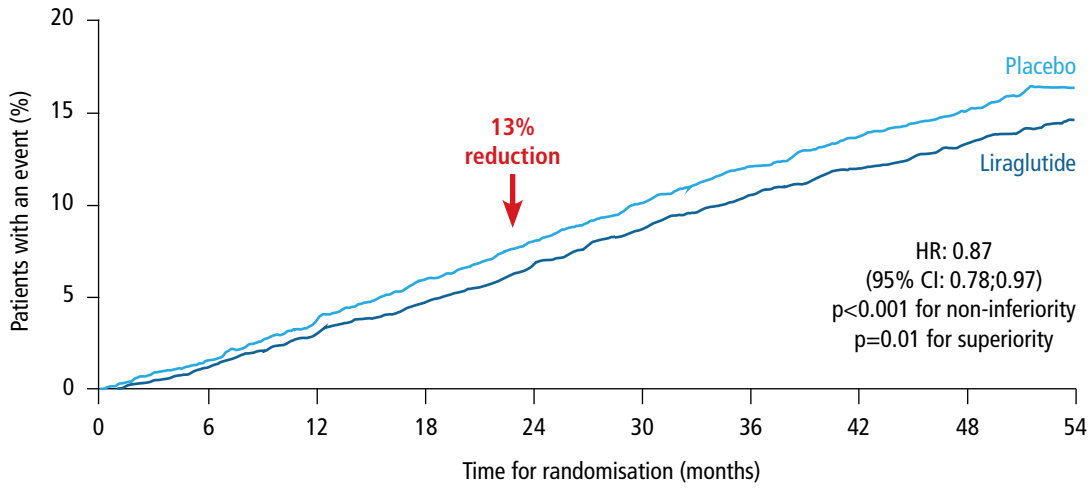
- There was a significant reduction in cardiovascular events in patients treated with liraglutide
- Death from cardiovascular causes was reduced by 22%, non-fatal MI by 12% and non-fatal stroke by 11%.

In a recent *post hoc* analysis,[3] it was shown that the greatest benefit of liraglutide therapy was seen in T2DM patients who had had a prior MI/stroke. This points to the life-sparing value of this medication. The LEADER trial results, together with other real-world data, led to liraglutide being registered for use in South Africa in T2DM patients to reduce their risk of major adverse cardiovascular events.

In daily clinical practice, the T2DM patient's cardiovascular risk should be addressed as early as possible in the continuum of T2DM-related atherosclerosis development.

Primary outcome

CV death, non-fatal myocardial infarction, or non-fatal stroke



Patients at risk

Liraglutide	4 668	4 593	4 496	4 400	4 280	4 172	4 072	3 982	1 562	424
Placebo	4 672	4 588	4 473	4 352	4 237	4 123	4 010	3 914	1 543	407

The primary composite outcome in the time-to-event analysis was the first occurence of death from cardiovascular causes, non-fatal myocardial infraction, or non-fatal stroke. The cumulative incidences were estimated with the use of Kaplan-Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months

Figure 2. Primary outcomes in the LEADER trial

ISSUE Is the data on the cardiovascular benefits of GLP-1 RAs impactful enough to change medical funders' attitudes and allow for the earlier introduction of these agents?

The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA), under the chairmanship of Dr Zaheer Bayat, will be addressing this issue. "International guidelines such as those from the ADA/EASD are clear on the benefits of the use of GLP-1 RAs, with proven cardiovascular and renal benefits in T2DM patients with established cardiovascular disease; South African guidelines, last published in 2017, will need to address this treatment option in greater depth," Dr Bayat noted.[4] Equally, cardiology as a specialist arena should be providing further guidance to clinicians.

ISSUE For which patients and at which point in a patient's journey should these newer agents, the GLP-1 RAs or sodium-glucose co-transporter-2 (SGLT-2) inhibitors, be introduced?

"The clinician should seek to choose the appropriate agent for the appropriate patient for the right indication," Professor Ntusi noted. "Liraglutide is a very powerful agent for the obese T2DM patient as it also reduces weight[5] and, additionally, it may be considered valuable therapy in patients with non-alcoholic liver disease, such as non-alcoholic steatohepatitis (NASH)." Three main categories for the use of liraglutide in T2DM are: Patients with established cardiovascular disease or at high cardiovascular risk, the obese patient and the patient with NASH.

Dr Bayat noted that liraglutide is useful in CKD patients with an eGFR <45ml/min/1.73m^2.

ISSUE Is there cardiovascular benefit from GLP-1 RAs in the non-diabetic patient at high cardiovascular risk?

This question is currently being investigated in the SELECT trial of a different GLP-1 RA, semaglutide.[6] South African patients are participating in the trial. Semaglutide is given as a once-a-week injection and clinicians are looking forward to the results of this study, which is likely to contribute to the overall acceptance of all GLP-1 RAs with proven cardiovascular benefit.

ISSUE At what point do you refer a newly diagnosed T2DM patient with existing cardiovascular disease, assessed at primary care level, to a cardiologist?

Professor Ntusi feels that because the mortality associated with T2DM is largely cardiovascular in nature, the clinician should not wait for cardiovascular complications to develop but rather refer the patient to a cardiologist early.

ISSUE What is a reasonable number-needed-to-treat (NNT) for a positive outcome with these relatively more expensive antidiabetic agents?

The most important consideration when balancing clinical algorithms against saving a single life is the patient in front of you, who is beyond price (Table 1).

Table 1. NNT for liraglutide benefit over three years

Achieve lowering of MACE in patients with a history of MI/stroke	39
Achieve lowering of MACE in patients without a history of MI/stroke	44
Prevent one cardiovascular death in patients with a prior history of an event	63
Prevent one cardiovascular death in patients without a prior event	82

Dr Saleem Dawood noted that one needs to convince patients of the benefit of their co-payment investment, if this is needed. "Shared decision-making is a rewarding process, although it may take time to convince patients that these agents are life-saving." Involvement of both the endocrinologist and cardiologist is helpful in motivating patients.

ISSUE What is the mechanism of GLP-1 RA cardiovascular protection?

Professor Ntusi noted that at this juncture, the exact nature of the protective mechanisms has not been established, although the drop in blood pressure, improvement in lipid profile and the increased metabolism of glucose in the liver are potential metabolic pathways. GLP-1 RAs also reduce levels of inflammatory cytokines such as TNF-α, IL-6 and IL-1β.[7] "In my view, the cardiovascular protection conferred by GLP-1 RAs is likely to be due to multiple mechanisms, rather than a single attribute of this class of agents."

Key learnings

- Both diabetes and the cardiovascular complications thereof lead to increased morbidity and a sharp reduction in lifespan
- There is increasing evidence that the GLP-1 RAs provide protection from cardiovascular disease in the patient with T2DM
- The LEADER trial has shown the superiority of liraglutide in respect of the three-point MACE of cardiovascular death, non-fatal MI and non-fatal stroke in T2DM patients at high cardiovascular risk
- SEMDSA is currently updating its guidelines for the management of T2DM to reflect current evidence on the benefits of GLP-1 RA and SGLT-2 inhibitor therapy
- It is best to introduce optimal therapy early in the T2DM disease continuum, and to refer to a cardiologist early if cardiovascular complications are evident upon diagnosis.

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This summary report was compiled for *deNovo Medica* by
Julia Aalbers
BSc Hons

Published by
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Reg: 2012/216456/07
70 Arlington Street, Everglen, Cape Town, 7550
Tel: (021) 976 0485 | info@denovomedica.com