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Diabetes

The importance of individualised approach to the treatment of T2DM

Learning objectives

You will learn:

- To understand the need for a flexible and individualised approach to the treatment of type 2 diabetes mellitus (T2DM) as advocated by expert guidance
- To evaluate the latest pragmatic primary care trial data on the benefits of using a glucagon-like peptide-1 receptor agonist (GLP-1RA) as first-added second-line therapy after metformin monotherapy
- To incorporate this practical evidence and the randomised clinical trial (RCT) data as a 'Call to Action' in primary clinical practice by introducing therapies with known cardiovascular and renal protective benefits earlier in the course of T2DM
- To develop this flexible approach with the involvement of patients who seek to avoid weight gain and other diabetes complications and to derive maximum benefit from an intensified approach to their diabetes control.

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Introduction

There is increasing awareness globally of the need to individualise therapies for people with T2DM in everyday clinical practice. This patient-centred approach has been endorsed by expert guidance from organisations such as the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA).

The 2017 South African guidelines also focused on the management of T2DM at primary care level, but currently place less emphasis on a patient-centred approach and the development of individual solutions to therapy.[1] They focus more on ensuring careful consideration of all clinical aspects of this chronic condition.

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The therapeutic challenge of the continuum of clinical change

A common thread, however, in all expert guidance is the need to tailor treatment to the individual's developing course of his/her disease in order to maintain glycaemic control, reduce the risk of diabetes-related complications, and improve prognosis. The ongoing scenario of clinical change in diabetes was recently acknowledged by Dr Landi Lombard in a presentation of clinical case studies from his practice. He noted: "Just when we as clinicians think we have good glucose control in place, something happens and again we have to play catch-up."

It is this ongoing change that provides a stimulus to develop more flexible approaches that fit the patient who, in South Africa as in many parts of the world, is most likely to be treated by a general practitioner or at a local private or public sector clinic. In fact, 90 % or more of patients with T2DM will be treated in primary care.

Another feature of diabetes care is that a substantial proportion of patients using oral monotherapy have poor glycaemic control for many years before treatment is intensified.

As part of the very recently published DISCOVER study programme, South African patients participating in this study were assessed in respect of their HbA_{1c} levels at the time of initiation of second-line therapy. More than 40 % of them had reached HbA_{1c} levels of ≥ 9 % before a second therapeutic agent was introduced.[2] This lack of clinical intervention is worse than the global experience, where some 75 % of patients were started on a second therapeutic agent much earlier when their HbA_{1c} levels reached 8 %.

This lack of progression of therapy may, in part, be due to patient fears associated with treatment-related weight gain and hypoglycaemia, along with fears of the regimen becoming more complex. Clinical inertia may also be a factor in this slower-than-desired intensification of therapy. Some of that inertia may be due to lack of evidence from RCTs in the primary care setting that might help guide clinical decision-making.

"Just when we as clinicians think we have good glucose control in place, something happens and again we have to play catch-up" – Dr Landi Lombard

Pragmatic primary care evidence to guide early therapy intensification

The first pragmatic randomised trial of early intensification of T2DM therapy using newer agents in primary care was completed in 2019 and explored everyday clinical outcomes that can be achieved in this setting with liraglutide, a GLP-1RA, added early after metformin monotherapy. The results of this multi-centre multi-country trial, known as the LIRA-PRIME trial, were presented at the 2020 ADA congress held virtually in June.

The trial aimed to bridge the gap between the results from the published series of RCTs using liraglutide which had proven its efficacy in reducing HbA_{1c} and body weight, and the lack of data from clinical trials to show the same or similar expected results in everyday primary care practice.

The LIRA-PRIME trial compared the efficacy of liraglutide to oral antidiabetic drugs (OADs) as the second-line addition to metformin in a multi-centre, randomised, two-arm, open label, active-controlled trial conducted in primary care.[3] It used less-restrictive inclusion criteria than those used in the LEAD trials, in which liraglutide showed clinically significant reductions in HbA_{1c},[4-7] along with weight loss and low risk of hypoglycaemia, and the LEADER trials showing a significant reduction in the risk of major cardiovascular events, all-cause mortality, and renal outcomes in T2DM patients at high cardiovascular risk.[8,9]

Trial design of LIRA-PRIME

The patients included in LIRA-PRIME represented a broad patient population with clinical visits as would occur generally in a primary care setting; there were four initial visits at two, four, 16 and 26 weeks. Thereafter, visits took place quarterly. The main inclusion and exclusion criteria are summarised in Table 1.[10]

The primary endpoint of LIRA-PRIME was 'time to reach inadequate glycaemic control', defined as an HbA_{1c} > 7 % at two scheduled consecutive visits after the 26-week point of the trial.

Secondary and safety endpoints are summarised in Table 2.[10]

The primary endpoint of LIRA-PRIME was 'time to reach an inadequate glycaemic control', defined as an HbA_{1c} > 7 % at two scheduled consecutive visits after the 26-week point of the trial

Table 1. Main inclusion and exclusion criteria of LIRA-PRIME[10]

Main inclusion criteria	Main exclusion criteria
• Male or female ≥ 18 years old with T2DM diagnosis ≥ 90 days prior to screening • HbA_{1c} 7.5-9 % (both inclusive) • Stable dose of metformin monotherapy (≥ 1 500 mg or MTD) for ≥ 60 days prior to screening • Patients for whom liraglutide and OAD treatment are indicated according to approved local label descriptions.	• Pregnancy or breastfeeding • Receipt of any investigational medicinal product ≥ 30 days before screening • Treatment with any diabetes medication, except metformin, ≥ 60 days before screening • Any disorder which, in the investigator's opinion, might jeopardise the patient's safety.

Table 2. Key secondary and safety endpoints of LIRA-PRIME[10]

Key secondary endpoints	Safety endpoints
• Time to premature treatment discontinuation for any reason • Change from baseline to week 104 (or premature treatment discontinuation) in HbA_{1c}, fasting plasma glucose, body weight, body mass index, systolic and diastolic blood pressure • Patients who, at the end of the trial or at premature discontinuation, had achieved: – HbA_{1c} ≤ 6.5 % – HbA_{1c} ≤ 7.0 % without weight gain and/or hypoglycaemia.	• Incidence of hypoglycaemic episodes • Serious adverse events • Adverse events leading to permanent discontinuation of trial product.

The baseline complications reflect the early nature of this second-line therapy trial, whether OAD or liraglutide was added, as seen in the characteristics of the cohort of 1 997 patients included in the trial (Table 3).[10]

Table 3. Baseline diabetes complications in the LIRA-PRIME cohort (N = 1 997)[10]

Complication	% of population
Diabetic nephropathy	4.3
Diabetic neuropathy	15.0
Diabetic retinopathy	3.2
Macroangiopathy	3.1
Normal eGFR/mildly decreased	92.3

Results of LIRA-PRIME and implications for primary care practice

The most significant result was that the time to loss of control was much longer using liraglutide versus OADs at 109 weeks vs 65 weeks, respectively

The use of liraglutide[10] (an initiation dose of 0.6mg/day with subsequent dose escalation to 1.8mg daily) was compared to the addition of OADs (DPP-4 inhibitors, alpha-glucosidase inhibitors, SGLT-2 inhibitors, thiazolidinediones or sulphonylureas) plus metformin given at a clinically acceptable dosage level (≥1 500mg or maximum tolerated dose). Table 4 shows the breakdown of second-line therapies given during the trial.

Table 4. Treatment breakdown of therapies used in LIRA-PRIME

	No. of patients	
Liraglutide	996	49.8 %
OADs	995	49.2 %
• SGLT-2 inhibitors	487	48 %
• DPP-4 inhibitors	398	40 %
• Sulphonylureas	110	11 %

The most significant result was that the time to loss of control was much longer using liraglutide versus OADs at 109 weeks vs 65 weeks, respectively. Premature treatment discontinuation also occurred later in patients on liraglutide compared to OADs (80 vs 52 weeks). Rates of serious adverse events and hypoglycaemic episodes were similar, but more gastrointestinal side-effects were seen in the liraglutide group.

Importantly, as part of this trial, patients did not receive any additional motivation/ support beyond normal pharmacy support in the form of timeous provision of medication. This is frequently a potential concern when extrapolating data from RCTs to everyday clinical practice

Extended time in control with liraglutide versus OADs

The longer period of control achieved with liraglutide is reassuring to primary care practitioners who can confidently expect that control will be maintained for at least 100 weeks (approximately 8/9 months) after reaching target HbA_{1c} on titrated doses of liraglutide. Interestingly, premature discontinuation was lower than with multiple OAD therapy.

Importantly, as part of this trial, patients did not receive any additional motivation/ support beyond normal pharmacy support in the form of timeous provision of medication. This is frequently a potential concern when extrapolating data from RCTs to everyday clinical practice.

Benefits of earlier use of a GLP-1RA (liraglutide)

The benefits of early and maintained glucose control, without hypoglycaemia and weight gain, were well recognised in the pivotal UKPDS trials; this is generally referred to as 'the legacy effect'.

The use of GLP-1RA therapy with an agent capable of achieving reductions in the risk of major cardiovascular events, all-cause mortality, and renal outcomes, provides additional reassurance to the primary care practitioner that he/she is prescribing therapies with established longer-term benefits.

Key learnings

- Early introduction of GLP-1RAs is supported by many expert clinical guidelines
- In this first pragmatic primary care trial, liraglutide was shown to be acceptable and effective as an add-on therapy to metformin
- As expected from the RCTs of GLP-1RAs, the period of time within target on liraglutide therapy in primary care practice was longer than when the traditional therapeutic route of adding OADs to metformin was taken.

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