

INCRETIN SUMMIT – SOUTH AFRICA'S PREMIER UPDATE ON INCRETIN THERAPY IN DIABETES



Professor Pankaj Joshi
MEDUNSA
Director
Diabetes Care Centre
Louis Pasteur Hospital
Pretoria

Unmet needs in type 2 diabetes

Introduction:

The annual Incretin Summit sponsored by Novo Nordisk was held recently in Johannesburg. It brought together international and South African experts to discuss clinical aspects of incretin-based therapy in type 2 diabetes.

Professor Joshi set the scene for improved type 2 diabetes care in South Africa and challenged clinicians to strive harder to reach targeted glycaemic control in their patients. "There are multifactorial challenges in managing type 2 diabetes – ideally we are seeking to restore β -cell function, reduce cardiovascular risk and avoid weight loss and hypoglycaemia," he said.

In South Africa, despite the paucity of published data on the treatment of black African patients with diabetes, Professor Joshi stressed that there is no ethnic factor affecting the way clinicians treat type

2 diabetes. "All patients deserve the best available therapy for their diabetes. We must also take note of the fact that effective treatment with sulphonylureas only lasts for 2-3 years; then progression of the condition requires intensification of therapy," he said (Figure 1).

"Ideally, we need therapeutic agents that restore β -cell and α -cell function, are weight neutral, have a low risk of hypoglycaemia, slow or reverse the complications of type 2 diabetes, improve blood pressure control and contribute to overall quality of life," he concluded.

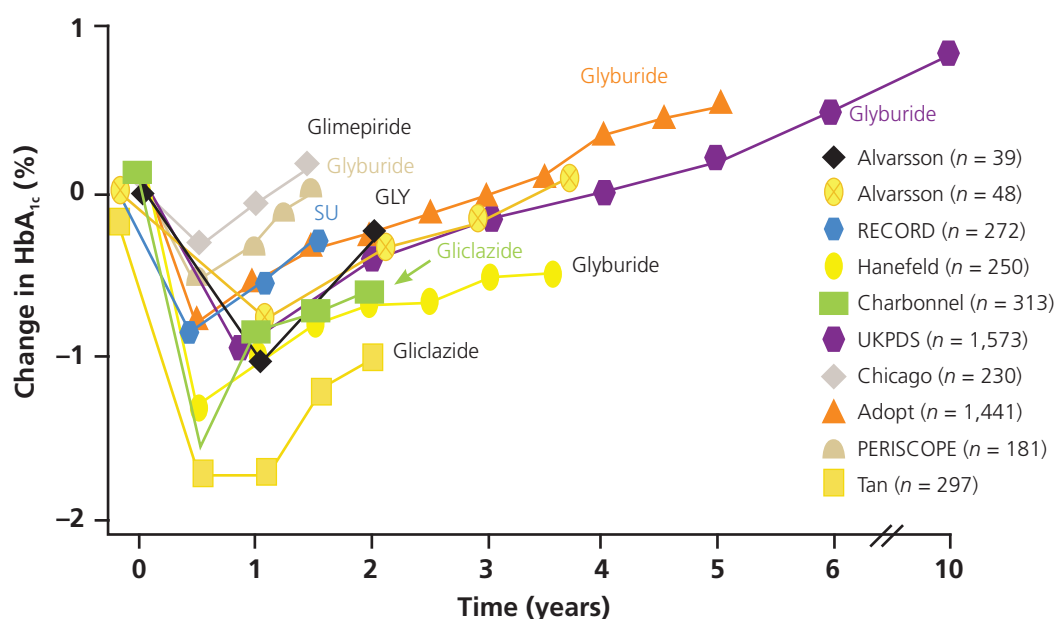


Figure 1. Durability of glycaemic control with sulphonylureas

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Wolfgang E. Schmidt, M.D., Ph.D.
Professor of Medicine and Chair,
Director, Department of Medicine
Chief, GI/Hepatology &
Diabetology Services
St. Josef-Hospital
Germany

Where to after metformin?

“Metformin is still the gold standard for therapy in type 2 diabetes because of its extremely favourable cost/benefit and risk/benefit ratio. However, newer agents offer advantages for the individual patient and the clinician needs to consider their appropriate use.”

Dr Schmidt noted that hypoglycaemia, weight gain and progressive β -cell loss contribute significantly to poorer outcomes. “We know now from trials such as ACCORD and VADT^{1,2} that

severe hypoglycaemia in cardiovascularly compromised patients is dangerous and results in increased mortality.”

Control of HbA_{1c} to 7% (or lower to 6.5%) is still a relevant therapeutic target but these levels should be reached without inducing hypoglycaemia or unnecessary weight gain. The VADT study showed that severe hypoglycaemia was a predictor of death and its occurrence is a signal of elevated cardiovascular risk (Figure 2).³

Variable	Hazard ratio		P-value
Prior CV event	3.12	(1.74 – 5.57)	0.0001
Age/10 yr	2.09	(1.52 – 2.88)	< 0.0001
HDL/10 mg	0.70	(0.54 – 0.91)	0.0079
Baseline HbA _{1c}	1.21	(1.04 – 1.42)	0.015
Severe hypos	4.04	(1.45 – 11.28)	0.0076

Figure 2. Predictors of cardiovascular death in the VADT study

Weight gain following glucose-lowering therapy, particularly with insulin and the sulphonylureas, presents a psychological problem for many patients. Studies have shown that body mass index (BMI) is related to mortality. A recent collaboration study using prospective data from more than 50 studies incorporating 900 000 adults showed that when BMI rises above 22.5–25 kg/m², there is a 30% increase in all-cause mortality, a 40% increase in cardiovascular mortality and an almost 120% increase in diabetes-related mortality for every 5 kg/m² that

the BMI increases.⁴ “There is also a 10% increase in cancer mortality as the BMI rises,” Dr Schmidt pointed out.

In 2014, the clinical objectives for improved therapy in type 2 diabetes are to:

- Avoid hypoglycaemia
- Avoid treatment-related weight gain
- Reconstitute/regain β -cell function and stop β -cell loss
- Provide stringent but safe glycaemic control early after diagnosis and maintain glycaemic control for as long as possible

Incretins and improved therapy for type 2 diabetes

The pivotal study of GLP-1, the incretin hormone which is released from the lower gut, was undertaken by Nauck and colleagues and showed that intravenous infusion of GLP-1 is capable of normalising glucose levels in poorly controlled patients with type 2 diabetes of long duration and with very high fasting blood glucose (FBG) levels – a role that until

then had only been assigned to insulin.⁵ The glucose normalisation resulted from β -cell stimulation in the face of raised glucose levels. As glucose levels normalised, insulin secretion dropped – illustrating the in-built protection from hypoglycaemia associated with GLP-1. Elevated glucagon levels were also reduced, an action that is also glucose-dependent.

There are currently two types of incretin-based therapy: firstly, the DPP-4 inhibitors that limit the degradation of GLP-1 and GIP, resulting in moderately raised levels of GLP-1. The second class of agents are GLP-1 receptor agonists, which are analogues of the natural GLP-1 peptide, given intravenously and which result in super-physiological levels of GLP-1.

These two agents, which bring about completely different levels of plasma

GLP-1 (Figure 3), have different clinical attributes. The higher GLP-1 levels achieved with the GLP-1 agonists exenatide and liraglutide result in greater HbA_{1c} lowering, as well as diminished appetite, increased satiety and delayed gastric emptying. “The DPP-4 inhibitors, on the other hand, achieve lower GLP-1 levels and have almost no effect on weight, but result in less nausea than the GLP-1 agonists,” Dr Schmidt pointed out.

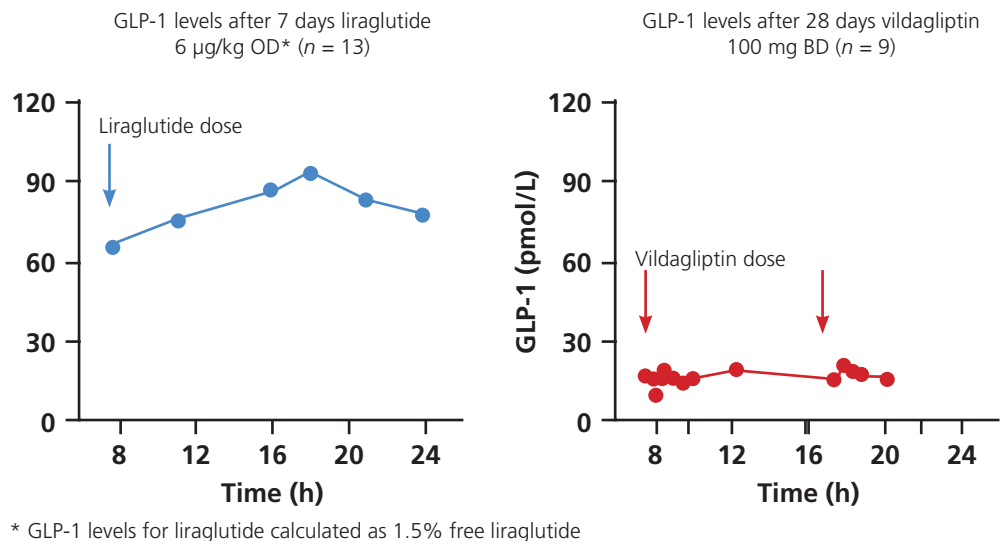


Figure 3. DPP-4 inhibitors result in lower levels of GLP-1 than exogenous administration of a GLP-1 analogue

Optimising the availability of incretin-based therapies

The ADA/EASD position statement issued in 2012 provides useful clinical guidelines and principles for optimising therapy using these agents (Figure 4).⁶

The most useful clinical principles from these guidelines can be summarised as follows:

1. Use metformin as first choice, as early as possible; even consider its use in pre-diabetics with a strong family history of diabetes
2. Check glycaemic control three months after initiating therapy; do not wait for six months or a year
3. Evaluate all agents in terms of their efficacy and effect on hypoglycaemia and weight gain
4. Increase metformin dose slowly to reduce side-effects and titrate up to therapeutic levels (2000-3000 mg daily)
5. Re-evaluate therapies early and

introduce combination therapy early to maintain glycaemic control

6. Consider the value of the only drug class that induces weight loss, namely the GLP-1 receptor agonists, noting they can be used with metformin and insulin
7. Individualise HbA_{1c} targets appropriately for the patient, based on risk, age and presence of co-morbidities.

“It is interesting to note that the American Association of Clinical Endocrinologists (AACE) has an innovative approach to therapy determined by the initial HbA_{1c} at the time of diagnosis.⁷

“The South African Guidelines are appropriate⁸ and their algorithm is similar to the ADA/EASD approach, except for the still significant emphasis on sulphonylurea use, probably for cost considerations,” Dr Schmidt concluded.

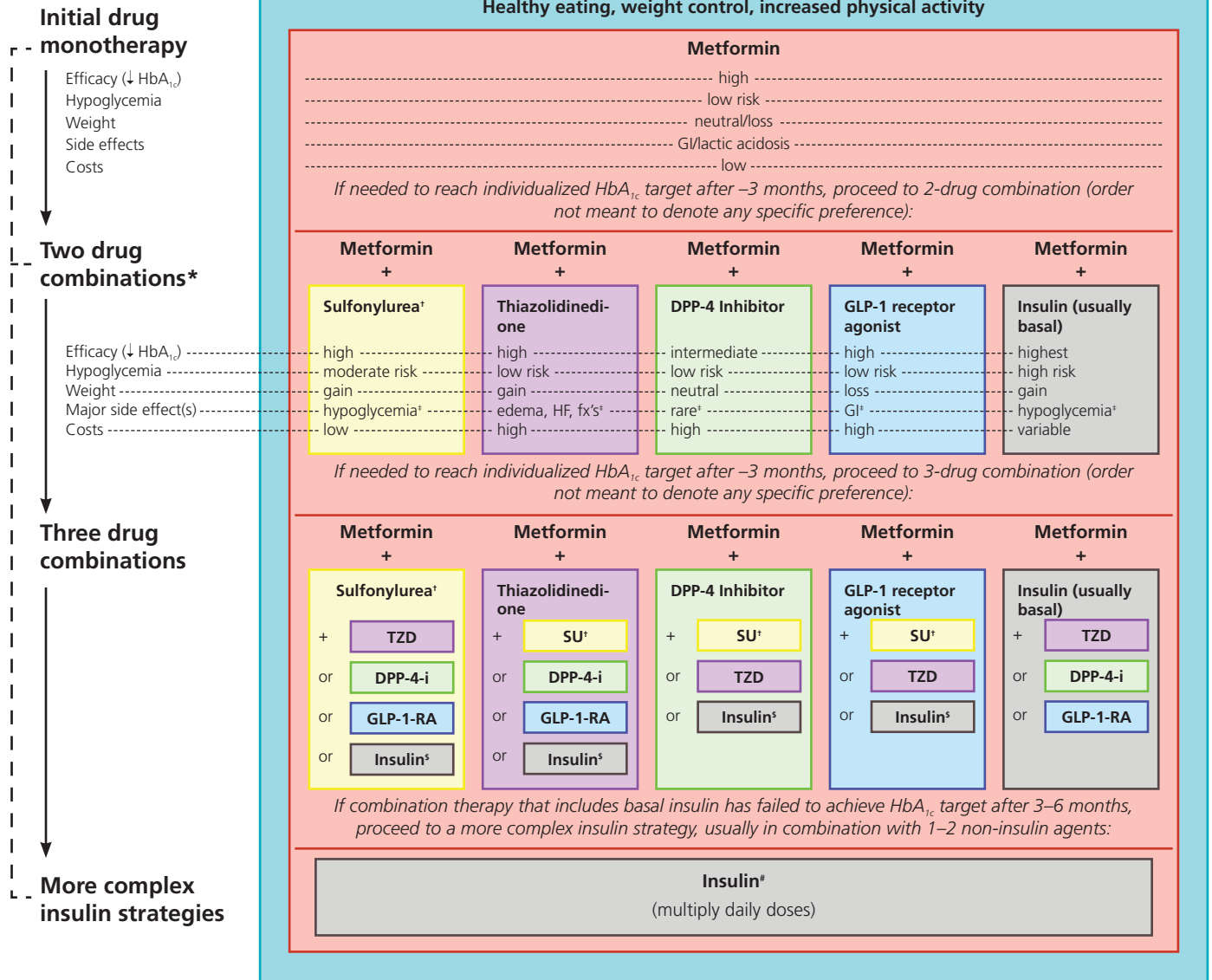


Figure 4. ADA/EASD position statement 2012 – individualised therapy in type 2 diabetes



Jeff Wing
Head of Clinical Medicine
University of the Witwatersrand
Johannesburg

Early treatment of type 2 diabetes – can incretins do it better (with particular reference to South Africa)?

“The physiology of incretins is key to our evaluation of the role of these agents in early treatment,” Professor Wing pointed out.

“Creating the background of our understanding of type 2 diabetes management are the so-called inflection studies that shape our therapeutic approaches.”

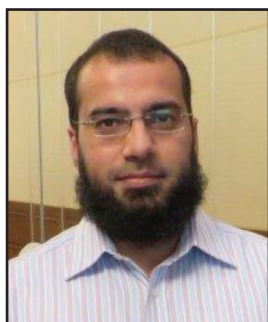
These include the UKPDS studies which over 20 years shaped the understanding of the progressive nature of type 2 diabetes and the benefits of early control and the ACCORD study,¹ which stressed that the key to therapeutic success is reaching targeted glycaemic control without causing hypoglycaemia and weight gain.

In South Africa the core of composite diabetes care is reaching glucose targets safely in a patient-centric manner. This has to take place at the primary care level – among general practitioners in the private sector and nurses/sisters in the public health sector. “We therefore need safe agents at this level of care,” Professor Wing pointed out.

“This also means that to optimise the legacy effect of good glycaemic control in the younger, newly diagnosed patient, we need to get to normal HbA_{1c} levels of 6.5% safely.”

In the tertiary sector, comprehensive care is required for patients at this level of care because of their extensive

“The evidence would suggest that incretin therapy is much more effective and a safer therapy to change the natural history of diabetes.”



Zaheer Bayat
Endocrinologist
University of the Witwatersrand
Johannesburg

co-morbidities. In addition to glycaemic control, comprehensive care encompasses controlling lipids and blood pressure, while reducing cardiovascular risk with HbA_{1c} levels that are not too stringent ($\pm 8\%$).

“In the future, hypoglycaemia is likely to be regarded as a major cardiovascular endpoint,” he noted.

“In type 2 diabetes care in South Africa, the average lag time before a step-up or intensification of therapy occurs is three years. This means we are missing the benefits of the legacy effect and are arguably doing too little too late,” Professor Wing stressed.

This situation is not helped by the South African guidelines, which are rigid and unfortunately use terminology like ‘preferred’ and ‘alternative’ which are used by funders to ‘disclaim’ the clinician’s and patient’s selection of newer agents,” he said.⁸

There is considerable evidence that earlier and appropriate intervention improves patients’ chances of reaching HbA_{1c} goals. This has led to the development of a clinical approach directed at changing the natural history of type 2 diabetes by targeting insulin resistance and β -cell decline (Table 1).⁹

Table 1. Type 2 diabetes mellitus: Changing the natural history of type 2 diabetes

Insulin resistance	Targeting beta-cell decline
• Antenatal care • Weight loss • Exercise • Metformin • Pioglitazone	• Antenatal care • Glucose toxicity • Lipotoxicity • Oxidative stress • Endoplasmic reticulum (ER) stress • Inflammation • Amyloid

In order to change the natural history of type 2 diabetes, we need to treat earlier, even in the pre-diabetic, use agents that

lower HbA_{1c} safely, address central adiposity and avoid weight gain,” Professor Wing concluded.

Are all incretins equal?

The development of incretin mimetics and DPP-4 inhibitors has evolved over the past 20 years, based on the much earlier observation of the incretin effect.¹⁰ We still understand little regarding the loss of incretin function in type 2 diabetes.

The peptide GLP-1 has numerous effects on target organs: in the brain, it promotes satiety; in the stomach, it slows gastric emptying; in the pancreas, it increases insulin secretion, lowers glucagon and has been shown in animal studies to promote β -cell proliferation and reduce apoptosis. It also has indirect effects on the liver (increased glycogen synthesis and reduced glucose production) and muscle tissue (increased glucose uptake).

Structurally different

The two incretin mimetics are structurally different. “Exenatide differs markedly

from human GLP-1, while liraglutide closely matches the human GLP-1 structure,” Dr Bayat pointed out.

The structures of the DPP-4 inhibitors are also different, translating into very different pharmacodynamic profiles.

Insulin mimetics in clinical trials

Liraglutide has been tested in the LEAD programme as monotherapy with diet and exercise and through the whole continuum of combination treatment, including dual and triple therapy with insulin. Results are summarised in Table 2.

The LEAD-6 study, which entailed a head-to-head comparison with exenatide, provides important data on differences between these two agents. While both lowered HbA_{1c} effectively, liraglutide had a greater effect in lowering FPG, and caused less nausea and post-prandial

hypoglycaemia. Drug concentrations of liraglutide were also more consistent than those of exenatide (liraglutide dosage 1.8mg; exenatide dosage 10g twice daily).

Table 2. Overall summary of LEAD studies

Patients treated with liraglutide as monotherapy or as add-on to one or two oral antidiabetic agents experience:

- Sustained HbA_{1c} reductions, up to 1.5%
- Reductions in fasting plasma glucose
- Clinically relevant and maintained weight reductions
- Reductions in systolic blood pressure
- Minimal hypoglycaemia
- A well-tolerated treatment; low and transient incidence of nausea



Wolfgang E. Schmidt, M.D., Ph.D.
Professor of Medicine and Chair,
Director, Department of Medicine
Chief, GI/Hepatology &
Diabetology Services
St. Josef-Hospital
Germany

Beyond glycaemic control – and composite endpoints

“Evidence of the effectiveness of liraglutide comes from a series of studies (LEAD 1-6) covering the use of this GLP-1 receptor agonist across all stages of the natural course of type 2 diabetes,” Professor Schmidt noted.

In a meta-analysis of these studies, early use of liraglutide achieved a greater change in HbA_{1c} than late use in patients with diabetes of longer duration.¹²

Liraglutide use was also not associated with hypoglycaemia or weight gain in these clinical trials. “There is, in fact, in-built protection against hypoglycaemia,” Professor Schmidt pointed out.

Importantly, liraglutide also improves β -cell function, mainly as a result of the resensitisation of the β -cells to glucose.

Weight loss

Seventy-five percent of patients lose weight on liraglutide (except where it is used with a sulphonylurea) and a quarter of these patients achieve very significant weight loss – an average of 7.7kg while on liraglutide therapy. “It is important to note that in the higher BMI patients, weight loss is even more significant. This can be a very useful tool to re-motivate and re-educate your patients; they are encouraged by the treatment-induced weight loss and will respond better to diet and lifestyle advice,” Professor Schmidt pointed out.

Liraglutide versus sitagliptin

In a head-to-head comparison of liraglutide versus sitagliptin,¹¹ more patients got to target with liraglutide and weight loss was three times higher. Minor hypoglycaemia was reported by very few patients using either of the medications. Safety and tolerability were similar with both agents.

“These studies emphasise some of the differences between incretin mimetics and DPP-4 inhibitors. Clinicians should choose the appropriate agents for individual patients,” Dr Bayat advised.

“With regard to pancreatitis and cancer risk, international expert groups such as the ADA/EASD and IDF agree that there are currently no safety signals that warrant modification or withdrawal of treatment with GLP-1s,” Dr Bayat concluded.

Two-thirds of the weight loss was fat tissue, primarily visceral fat. The mechanism of weight loss has been shown to be related to activation of the postrema area of the brain, an area outside the blood brain barrier (BBB), resulting in appetite suppression via the hypothalamus.

Cardiovascular effects

Liraglutide reduces systolic blood pressure significantly (2-5mmHg) within the first two weeks of treatment; this occurs before weight loss and is evident regardless of whether patients are treated or untreated with antihypertensive agents.¹³ “The mechanism is likely to be vasodilation and a pro-diuretic effect,” Dr Schmidt noted.

It is important to note that all GLP-1s tend to increase the basal heart rate by approximately four beats/minute. “This is an unwanted effect that can be partially counteracted with beta-blockers, although this does not work for all patients,” Dr Schmidt said.

In summary, the GLP-1 agonists assist more patients to reach target glycaemic control without hypoglycaemia or weight gain and with a drop in systolic blood pressure. “Further cardiovascular assessment of these agents will only be possible after the results of the cardiovascular outcome studies become available, e.g. those of the LEADER trial of liraglutide in 2018,” Professor Schmidt added.

Concluding this review, Professor Schmidt provided clinical guidance as to

which patients would benefit most from GLP-1 agonist therapy (Table 3).

Table 3. Which patient will benefit most from GLP-1 based incretin therapy?

	Comment
Patients not achieving glycaemic control on metformin monotherapy or with a high HbA _{1c} at diagnosis	Try early or initial combination: metformin
Patients with intolerance of or contraindications to metformin treatment	Try mono- or alternative combination therapy: sulphonylurea, pioglitazone, insulin
Patients with recurrent hypoglycaemia on existing sulphonylurea treatment and risk groups: taxi driver etc.	Substitute sulphonylurea! No risk of hypoglycaemic episodes!!
Patients at all ages and stages of disease	Early better than late!!
Obese and lean patients with type 2 diabetes	
Patients who want and need to lose weight	Metformin + GLP-1 analogue



MAK Omar
Endocrinologist
Durban

Everyday clinical use of GLP-1s outside clinical trials

In this presentation, Professor Omar pointed out that clinical trials, even the best prospective, double-blinded, randomised trials do not always meet everyday clinical expectations.

The results of the LEAD clinical trial studies of liraglutide were compared to an everyday clinical situation in an observational trial (EVIDENCE) conducted in France.¹⁴ This study included more than 3000 patients and monitored HbA_{1c}, FPG, body weight change and long-term safety. Patients were typical of those seen in an average diabetic practice.

At the end of two years, 64% of patients were still receiving liraglutide and remained in the study (50% on 1.2mg; 50% on 1.8mg). The reductions in HbA_{1c}, FPG and body weight were within the

range of clinical trial expectations, as was the 40% of patients who achieved HbA_{1c} levels less than 7%. Major and minor hypoglycaemia was extremely rare – 0.1% and 4.4% respectively – while gastrointestinal disorders were reported by 8.6% of the patients. The incidence of acute pancreatitis was 0.8% per 1000 patient years, less than the background incidence in people with type 2 diabetes.

“In summary, the results suggest that the clinical trial data for liraglutide translate into similar therapeutic benefits in routine clinical practice, with the limitation in this study being the exclusion of patients who dropped out of the everyday clinical practice study,” Professor Omar concluded.



Jeffrey King
Cardiologist
Sunninghill Hospital
Johannesburg

Potential impact of GLP-1 analogues on cardiovascular risk factors

In his presentation, Dr King appealed for earlier and appropriate treatment with agents that are evaluated on the basis of their scientific evidence and long-term cost/benefit, not only on the single factor of the drug cost.

“The pathogenesis of cardiometabolic risk is complex and treatment needs to be tailored to comprehensively address all cardiovascular risk including diabetes, obesity, hypertension, lipids and lifestyle,” he noted (Figure 5).

“In terms of clinical effects of glucose-lowering drugs, the FDA has issued guidance for cardiovascular safety studies,” Dr King noted. “In the interim, before the results of outcome studies on oral DPP-4 agents and parenteral GLP-1 drugs become available, it is vital not to aggravate known cardiovascular risk factors – e.g. weight, lipids and hypertension – and the adverse effects of glucose-lowering drugs that aggravate weight gain, hypoglycaemia and hospitalisation.

Conflict of interest

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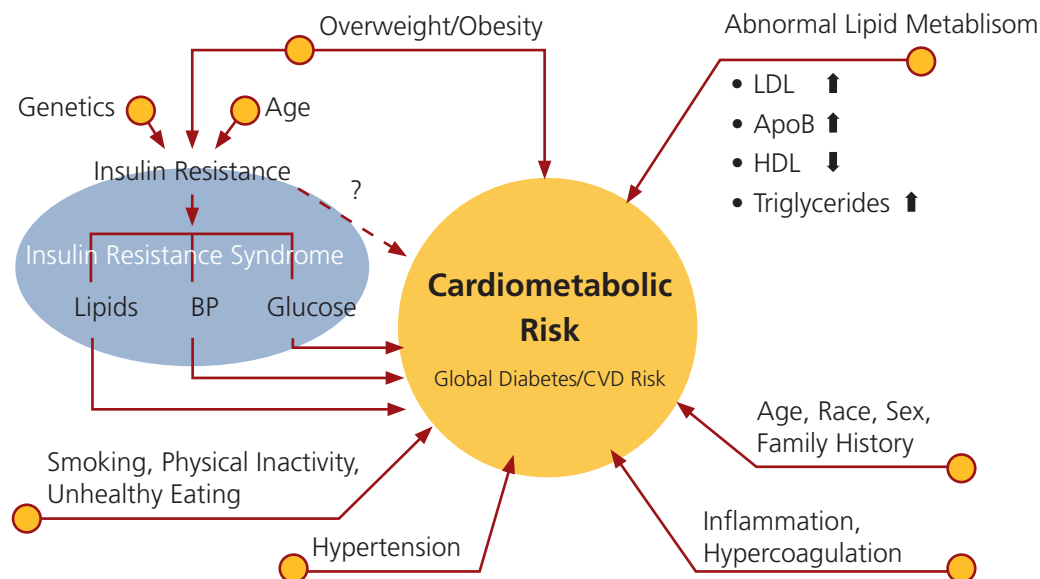


Figure 5. The pathogenesis of cardiometabolic risk

Source: World Health Organization (WHO). A Global Brief on Hypertension. 2013. www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en

“So select therapeutic modalities that do not add to overall cardiovascular risk in your patients,” Dr King concluded.

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