START

the transition to **insulin**

Initiating insulin

Created by South African experts, this unique interactive learning programme will help you to successfully initiate insulin therapy in your patients with diabetes and to confidently manage their continuing care.

What you will gain…

Participation in this fully accredited CPD programme gives you the opportunity to learn how:

- Appropriate selection of patients for insulin therapy can significantly improve prognosis;
- Insulin can be easily and safely initiated by understanding and applying some simple steps; and
- To select the right insulin for the right patient at the right time

How you will learn…

START offers you the opportunity to freely obtain CPD points

- **e-based learning** in five modules – each module earns 3 CPD points
- **Watch** accompanying advice and tips from South African experts
- **Download** practical materials supporting you and your patients when you initiate insulin

Expert panel

Dr Adri Kok
Physician
Johannesburg

President of the International Society of Internal Medicine

Dr Bukiwe Peya
Specialist Physician & Endocrinologist
Alberton

Dr Sundeep Ruder
Endocrinologist
Life Fourways Hospital
Johannesburg

Prof David Segal
Endocrinologist
Wits Donald Gordon Medical Centre
Johannesburg

Dr Zane Stevens
Endocrinologist
Christiaan Barnard Hospital
Cape Town

deNovo Medica

SANOFI

Module editor

Dr Adri Kok
Physician
Johannesburg,
South Africa

President of the
International Society of
Internal Medicine

▶

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*"In South Africa,
we can and must
continue to make
every effort, through
careful stewardship
of resources and
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of multidisciplinary
diabetes teams, to
enable all people
with diabetes, in
both private and
public sector, to
achieve similar
glycaemic control
and improved health
outcomes."*

Dr Stan Landau

Module 1: Initiating insulin

Objectives of this module
- To explain when insulin use is appropriate and essential
- To understand the South African experience

The South African experience

A recent study evaluated HbA_{1c} control in type 2 diabetes mellitus (T2DM) patients attending government health services in South Africa, as compared to those from similar middle-income countries (Indonesia, Peru and Romania).[1] HbA_{1c} levels in these Cape Town clinics were much higher (HbA_{1c} of 10.4%) than the median level across all similar middle-income country sites (HbA_{1c} of 8.7%). At the South African sites, 38% of T2DM patients were treated with insulin, yet only 5% reached the target HbA_{1c} of 7%. The average duration of diabetes in the study was 5 years, and disease complications were already extremely common with many patients suffering from cardiovascular disease, eyesight problems and renal disease.

In an accompanying comment on this study,[2] Dr Stan Landau, Centre for Diabetes and Endocrinology, Johannesburg, appealed to South African clinicians: "In South Africa, we can and must continue to make every effort, through careful stewardship of resources and effective utilisation of multidisciplinary diabetes teams, to enable all people with diabetes, in both private and public sector, to achieve similar glycaemic control and improved health outcomes."

The impact on South Africans of diabetes is seen in recent mortality data (2016) which shows that diabetes is responsible for more deaths than either cerebrovascular or other heart diseases, or HIV (Figure 1).

Cause	%
Tuberculosis	6.5%
Diabetes mellitus	5.5%
Cerebrovascular	5.1%
Other heart disease	5.1%
HIV	4.8%
Hypertensive diseases	4.4%
Influenza and pneumonia	4.3%
Other viral diseases	3.6%
Chronic lower respiratory diseases	2.8%
Ischaemic heart diseases	2.8%
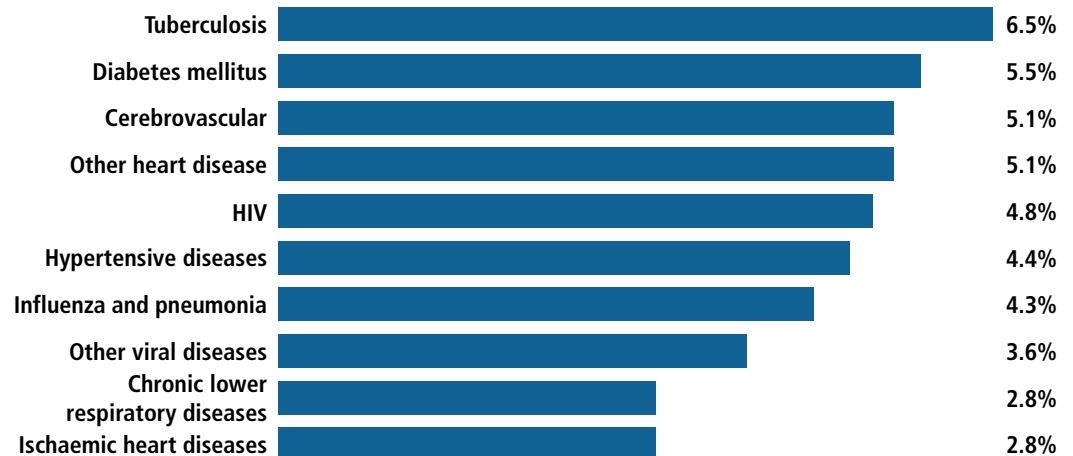
Figure 1. Natural causes of death in South Africa, 2016

While people with diabetes hold major responsibility for their day-to-day management of this chronic condition,[3] the responsibility of the clinician and the multidisciplinary team is to treat appropriately and support, encourage and educate every person with diabetes.

Other modules

Module 2
To provide clinical guidance on insulin choice in South Africa

Module 3
To support clinicians and build confidence in initiating insulin and intensifying therapy

Module 4
To provide tools and guidance in the effective use of patient-centred insulin regimens

Module 5
To provide key clinical messages and tips from expert clinicians that are practical and easy to introduce in daily practice

Ensuring continuum of care

Improve diabetes screening in your practice

A recent evaluation of the continuum of care for cardiovascular disease and diabetes at public sector facilities in two South African communities (rural and peri-urban) showed that, compared to hypertension diagnosis, diabetes diagnosis was better in terms of the percentage of overall prevalence. In this study in a rural area, only 10% of diabetes cases were not identified, although in the higher diabetes prevalence areas of KwaZulu Natal, this rose to 25%.

Of the identified diabetic patients, 75% were treated, but in these communities, only 10% of rural and 26% of urban patients reached target HbA_{1c} of <8% (Figure 2).[4]
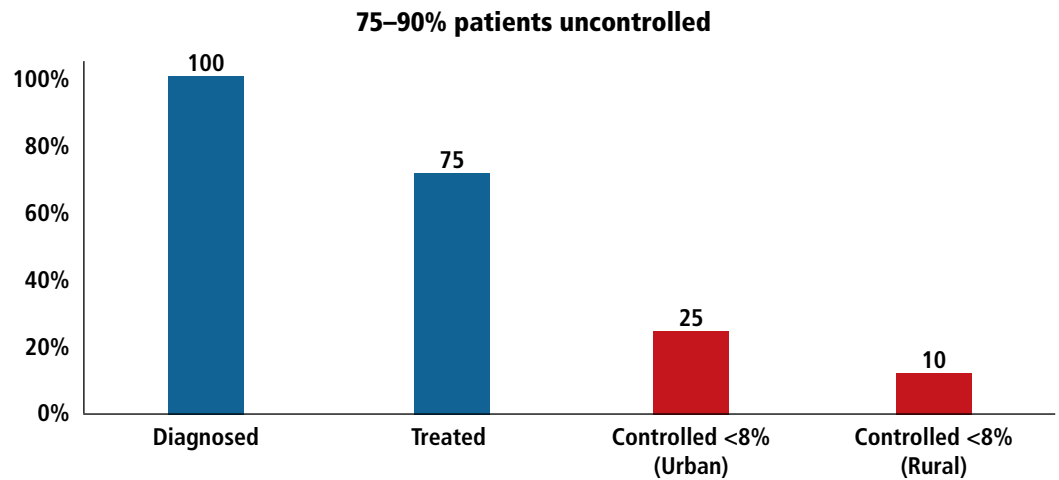
75–90% patients uncontrolled

Figure 2. Healthrise 2018: Contemporary study of diabetes care in the South African public sector – rural and urban environments

In order to expand screening and improve diagnosis, the latest SEMDSA Guidelines provide useful guidance on priorities for diabetes testing in everyday general practice (Table 1).

Table 1. Priority for testing for presence of diabetes in everyday practice

- All patients aged 45 years and older
- This test, if normal, should be repeated every year
- If borderline levels are obtained, test annually e.g. fasting plasma glucose (FPG) 6.1-6.9mmol/L
- In patients on medication with an increased risk of diabetes onset e.g. glucocorticoids, thiazide diuretics and atypical antipsychotics
- In HIV-positive patients, diabetes screening should be done before starting treatment and after 3/12 months of treatment with protease inhibitors (PIs) as well as nucleoside reverse transcriptase inhibitors (NRTIs).

Define the type of diabetes mellitus

Several pathological processes are involved in the development of diabetes. Traditionally, this pathology has been used to classify diabetes into different types, each with their own natural history (Table 2). However, it is important to note that patients with all forms of diabetes are likely to require insulin therapy at some stage of their disease.

Table 2. Classification of diabetes (Summarised from the SEMDSA guidelines) Full SEMDSA guidelines (Click Here)	
Type 1	β-cell destruction, usually absolute insulin deficiency, immune-mediated positive glutamic acid decarboxylase (GAD) and Islet cell antibodies
Type 2	Progressive loss of insulin secretion due to β-cell failure, together with insulin resistance
Diabetes mellitus in pregnancy	New diabetes diagnosed in pregnancy, gestational diabetes mellitus (GDM) 2nd or 3rd trimester of pregnancy, previously diagnosed DM
Specific types	Monogenic syndromes, maturity onset diabetes of the young (MODY), disease of exocrine pancreas e.g. cystic fibrosis, drug or chemical-induced e.g. glucocorticoids, treatment of HIV/AIDS, after organ transplantation

Regardless of the diabetes classification, the most important action in the face of diagnostic uncertainty is: Do not delay treating the hyperglycaemia

While the classification is useful, clinical differences between type 1 diabetes mellitus (T1DM) and T2DM are rarely simple, and 'mixed' diabetes presentations are not uncommon.

However, regardless of the diabetes classification, the most important action in the face of diagnostic uncertainty, is:

- Do not delay treating the hyperglycaemia
- If in any doubt as to classification, refer to a specialist endocrinologist or a local diabetes clinic which may have more extensive experience
- Follow-up on their diagnosis and use this event as a 'self-teaching' opportunity.

Principles of care in T1DM

In T1DM treatment, insulin is <u>the</u> therapy. The clinical principles of caring for this patient are:
- Tight glycaemic control with multiple daily injections
- Targeting $HbA_{1c} \leq 7\%$
- Regular home-based glucose monitoring (see module 4)
- Education and patient support (see module 5)
- Involving family/friends and the school (see module 5).

The patient's journey starts at diagnosis

From the outset, after the initial diagnosis of T2DM, the clinician needs to engage with their patient and describe the typical patient journey of (i) alleviating/modifying symptoms with lifestyle changes and (ii) the introduction of medication including insulin.

This advice is based on data from many studies, including the United Kingdom Prospective Diabetes Study (UKPDS),[5] which has shown that glycaemic control progressively deteriorates over time. The need to intensify therapy to maintain control has been attributed chiefly to progressive loss of β-cell function that occurs over time (Figure 3).[6]

The clinician should explain this natural history of T2DM, which is characterised by increasing β-cell dysfunction against a background of insulin resistance.
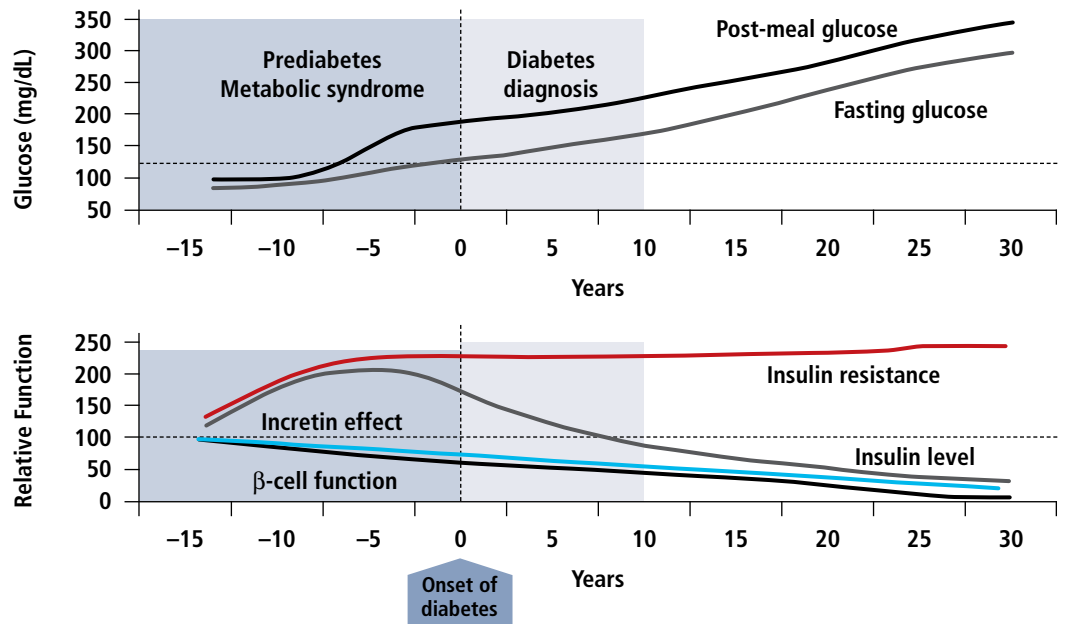
Figure 3. Natural history of type 2 diabetes[6]

Pathogenesis is key to understanding therapeutic agents

β-cell dysfunction combined with insulin resistance in muscle and liver tissue represents the core physiological changes in T2DM. Initially, this pathogenesis was considered to be a simple three-factor induced change, referred to as 'the triumvirate' of causes (Figure 4).

HGP: hepatic glucose production
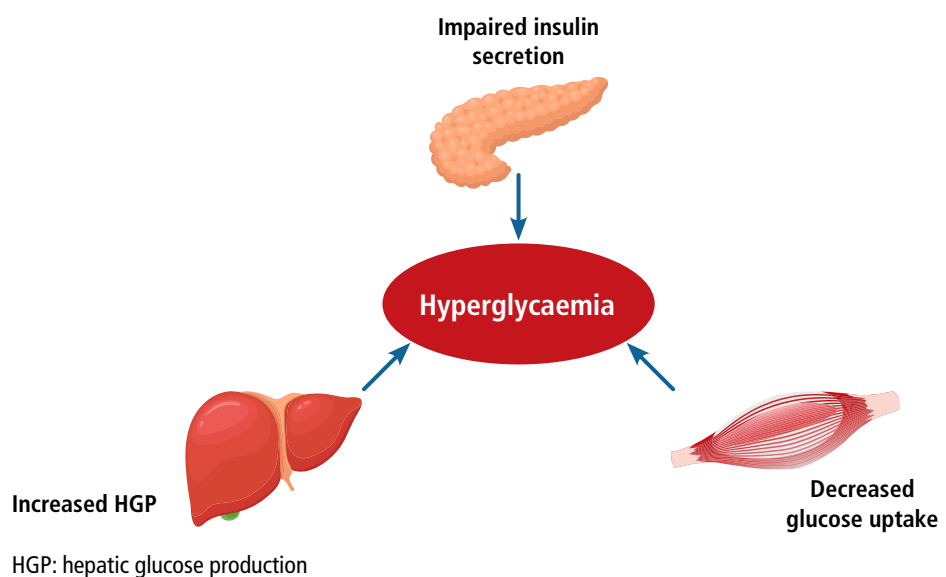
Figure 4. Pathogenesis of T2DM: the triumvirate

Insulin resistance in muscle and liver and impaired insulin secretion represent the core defects in T2DM. Today's increased understanding of the complexity of the disease has led to the development of the modern concept of pathophysiology referred to as the 'octet' (Figure 5), consisting of multiple factors involved in the development of T2DM.[7-9]
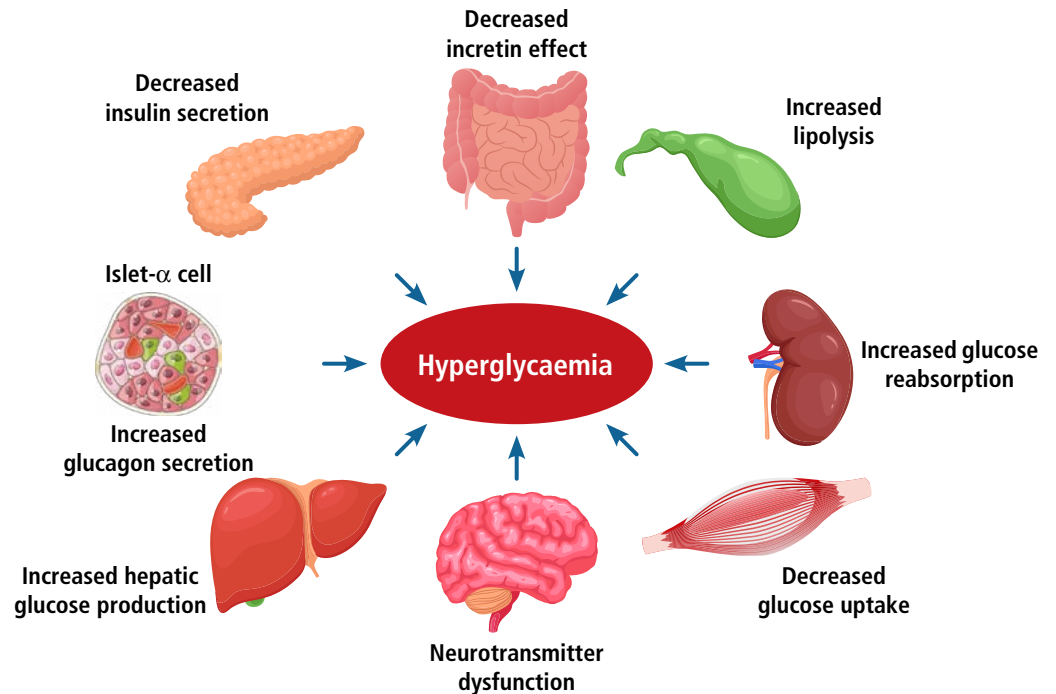
Figure 5. T2DM is a complex disease involving several organs

New oral agents

Newer agents, the dipeptidyl peptidase-4 (DPP-4) inhibitors sitagliptin and vildagliptin, and the glucagon-like peptide-1 (GLP-1) receptor agonists exenatide and empagliflozin, have increased the available options for lowering glucose and reducing the pace of β-cell loss (Figure 6). The latest class of agents is the sodium-glucose co-transporter-2 (SGLT-2) inhibitors, which increase renal excretion of glucose (Figure 7) by blocking the glucose transport mechanism in the kidneys.

Newer agents have increased the available options for glucose lowering
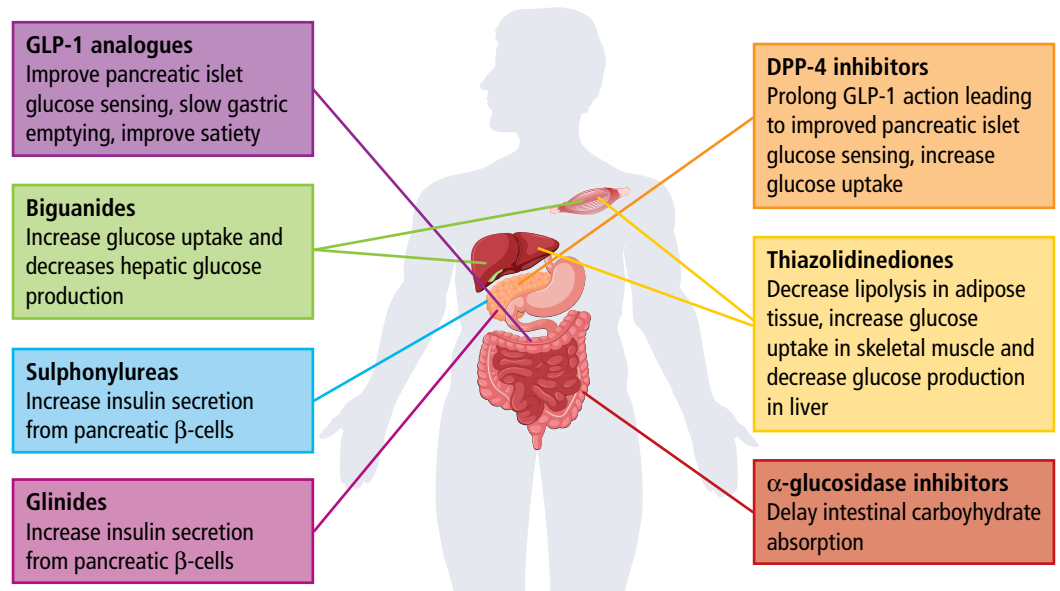
Figure 6. Physiological targets of current oral agents used in the treatment of T2DM[8,9]
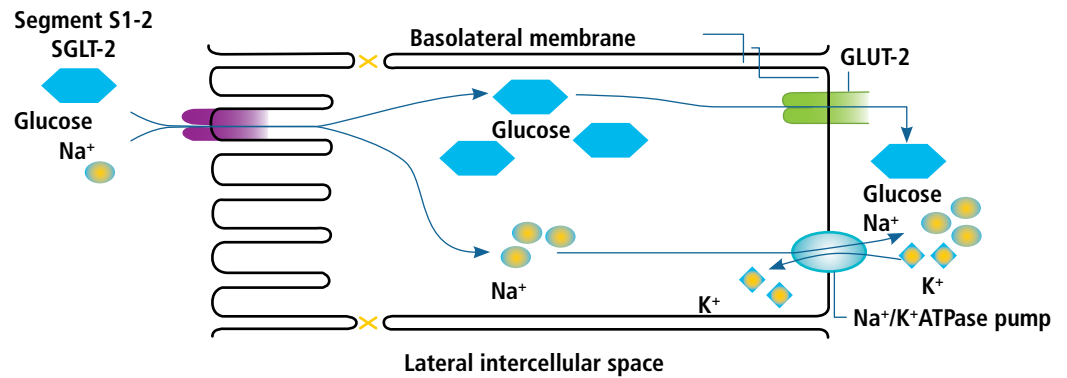
Figure 7. SGLT-2 is a sodium-glucose co-transporter in the kidney

SGLTs transfer glucose and sodium (Na$^+$:glucose coupling ration for SGLT-1=2:1 and for SGLT-2=1:1) from the lumen into the cytoplasm of tubular cell through a secondary active transport mechanism.

Introduce insulin to fulfil the continuum of care

Sustaining the target HbA$_{1c}$ remains key to reducing diabetic complications and, in most T2DM patients, this will demand the introduction of insulin.

For newly diagnosed T2DM patients in good health with reasonable life expectancy, target HbA$_{1c}$ <6.5%

Key principles of individualising HbA$_{1c}$ targets

- For most patients, the recommended HbA$_{1c}$ target is <7% to prevent microvascular and macrovascular complications
- For newly diagnosed T2DM patients in good health with reasonable life expectancy, target HbA$_{1c}$ <6.5%
- For those who have multiple comorbidities, severe vascular or cardiac disease, or advanced renal disease, HbA$_{1c}$ target 7.1-8.5% is reasonable
- HbA$_{1c}$ should ideally be measured every 6 months or, without fail, annually
- These HbA$_{1c}$ targets have been related to target FPG and target post-prandial glucose (PPG) (Table 3).

Table 3. HbA$_{1c}$ and relationship to fasting and post-prandial glucose levels		
Target HbA$_{1c}$	**Target FPG**	**Target PPG**
<6.5%	4-7mmol/L	<8mmol/L
<7%	4-7mmol/L	<10mmol/L
<8%	4-7mmol/L	<12mmol/L

Critical insights that underpin insulin use in T2DM

- Timely achievement of glycaemic control demands insulin usage in all T2DM
- Insulin is the most potent weapon in the fight against high blood glucose
- Clinical inertia, seen throughout the management of this chronic condition, is most pronounced at the point of intensification with insulin.

It is vitally important to maintain the continuum of care in diabetes since a 1-year delay in treatment intensification in uncontrolled patients significantly increases the risk of myocardial infarction (MI), heart failure (HF), stroke and a composite endpoint of cardiovascular events (Figure 8).
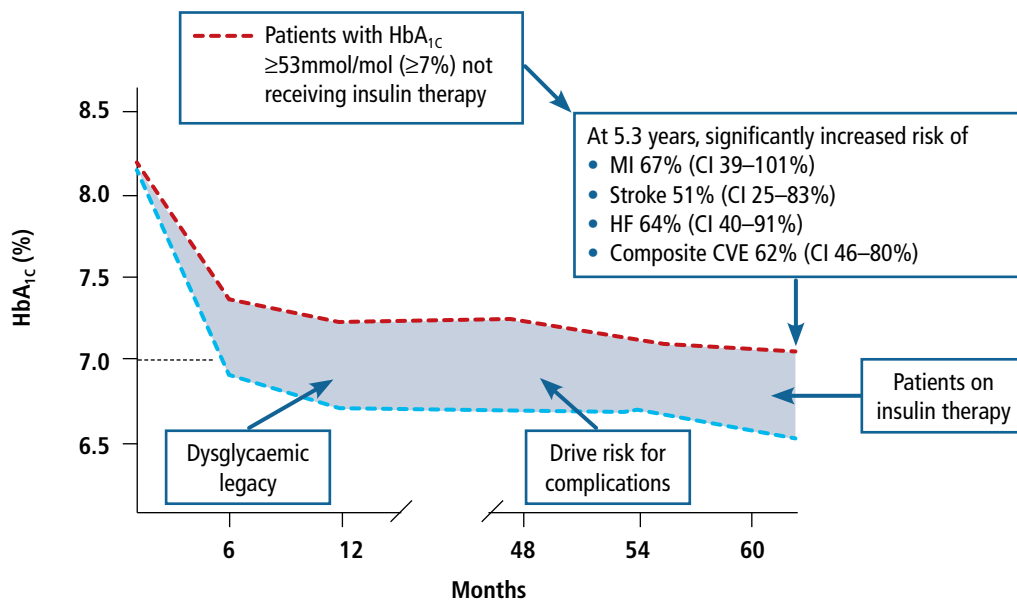
Figure 8. Consequences of delayed intervention in patients without previous cardiovascular disease[10]

Conclusion

Insulin use is essential and must form part of the clinician's approach to diabetes care. Insulins, insulin initiation, insulin intensification and the patient-centred approach to successful insulin therapy will be discussed in the next available modules.

References

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Module 1

Initiating insulin

Complete, scan and email to **cemarir@denovomedica.com** or **admin@denovomedica.com**. Alternatively, you can complete this questionnaire online at **www.denovomedica.com**. Fill in your details using **clear block letters** and mark the answers with a tick (✔).

I agree that my CPD-accredited certificate will be forwarded to my e-mail address. _____
(Online)
(Signature of healthcare professional)

First Name		Profession	
Surname		Telephone	
HPC No.		City	
E-mail		Sales Rep.	

1. Average HbA$_{1c}$ in T2DM patients attending Cape Town state clinics was:

☐ **A** 8.7%   ☐ **B** 10.4%

2. Of these T2DM patients treated with insulin, what percentage reached target HbA$_{1c}$ of 7%?

☐ **A** 5%   ☐ **B** 10.4%   ☐ **C** 38%

3. From South African mortality data (2016), natural causes of death were:

☐ **A** TB > DM > cerebrovascular > other heart disease > HIV > hypertensive disease
☐ **B** TB > hypertensive disease > HIV > cerebrovascular > DM > other heart disease

4. Which of the following patients should be a priority for diabetes testing in everyday clinical practice?

☐ **A** ≥45 years old   ☐ **B** Taking glucocorticoids, thiazide diuretics
☐ **C** Taking atypical antipsychotics   ☐ **D** Taking PIs or NRTIs
☐ **E** All the above   ☐ **F** A, B and D

5. Patients with all forms of diabetes are likely to require insulin therapy at some stage of their disease.

☐ **A** True   ☐ **B** False

6. Regardless of diabetes classification, the most important action is:

☐ **A** Do not delay treating the hyperglycaemia
☐ **B** Refer all recently diagnosed diabetes to a specialised endocrinologist
☐ **C** To involve family and friends

7. At initial diagnosis of T2DM, the clinician and patient should discuss:

☐ **A** Alleviating/modifying symptoms with lifestyle changes
☐ **B** The introduction of medication including insulin
☐ **C** A and B

8. To maintain glycaemic control over time requires therapy intensification. The primary reason for this is:

☐ **A** Immune-mediated Islet cell antibodies   ☐ **B** Progressive loss of β-cell function

9. β-cell dysfunction, and insulin resistance in muscle and liver tissue, are the only core physiological changes that characterise T2DM.

☐ **A** True   ☐ **B** False

10. Which of these oral diabetes agents reduce the pace of β-cell loss?

☐ **A** DPP-4 inhibitors   ☐ **B** GLP-1 receptor agonists
☐ **C** SGLT-2 inhibitors   ☐ **D** All the above
☐ **E** A and B

11. Which of these oral diabetes agents increase renal excretion of glucose?

☐ **A** DPP-4 inhibitors   ☐ **B** GLP-1 receptor agonists
☐ **C** SGLT-2 inhibitors   ☐ **D** All the above
☐ **E** B and C

12. Thiazolidinediones:

☐ **A** Delay intestinal carbohydrate absorption   ☐ **B** Decrease hepatic glucose production
☐ **C** Increase glucose uptake in skeletal muscle   ☐ **D** B and C

13. Which agent(s) increase insulin secretion from pancreatic β-cells?

☐ **A** Biguanides   ☐ **B** Sulphonylureas
☐ **C** Glinides   ☐ **D** B and C

14. Recommended HbA$_{1c}$ target, to prevent microvascular and macrovascular complications in most patients, is:

☐ **A** <6.5%   ☐ **B** <7%   ☐ **C** <8%

15. In the uncontrolled diabetes patient, significantly increased risk of MI, HF and stroke is associated with how long a delay in treatment intensification?

☐ **A** 1 year   ☐ **B** 2 years   ☐ **C** 3 years