OPTIMISING THERAPY AFTER METFORMIN IN TYPE 2 DIABETES

The latest ADA/EASD guidelines[1] of 2012 and the modern trend towards personalised management of type 2 diabetes have placed sulphonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 agonists and insulin within the ambit of agents to use with metformin in two-drug combinations.

"This has focused our attention on the differences among these agents in respect of mechanisms of action, efficacy, cost and, most importantly, safety," Dr Moore noted at the Diabetes Update Symposium held in Cape Town in January.



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Considering the next step after metformin

KEY MESSAGES

- All antidiabetic agents available at stage 2 (sulphonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 agonists and insulin) for use in combination with metformin have a wide margin of safety when used appropriately
- Therapeutic decisions rely more than ever on a personalised approach and making patients partners in decision-making
- The overarching goal is to safely achieve glycaemic control at the earliest possible stage with least risk of side-effects, thereby increasing long-term durability of control and avoidance of future complications.

"Risk of hypoglycaemia and weight gain can be managed by careful selection of insulin formulations and regimens."

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Insulin added to metformin

Insulin is frequently introduced very late in the course of the disease, perhaps because of safety concerns (hypoglycaemia) and weight gain. Yet the advent of basal insulin analogues has provided the opportunity for safe and effective implementation. For example, insulin glargine was shown in a Cochrane analysis review in 1997 to result in a 15% reduction in overall risk of hypoglycaemia and a 35% reduction in nocturnal hypoglycaemia compared to NPH insulin.[2] With regard to safety, a well-designed prospective study (the ORIGIN study)[3] of insulin glargine added to metformin and compared to oral antidiabetic agents in newly diagnosed patients over 6-8 years showed a neutral effect of this insulin on cardiovascular events. The recently reported two-year extension study also showed similar results. The risk of severe hypoglycaemia in the ORIGIN study was relatively low but still greater than in the standard group (1.0 vs 0.3 events per year). The risk of cardiovascular events was increased in those who experienced severe hypoglycaemia. Other potential concerns, particularly with regard to an increased risk of cancer in patients taking insulin glargine, were also set aside by this study.

Sulphonylureas

Early use of second-generation sulphonylureas with metformin in the first six months is warranted after diagnosis of diabetes and in patients with impaired glucose tolerance (IGT). "Later use of sulphonylureas does not have the same robust effect in the long term. In addition, glibenclamide use should be restricted due to the increased risk of hypoglycaemia with this sulphonylurea. Modified-release gliclazide has the greatest amount of trial data with regard to

cardiovascular events and is probably the agent of choice," Dr Moore advised.

Incretins

The development of incretin-based therapies (the GLP-1 receptor agonists (GLP-1s) and DPP-4 inhibitors) is important as they do not cause hypoglycaemia or weight gain.[4] Common side-effects of GLP-1s are common transient nausea, vomiting and diarrhoea, but these symptoms can largely be prevented by taking small meals low in fat and starting with half doses for the first month.

The SAVOR trial of the DPP-4 inhibitor, saxagliptin, showed an increased rate of hospitalisation for heart failure, but no overall increase in cardiovascular events.[5]

DPP-4 inhibitors have a very good safety and tolerability profile, similar to placebo. In the DURATION-2 trial, sitagliptin added to metformin resulted in a reduction of 0.5% in HbA_{1c} (if baseline HbA_{1c} was <9%) and –1.3% if baseline HbA_{1c} was >9%.[6] The incretin-based therapies should be avoided in people with a history of pancreatitis, Dr Moore warned.

Dr Moore concluded that the potential risks for serious rare events with incretin-based therapies remain controversial, although both the FDA and European Medicines Agency (EMA) have reviewed the data on pancreatic and medullary thyroid cancers and have said that no changes in recommendations are necessary until firm data are available.

Early initiation of insulin therapy in type 2 diabetes



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KEY MESSAGES

- The ongoing challenge for physicians is to aim for near normal glycaemic control
- Intensification of therapy is essential to extend β-cell life
- The pathophysiology of type 2 diabetes underscores the value of early insulin therapy
- All cardiovascular risk factors should be treated, including hypertension and dyslipidaemia

"The natural history of type 2 diabetes should guide our therapy, so that therapeutic agents are selected to match each stage of the disease," Professor David Owens proposed to delegates attending the Diabetes Update Symposium held in Cape Town in January.

Early changes in type 2 diabetes

Impaired insulin secretion in type 2 diabetes was first ascribed to loss of β-cell mass and function. Further studies of pancreatic tissue from autopsy cases of IGT and type 2 diabetes showed that this decrease in β-cell volume was actually due to increased apoptosis of the beta cell.[7] Loss of β-cell volume occurred also in tissue from IGT cases, confirming that β-cell loss is an early process in the development of type 2 diabetes.

Studies of the deterioration of glucose homeostasis in type 2 diabetes showed a stepwise change with glucose concentrations increasing sequentially from postprandial to fasting hyperglycaemia with rising HbA_{1c} levels (Figure 1). The first step is a gradual loss in daytime postmeal glycaemic control; the intermediate step an increase in glucose excursions in the morning period (the Dawn phenomenon) with, finally, the loss of fasting control as HbA_{1c} levels increases above 7%.[8]

Accompanying the glucotoxicity in the type 2 diabetic, is an increase in circulating free fatty acids (FFA) resulting in lipotoxicity, a feature of increased oxidative stress, to which the β-cell is also exposed. Oxidative stress leads to endothelial dysfunction, increasing the overall cardiovascular risk of the diabetic patient.[9]

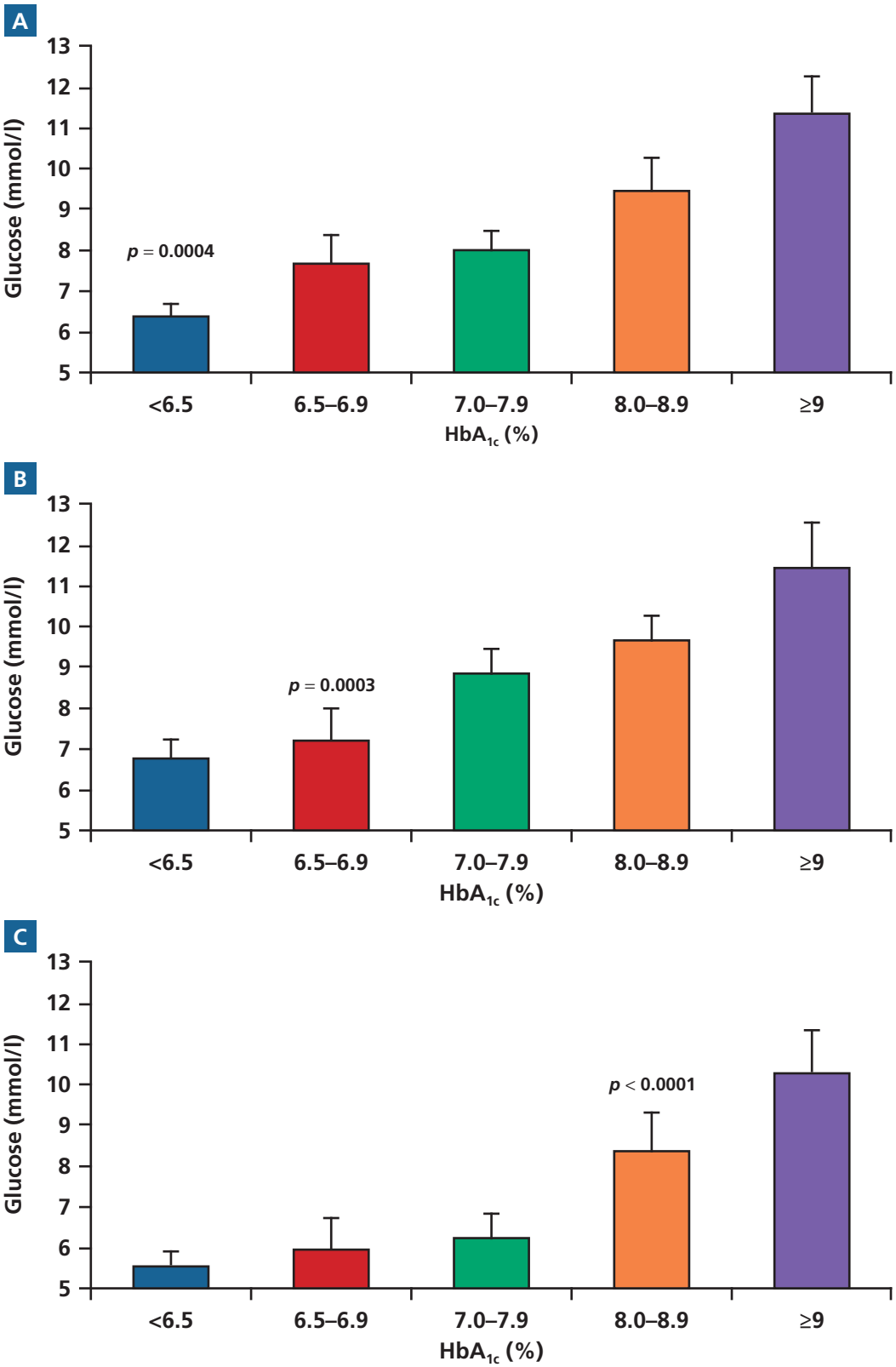


Figure 1. Progressive deterioration of the glycaemic profiles according to HbA_{1c} levels in three periods studied[8]: daytime postmeal period (A), morning period (dawn phenomenon) (B), and nocturnal fasting period (C).

An analysis undertaken by the Emerging Risk Factors Collaboration of data from almost 700 000 people, without a history of myocardial infarction (MI), angina or stroke at baseline, showed that fasting blood glucose concentration is non-linearly related to vascular risk. Furthermore, increased vascular risk in diabetics occurred very early at fasting blood glucose levels just above 7mmol/l.[10] In this meta-analysis, diabetes was found to confer a two-fold excess risk for a wide

range of vascular diseases, including stroke and fatal MI, compared to people without diabetes.

The understanding of the natural history and progression of this disease has been given a firm clinical foundation by the UKPDS series of studies of newly diagnosed type 2 diabetes.

Intensification of therapy using insulin in the UKPDS intensive arm reduced the overall risk of diabetes-related sequelae by 12%, driven by a 25% reduction in microvascular events.[11] Macrovascular events were not reduced, although in an arm's length further 10-year follow-up, cardiovascular reduction reached significance. This early beneficial effect is now referred to as 'the legacy effect'.[12]

Further intensive trials such as ACCORD and VADT illustrated the difficulties in treating diabetic patients who already have longstanding poor glucose control and multiple cardiovascular risk factors. Analysis of data from these intensive trials has shown, however, that intensive glucose control reduces non-fatal MI, but not deaths from coronary events such as stroke and MI.[13]

Where do we stand today with insulin therapy in type 2 diabetes?

A study of insulin therapy undertaken in 12 countries (one each in North America and Asia, the rest in Europe, including Eastern Europe) has shown that insulin is generally prescribed at a late stage, after a mean duration of 10 years of type 2 diabetes, when HbA_{1c} levels are already at 9.5% and 34% of patients have a history of cardiovascular disease.[14] "This certainly reflects clinical inertia in terms of advancement of therapy," Professor Owens noted. "It also reflects barriers, myths and misconceptions on the part of the physician, patient and the health care system".

Experience of early insulin therapy in newly diagnosed type 2 diabetes patients

As early as 1976, Dr RC Turner, the initiator of the UKPDS studies, showed that insulin infusion early in diabetes 'saves and rests' β-cells.[15]

Another early study in the 1980s[16] showed that three weeks of continuous subcutaneous human insulin infusion resulted in improved insulin secretion, enhancement of the second-phase insulin response, as well as improvement of the glucagon response after exogenous insulin therapy. "This is indicative of a very significant increase in β-cell capacity," Professor Owens noted.

Recent use of early intensive insulin therapy with either continuous subcutaneous insulin infusion or multiple daily injections has been explored in newly diagnosed type 2 diabetics in China. Insulin therapy was given in order to attain normoglycaemia for two weeks, thereafter patients were maintained for 12 months on diet and exercise alone. This study showed favourable outcomes, maintenance of β-cell function and protracted glycaemic remission (50%) at year one, following early intensive insulin therapy.[17] Oral hypoglycaemic agents were used in a third-treatment arm and achieved a much lower remission rate of diabetes (26%).

"The patients who did best were those given insulin, as compared to the oral agents. Also heavier patients and patients with a baseline fasting plasma glucose (FPG) of 7-11mmol/l did better than patients with higher FPG levels at the start of the study," Professor Owens pointed out.

An alternative approach of using insulin for newly diagnosed type 2 diabetes patients presenting with raised FPG (>15mmol/l) and HbA_{1c} (>11%) has offered benefits over continuing oral antidiabetes drugs.[18] In this study, patients were hospitalised and treated with intensive insulin injections for 10-14 days. They were then randomised to either insulin injections for six months or to oral antidiabetic agents and then followed for a further six months. "The results were indisputable and showed that a six-month course of insulin therapy achieved glycaemic control and significantly better improvement of β-cell function than oral therapies," Professor Owens pointed out.

In another study of newly diagnosed type 2 diabetes, patients with and without a family history of diabetes were treated with continuous subcutaneous insulin infusion.[19] Both groups showed improved insulin resistance and β-cell function, but these improvements were less significant in patients with a family history of diabetes.

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Basal insulin as early insulin

"The use of subcutaneous infusions of insulin is perhaps not practical, but similar results can be obtained by using basal insulin, although the process of reaching normoglycaemia is slower," Professor Owens noted.[20]

Another important benefit of insulin is its ability to reduce oxidative stress which is not achievable with oral agents.[21] "This is another major modification of the natural history of type 2 diabetes as it lowers the patient's cardiovascular risk," Professor Owens noted.

In a pooled meta-analysis of early versus later administration of basal insulin (insulin glargine), added to metformin, insulin glargine provided efficient glucose control overall with 70% of patients reaching HbA_{1c} levels lower than 7%, with the least weight gain. When insulin was given early, smaller doses were needed and there was a lower risk of hypoglycaemia.[22] This reinforces the ADA/EASD guidelines in respect of initial introduction of basal insulin.

"There are a large series of insulin glargine studies showing the value of this basal insulin; these include the EASIE[23] (insulin glargine versus sitagliptin) in insulin-naïve patients in which I was involved and the recently published EASIE-Extension trial," Professor Owens noted.

The EASIE-Extension trial showed that in patients uncontrolled with metformin-sitagliptin or metformin-glargine, a higher fasting blood glucose predicted greater HbA_{1c} reductions when glargine was added, as compared to sitagliptin.[24] In subjects uncontrolled on six-month dual therapy of metformin-sitagliptin, or metformin-glargine, 50% reached HbA_{1c} levels below 7% within 12 weeks on the added glargine therapy.

The ORIGIN trial also showed the benefit of treating type 2 diabetes patients with a low HbA_{1c} (6.5%) but at high cardiovascular risk with insulin glargine. Good control, maintaining these low HbA_{1c} levels, was achieved with a relatively low dose of glargine and maintained for a five-year period.[25] "Also, 20% of prediabetics maintained their prediabetic status and did not progress to diabetes during the five-year period," Professor Owens pointed out.

In the ORIGIN-GRACE trial involving more than 1 000 people with dysglycaemia and/or cardiovascular disease/risk factors, insulin glargine was used to target normoglycaemia; it reduced carotid intima media thickness (CIMT), whereas n-3 polyunsaturated fatty acid supplementation had no effect on CIMT progression.[26]

There are also other clear cardiovascular benefits to be derived from insulin therapy including improvement in endothelial function as a result of increased antioxidant production and reduction in inflammatory processes.

"In summation, while following an individualised patient-centred approach, there is an ongoing challenge and opportunity to use insulin earlier in type 2 diabetes. There is an opportunity to treat a particular group of type 2 diabetes patients with early insulin: those with an HbA_{1c} above 9% and FPG >11mmol/l.

"The ongoing challenge for physicians is to aim for near normal glycaemic control. Adopt an uncompromising therapeutic insistence on intensification of therapy, consider the pathophysiology of diabetes and treat all risk-factors for cardiovascular disease, including hypertension and dyslipidaemia," Professor Owens concluded.

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