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"POSITION PAPER" TIMELY INSULINISATION IN TYPE 2 DIABETES PATIENTS

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Abstract

The objective of this position paper is to review the current medical evidence and guidelines regarding the treatment of type 2 diabetes (T2DM) and to issue medical recommendations strengthening the timely use of insulin in patients with T2DM uncontrolled on noninsulin therapy. When noninsulin therapy fails to achieve or to maintain HbA1c targets, insulin therapy is required. Timely insulin therapy could provide proper metabolic control that might prevent complications, lead to improvement of life expectancy and quality of life.

key words: *type 2 diabetes, HbA1c targets, timely insulin use*

Diabetes mellitus is a growing international public health problem. The number of people with diabetes in Europe in 2011 is estimated to be 52.6 million, or 8.1%

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of the adult population. New data projected that the number of people with diabetes will rise worldwide to 552 million by 2030, this means that every 10 seconds approximately 3 more people will be diagnosed with diabetes [1]. T2DM is the most common form of diabetes, accounting for more than 90% of cases [2]. T2DM remains the leading cause of cardiovascular disorders, blindness, end-stage renal failure, amputations, and hospitalizations. It is established that the risk of microvascular complications is mainly related to hyperglycaemia, as measured by HbA1c; therefore, this remains an important focus of therapy. In an analysis published in 2010 has shown that diabetes confers about a two-fold excess risk for coronary heart disease, major stroke subtypes, and deaths attributed to other vascular causes [3].

The UK Prospective Diabetes Study has shown that β-cell function progressively deteriorates over time in people with newly diagnosed T2DM, irrespective of lifestyle and existing pharmacological interventions [4,5]. The loss of beta-cell function was assessed to be at least 50% at the time of diabetes diagnosis [6].

Beyond lifestyle modification, hyperglycaemia can be controlled initially with metformin (±sulfonylurea) as the most widely used therapeutic regimen in our region. Recently, incretin-based therapies became more popular as part of the combination therapy. When glycaemic control can no longer be achieved with oral agents, insulin treatment can be started. Adding a single injection of long-acting insulin is widely accepted as the initial step for insulin treatment in patients with T2DM [7]. Early intensive insulin therapy in patients with newly diagnosed T2DM has favourable outcomes on recovery and maintenance of beta-cell function and protracted glycaemic remission as compared to treatment with oral hypoglycaemic agents [8].

According to the last Position Statement of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), the targets recommended for metabolic control in T2DM patients are given in Table 1.

Table 1. Recommended targets for metabolic control in T2DM patients according to the Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), 2012 [9].

HbA1C	< 7.0% (individualized)
Preprandial glucose	<130 mg/dl
Postprandial glucose	<180 mg/dl

It is also mentioned that if monotherapy alone does not achieve/maintain the HbA1c target over 3 months, the next step would be to add a second drug, as shown in Figure 1. The higher the HbA1c, the more likely insulin will be required. When advancing to triple combination therapy (if the HbA1c target is not achieved/maintained over 3 months) the most robust response will usually be achieved by using insulin. Indeed, since diabetes is

associated with progressive beta-cell loss, many patients, especially those with long-standing disease, will eventually need to be transitioned to insulin, which should be favored when the degree of hyperglycaemia (e.g. HbA1c >8.5%) makes it unlikely that another drug will be of sufficient benefit [9].

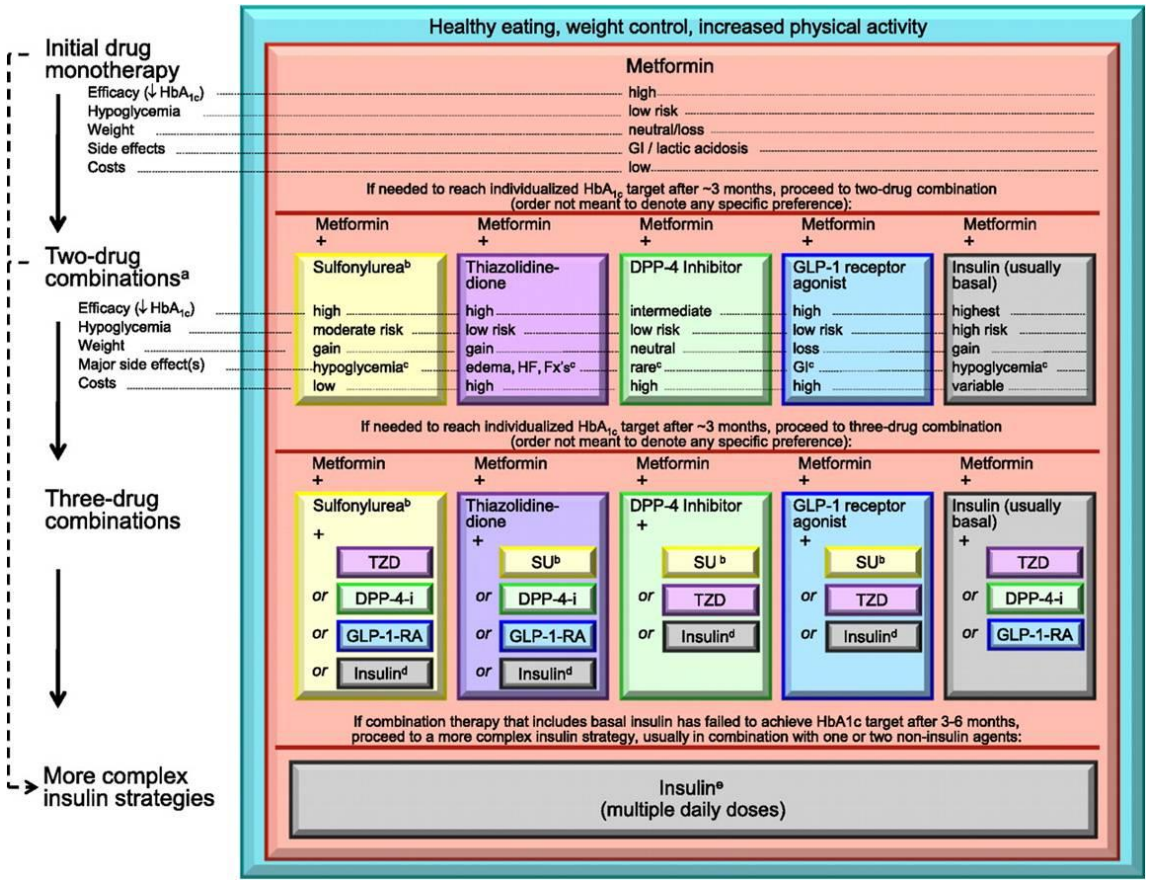

Figure 1. Antihyperglycemic therapy in type 2 diabetes: general recommendations – reproduced from [9]

In a recent study which has included 1139 patients with T2DM the authors examined a wide variety of demographic, clinical, and therapy-related variables in an effort to identify factors that contributed to A1C goal attainment and that were associated with glycaemic response to insulin initiation. They found that the level of A1C prior to starting insulin was by far the single most important factor, accounting for 95% of the discriminatory ability to predict the probability of goal attainment and 96% of the explainable variance in A1C change. Shorter diabetes duration also was independently associated with A1C and greater A1C reduction. Thus, the authors concluded that initiating insulin earlier in the course of oral agent failure seems to improve glycaemic goal attainment as well as to improve glycaemic response [10].

Expert Position

- A certain number of patients with T2DM will require insulin during the natural history of the disease.
- When noninsulin therapy fails to achieve or to maintain HbA1c targets, insulin therapy is required.

- T2DM should be considered as a progressive, chronic disease. At the time of the diagnosis, nearly 50% of the beta-cell function proved to be lost. Accordingly, treatment options with a protective effect on beta-cell dysfunction/loss are of great importance.
- Based on several experimental and indirect clinical data, early insulin treatment might result in protection of residual beta-cell function when treatment with metformin-monotherapy fails.
- It seems plausible to use timely insulin therapy especially in young patients with long life expectancy but poorly controlled on maximal tolerated doses of noninsulin therapy.
- Timely insulin therapy could provide proper metabolic control that might prevent complications, lead to improvement of life expectancy and quality of life.

Duality of Interest: All the authors are members in Sanofi Advisory Board

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