INSULIN THERAPY FOR TYPE 2 DIABETES MELLITUS AND CARDIOVASCULAR RISKS

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Abstract*. Insulin therapy increased cardiovascular (CV) risk and mortality among type 2 diabetes (T2D) patients in several recently reported clinical outcomes trials. To assess whether this association is causative or coincidental, PubMed searches were used to query the effects of insulin therapy for T2D on CV health and longevity from large-scale outcomes trials, meta-analyses, and patient registry studies, as well as basic research on insulin's direct and pleiotropic actions. Although several old studies provided conflicting results, the majority of large observational studies show strong dose-dependent associations for injected insulin with increased CV risk and worsened mortality. Insulin clearly causes weight gain, recurrent hypoglycemia, and, other potential adverse effects, including iatrogenic hyperinsulinemia.*

Keywords: *Cardiovascular outcomes; Hypoglycemia; Iatrogenic hyperinsulinemia; Insulin safety; Type 2 diabetes.*

A number of landmark randomized clinical trials established that insulin therapy reduces microvascular complications (1,2). In addition, recent follow-up data from the U.K. Prospective Diabetes Study (UKPDS) suggest that early insulin treatment also lowers macrovascular risk in type 2 diabetes (3). Whereas there is consensus on the need for insulin, controversy exists on how to initiate and intensify insulin therapy. The options for the practical implementation of insulin therapy are many. In this presentation, we will give an overview of the evidence on the various insulin regimens commonly used to treat type 2 diabetes.Secondary analyses of the aforementioned

landmark trials endeavored to establish a glycemic threshold value below which no complications would occur. The UKPDS found no evidence for such a threshold for A1C, but instead showed that better glycemic control was associated with reduced risks of complications over the whole glycemic range ("the lower the better") (4). For the management of type 2 diabetes, this resulted in the recommendation to "maintain glycemic levels as close to the nondiabetic range as possible" (5). However, in contrast to the UKPDS, the Kumamoto study observed a threshold, with no exacerbation of microvascular complications in patients with type 2 diabetes whose A1C was <6.5%, suggesting no additional benefit in lowering A1C below this level (2). Moreover, the intensive glycemia treatment arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, targeting A1C <6.0%, was discontinued because of higher mortality in this group compared with the standard therapy group targeting A1C from 7.0 to 7.9% (6). Therefore, the American Diabetes Association (ADA) recommendation of an A1C target <7.0% seems the most balanced compromise at present (7).Another important conclusion of the UKPDS was that the risk reductions in long-term complications were related to the levels of glycemic control achieved, rather than to a specific glucose-lowering agent (1). This has left health care providers and patients with the difficult task of choosing from the wide variety of glucose-lowering interventions currently available. When considering the effectiveness, tolerability, and cost of the various diabetes treatments, insulin is not only the most potent, but also the most cost-effective intervention (8). Although insulin has no upper dose limit and numerous trials established that glycemic goals could be attained by using adequate insulin doses (5,8), in clinical practice, many patients have elevated A1C levels and experience years of uncontrolled hyperglycemia (9). Moreover, the Steno-2 Study demonstrated that only a minority of patients reached the intensive A1C target of <6.5%, compared with a far greater percentage of patients who reached the respective intensive treatment goals for blood pressure and serum lipid levels (10). Apparently, the initiation and intensification of insulin therapy is not as straightforward

and simple as we had hoped. In accordance with the ADA and the European Association for the Study of Diabetes (EASD) (5,7), we advocate an algorithmic approach for the start and adjustment of insulin treatment, with modifications for individual patients as needed. This review contains an overview of the currently available insulin preparations and an outline of the merits and disadvantages of the various regimens commonly used for the initiation and intensification of insulin therapy in patients with type 2 diabetes. Our aim is to assist clinicians in designing individualized management plans for insulin therapy in type 2 diabetic patients. Insulin therapy with the conventional mealtime and basal insulin preparations has many shortcomings. First, the absorption of regular human insulin from the subcutaneous tissue is slow, and the metabolic action takes effect only 30–60 min after injection and peaks after 2–3 h. Consequently, treatment with regular insulin is associated with postmeal hyperglycemia and an increased risk of late-postprandial hypoglycemia. Second, the conventional basal NPH insulin has a distinct peak glucose-lowering effect, has a duration of action considerably shorter than 24 h, and is absorbed from the subcutaneous tissue at variable rates. These pharmacodynamic limitations predispose users to elevated glucose levels before breakfast and nocturnal hypoglycemia (11,12). To overcome these difficulties, insulin analogs with a modified amino acid sequence from the human insulin molecule were developed. The three rapid-acting analogs (aspart, glulisine, lispro) are absorbed more quickly than regular insulin because of reduced self-association. Their onset of action is within 15 min after subcutaneous injection, and they have a faster and greater peak action. Insulin glargine, the first long-acting insulin analog to reach the market, was initially proclaimed to have the ideal “peakless,” nearly 24-h duration of action (13). However, these initial pharmacodynamic studies raised some criticism, and it should be concluded that there is no such thing as a “peakless” insulin preparation (12,14,15). Nevertheless, both long-acting insulin analogs (detemir and glargine) have a limited peak effect and a longer mean duration of action compared with NPH insulin (with glargine having a slightly

longer action than detemir [13,16,17]).It was expected that the rapid-acting and long-acting analogs, which more closely approximate physiological insulin secretion, would confer important clinical benefits (11). With respect to type 2 diabetes, the topic of this review, it is important to note that most patients with type 2 diabetes have residual endogenous insulin secretion in the context of insulin resistance. Therefore, the rationale for imitating the insulin secretion pattern of human physiology is less convincing than in type 1 diabetes. Indeed, in patients with type 2 diabetes, the rapid-acting analogs were not found to be superior to regular insulin in reducing A1C levels or rates of overall hypoglycemia (18). The clinical benefits of the long-acting insulin analogs compared with NPH insulin are limited to a reduction in (nocturnal) hypoglycemia (19).This paper seeks to interpret findings of CV outcome studies associated with insulin treatment for T2D, particularly regarding increased risks of CV events and/or mortality. We evaluated prospective trials and patient registry studies found on PubMed that reported long-term outcomes in T2D patients for insulin (primarily) and alternate therapies (secondarily). The following discussion includes a review of the published literature; no independent meta-analysis was performed. Additionally,Insulin linked to CV risk and all-cause mortality.Despite a century of improvements in disease management, nearly 2 of 3 patients with T2D still die from CV disease.1., 2., 3., 4. Fortunately, we are entering a new and exciting era for T2D management. Large randomized trials have recently demonstrated that several agents, including two sodium-glucose transport protein-2 (SGLT-2) inhibitors, two glucagon-like peptide-1 (GLP-1) receptor agonists, and pioglitazone effectively reduce risk of adverse CV events in T2D.11., 12., 13., 14. Therefore,Recurrent asymptomatic hypoglycemia (about half of hypoglycemic episodes are unrecognized) is common in insulin-treated patients and can set into motion or exacerbate existing organ damage.9., 55. The increased risk of mortality with insulin treatment may persist for up to 5 years after severe hypoglycemic events.56 Hypoglycemia potently stimulates catecholamine release and prolongs the QT interval, which can precipitate arrhythmias and increase

risk of adverse CV events.2 Additionally,First do no harm: favorable outcomes with noninsulin therapies.We now have T2D drugs that have been shown to lower risks of MI, stroke and CV death while lowering A1c levels.11., 12., 13., 14. Clinical outcomes for most non-insulin therapies, particularly the newer therapies, have generally been associated with favorable or neutral outcomes, even in advanced T2D. Selected results are shown in Table 1. Metformin's CV risk lowering has already been discussed. Notably, metformin led to improved outcomes in the same T2D trials in which insulin cohorts fared.Evolving treatment paradigms in T2D.Due to concerns about potential insulin-mediated CV risks, some experts have proposed that the assessment of patient risk factors be performed before prescribing insulin therapy in T2D.85., 86. In 2016, the American Diabetes Association and other key societies called for the deconstruction of current T2D guidelines to make room for more precise and patient-centered algorithms.87 Preference should be given to use evidence-based agents shown to reduce CV risk, such as empagliflozin,Potential for physical activity, exercise and fitness to reduce obesity and insulinAlthough this paper focuses on the toxicity of injectable insulin, endogenous insulin also plays a major role in promoting obesity and its adverse effects on CV diseases, including CHD and HF.89., 90. Reducing simple sugars and carbohydrates in the diet can improve insulin sensitivity.91., 92. Increasing physical activity, exercise, and cardiorespiratory fitness will also reduce T2D, along with the CV complications in cardiometabolic disease and T2D, which should be emphasized throughout.

Conclusions. Insulin therapy for T2D causes hyperinsulinemia, hypoglycemia and weight gain, and is increasingly associated with adverse CV outcomes. Insulin therapy should be relegated to a lower tier status in treatment algorithms for T2D, and should be used only when absolutely necessary to achieve glycemic control. Numerous T2D drugs have been proven to reduce adverse CV outcomes and mortality, and also reduce weight; these agents should be used in preference to insulin.

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