

Cardiovascular Safety of Incretin-Based Drugs in Type Two Diabetes Mellitus Patients

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Abstract

Diabetes Mellitus (DM) is a chronic metabolic disease with complicated complex pathogenesis. Frequency of newly DM arises worldwide and associated with steadily increased morbidity and mortality due to DM-related complications. The incretin-based drugs are posed as remedies modulated effects of natural incretin hormones: GLP-1 (glucagon-like peptide 1), GIP (glucose-dependent insulinotropic peptide) and dipeptidyl peptidase enzyme 4 (DPP4). At the beginning of the era of the incretin-based therapy the treatment of T2DM with GLP-1 analogs and DPP-4 inhibitors was introduced. In fact, incretin-based drug exposure was associated with clinically significant cardiovascular protection. However, it is not known whether all GLP-1 analogs and DPP-4 inhibitors are similar in their capacities to improve cardiovascular outcomes or not that is required a continuous studies in this direction.

Keywords: Cardiovascular risk; Diabetes mellitus; Dipeptidyl peptidase-4 inhibitors; Glucagon-like peptide-1 analogs; Incretin-based drugs

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Diabetes mellitus (DM) is becoming as serious public problem that have reached pandemic level [1]. It is well known that DM-related complications affected heart; kidney, liver, muscles and vasculature are considered as one of the major cause of cardiovascular mortality worldwide [2]. In this context, achieving of full control of hyperglycemia allows to suppress the risk of the all-cause and cardiovascular mortality in Type 2 Diabetes Mellitus (T2DM) in follow-up [3]. However, the different intervention strategies can lead to expectant and sometimes bidirectional outcomes in T2DM patients.

The early clinical trials have been shown that almost all antidiabetic medications were associated with worsening of cardiovascular risk in T2DM patients compared to no antidiabetic exposure [4]. However, an increased likelihood of newly incidences of Chronic Heart Failure (CHF) was found when there was a perception of sulphonylureas (Odds Ratio [OR] = 1.17; 95%CI = 1.00-1.37) and metformin monotherapies (OR = 1.22; 95%CI = 0.97-1.52). It was also determined 1.6-fold increased risk of CHF with combinations of metformin and sulphonylureas (OR = 1.62; 95%CI = 1.30-2.02), at 2.2-fold increased risk with oral triple combination exposure (OR = 2.16; 95%CI = 0.96-4.86) and a 1.5-fold increased risk of insulin treatment in comparison with no exposure (OR = 1.52; 95%CI = 1.06-2.17) [4]. Later AzoulayL, et al. [5] have analyzed the T2DM cohort of 84 231 users of oral hypoglycemic agent exposure (metformin and sulphonylureas) of whom 14 996 died from any cause during a mean of 4.3 years

of follow-up and did not find a negative effect of a combination of sulfonylureas and metformin, as well as metformin monotherapy on death from all causes when compared with sulfonylurea monotherapy. At the same time, the risk of incident strokes in patients with T2DM treated with thiazolidinediones appears to be similar with other oral hypoglycemic agents [6], while thiazolidinediones may increase the risk of acute myocardial infarction and CHF [7]. Moreover, several thiazolidinediones, such as rosiglitazone compared to pioglitazone, were not equivalent in terms of risks of death due to cardiovascular reasons [8]. The explanation of overall clinical harm of antidiabetic medications in T2DM patients might suggest as a result, an inadequately controlled glucose metabolism, including hypoglycemia, fluid retention, and increased weight gain [9, 10]. In fact, cardiovascular complications associated with antidiabetic medications in T2DM patients were reported to have a statistically significant effect for long-term survival, quality-of-life and well-being [11]. Novel treatment strategies were required to be improving clinical outcomes in T2DM patients.

The incretin-based drugs are defined as specific modulators of endogenous effects of natural incretin hormones: GLP-1 (glucagon-like peptide 1), GIP (glucose-dependent insulinotropic peptide) and dipeptidyl peptidase enzyme 4 (DPP4), which rapidly degrade them in the systemic circulation. Incretins are able controlling appetite, reducing glucagon production, stimulating insulin secretion, decreasing postprandial glucose level, improving lipid profile through circulating phospholipase activity, and providing important metabolic tissue effects, such as inhibition of liver steatosis and fibrosis, mediation of neuronal and cardiovascular protection.

As well-known incretin-based therapy was introduced for the treatment of T2DM with GLP-1 analogs and DPP-4 inhibitors that have the important advantages before old antidiabetic drugs associated with minimal or no influence on weight gain and low risk of hypoglycemia [12-14]. There are data that DPP-4 inhibitors may suppress a sympathetic activation, vascular smooth cell proliferation, and oxidative stress activity in various cells, as well as contribute in neuropeptide Y-mediated vascular

responses [15]. The multiple favorable nonglycemic functions were described in GLP-1 analogs [16]. On the other hand, Butler PC [17] reported about increase in pancreas weight and pancreatic dysplasia in individuals with T2DM exposed GLP-1 based therapy with DPP-4 inhibitors and GLP-1 analogs. Therefore, rarely incidences of pancreatitis related DPP-4 inhibitors and GLP-1 analogs exposure are expected. Although American Diabetes Association and the European Association for the Study of Diabetes recommended incretin-based drugs for combined therapy with old antidiabetic drugs, such as metformin, along with diet and exercise, incretin-based drugs may be useful in monotherapy as a component of contemporary patient-centered approach in T2DM. However, HbA1c decreased on average by 0.9-1.0% (9 mmol/mol) when incretin-based drugs given as monotherapy with diminished risk of hypoglycemia. It is considered that incretin-based drugs are serious therapeutic alternatives before old antidiabetic drugs when favourable pleiotropic effects are expected.

Because the risk of hypoglycemia in T2DM patients treated with DPP-4 inhibitors and GLP-1 analogs is diminished, it has been expected that exposure of these drugs may lead to decrease a risk for adverse outcomes, including falls leading to bone fracture, seizures, cognitive dysfunction, and prolonged hospital stays. Therefore, DPP-4 inhibitors and GLP-1 analogs may have a direct cardio protective effect and probably are able to improve survival among subjects with T2DM. Overall, incretin-based drugs might contribute in the cardio protective effects by various mechanisms, multiple factors, including improving insulin resistance and dyslipidemia, suppression of oxidative stress, as well as modulation of adipose tissue dysfunction, dysfunctional immunity and anti-apoptotic properties [18]. Therefore, slight but significant reduction in systolic blood pressure associated with exposure of DPP-4 inhibitors and GLP-1 analogs was reported [19].

The clinical relevance of nonglycemic effects of incretin-based drugs are required evidences in randomized trials. A large number of randomized clinical studies have also evaluated the cardiovascular safety of novel incretin-based drugs [10]. The main issue of the obtained results is that novel medications

might produce favourable cardiovascular effects, including potential antiatherogenic properties without expecting negative effect of CHF manifestation [20]. Despite DPP-4 inhibitors improve glycemic control and prevent hypoglycemia, they appear not to be similar to reduce cardiovascular risk in T2DM patients. Indeed, results of the SAVOR-TIMI-53 study (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction) revealed that DPP-4 inhibition with saxagliptin did not increase or decrease the rate of ischemic events, although the rate of hospitalization for CHF was increased [21]. Later, Yu OH et al. [22] reported that current use of incretin-based drugs (GLP-1 analogs and dipeptidyl peptidase-4 inhibitors) was not associated with an increased risk of CHF (adjusted OR = 0.85 [95% CI = 0.62 to 1.16]). The differences between DPP-4 inhibitors and GLP-1 analogs in cardiovascular safety are discussed while their ability in protective or even regenerative capacity shows to be promised.

In conclusion, the results of the large-scale randomized controlled studies are suggested that incretin-based drugs may provide a clinically significant cardiovascular protection. However, we did not know whether all GLP-1 analogs and DPP-4 inhibitors are similar in their capacities to improve cardiovascular outcomes or as minimum modulate a high cardiovascular safety of T2DM person. More clinical investigations are required to be resolving new questions among this old new question.

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