EDITORIAL

Efficacy and Cardiovascular Safety of Antidiabetic Medications

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Abstract: Diabetes mellitus (DM) has already affected one in every eleven person in the global population, and the disease prevalence continues to increase because of the obesity pandemic. Even with the availability of a multitude of antidiabetic medications for optimal glycaemic control, cardiovascular morbidity and mortality were not largely altered until recently when newer antidiabetic drugs such as glucagon-like peptide-1 receptor analogues (GLP-1RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors were introduced. Cardiovascular safety of antidiabetic drugs has also been a hot topic for global scientific debate after the US Food and Drug Administration (FDA) enforced restrictions on Rosiglitazone in 2010 with the suspicion of increased mortality and myocardial events (with subsequent uplift of the ban on the drug in 2013 following the emergence of additional evidence on safety). After this debate, all antidiabetic should go through rigorous safety checks with cardiovascular outcome trials (CVOTs). Recent CVOTs with GLP-1RAs and SGLT2 inhibitors have revealed markedly positive outcomes that have changed the landscape of diabetes management across the world. Thus, the therapeutic algorithm for optimal management of DM should consider not only the glycaemic control efficacy of the individual antidiabetic agent but also the cardiovascular safety and modifications in other anticipated long-term DM complication profiles. Therefore, it is imperative to critically appraise the efficacy and cardiovascular safety of all antidiabetic drugs to improve the scientific practice of our diabetes care globally. This Journal issue, "Efficacy and cardiovascular safety of antidiabetic medications," provides readers the back-up of up to date evidence.

Keywords: Antidiabetic medications, Diabetes mellitus, Cardiovascular safety, Glycaemic control, HbA1c, Cardiovascular outcome trials (CVOTs).

Prevalence of diabetes mellitus (DM) continues to increase exponentially over the past few decades, affecting 463 million adults across the globe in 2019 [1]. The morbidity and mortality related to diabetes result mainly from vascular disease as the consequence of an accelerated atherosclerotic process. Diabetes-induced vasculopathy involves both the microvascular and macrovascular beds of the entire human body, and the macrovascular disease results in various cardiovascular disorders such as ischemic heart disease, stroke, and peripheral vascular disease. Cardiovascular diseases (CVD) account for the majority of DM-related mortality, with an estimated 1.6 million deaths worldwide, resulting directly from diabetes in the year 2016 alone [2].

Although rigorous management of DM from the disease onset was shown to reduce the microvascular complications remarkably, the incidence of macrovascular disease from type 1 diabetes mellitus (T1DM) showed a significant reduction only after many years of treatment [3]. On the contrary, among patients with type 2 diabetes mellitus (T2DM), tight glycaemic control was found to be associated with a higher incidence of macrovascular complications such as strokes and myocardial infarctions as evidenced by major randomized controlled clinical trials like the Action to Control Cardiovascular Disease in Diabetes (ACCORD) trial [4] and the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial [5]. Though there is a clear link between the severity of prolonged hyperglycaemic state in uncontrolled T2DM and the incidence of CVD, the lack of benefit or even potential harm from rigorous DM control in such patients may be due to the presence of established vasculopathy that gets aggravated by such treatments [6]. Therefore, it is imperative to tailor individualised treatment targets and medication regimes to each DM case with due considerations of their age, gender, ethnic and cultural backgrounds, and the other disease comorbidities to ensure that we are not harming our patients.

In 2007, the New England Journal of Medicine published a meta-analysis by Nissen et al. from the Cleveland Clinic that demonstrated an increased risk of myocardial infarction and other cardiovascular events with Rosiglitazone, an antidiabetic drug widely used in patients with T2DM [7]. Although there was controversy on the methodological accuracy of this study in 2007 itself, the huge public apprehension from media and the concerns raised by the scientific fraternity resulted in the enforcement of sanctions on the drug molecule by the United States Food and Drug Administration (US FDA) and the European Medicine Agency (EMA) in 2010 [8, 9]. Though the FDA restriction was subsequently uplifted in 2013, the drug molecule has never been used commonly since the controversy shook the global drug market. With the eye-opening results from the ACCORD and ADVANCE Trials and Rosiglitazone controversy, the FDA has made it mandatory to ensure cardiovascular safety studies for all the antidiabetic medications before final approval and recommended continued post-marketing surveillance for further safety monitoring. Therefore, now the clinicians across the world are clear that they are not only ensuring the most effective pharmacotherapy for DM, but also the cardiovascular safety in every patient, DM being identified as a CVD equivalent historically from 1998 by the American Heart Association. This Journal special issue of Current Drug Safety is an update on

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the efficacy and cardiovascular safety of all classes of antidiabetic medications available in the global market to empower clinicians to fight diabetes most judiciously and scientifically. Each review in this special issue critically analyses individual classes of the antidiabetic drugs currently in use.

Insulin, being the best drug molecule for glycaemic management since its discovery in the early 19th century and the life-saving treatment option in patients with T1DM, a critical appraisal of the efficacy and safety of the molecule is crucial in any analysis of the efficacy of antidiabetic drug classes. In their review titled "Efficacy and cardiovascular safety of Insulins," Fernandez and Radhakrishnan provided a detailed review of the efficacy, safety issues, and pharmacological properties of different insulins currently available in the global market [10]. The glycaemic response of insulins are clearly dose-dependent in contrast to all other antidiabetic medications, and therefore, the efficacy analysis should address the issue of targeted glycated haemoglobin (HbA1c) reduction without the risk of hypoglycaemia. Based on multiple large randomised controlled trials (RCTs) and meta-analyses, the authors have portrayed a detailed analysis of the efficacy of individual short acting and long acting insulin molecules in their review. They have also provided us summaries of switching between different insulin molecules, cost-effectiveness of some insulins, the differences in the use of some formulations of insulins such as premixed insulins, biphasic insulins, and biosimilar insulins, a combination of insulins with glucagon-like peptide-1 receptor analogues (GLP-1RA), and also concentrated insulin (U500), in different situations of DM management. In addition, the use of insulin for the treatment of severe hypertriglyceridemia, emergency management of hyperkalemia, and the potential use in wound management are briefly discussed.

Presently, there is only a limited number of CVOTs on insulins since most insulins do not qualify the FDA mandate. The DEVOTE Trial (comparing cardiovascular safety of insulin Degludec vs. insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events) showed noninferiority of degludec use compared to glargine among patients with T2DM at high risk for cardiovascular events [11]. Similarly, the ORIGIN (outcome reduction with initial glargine intervention; the CVOT for glargine) trial comparing insulin glargine with standard care did not exhibit any adverse cardiovascular safety issues [12]. However, several observational/ cohort/ retrospective studies, [13-18] revealed possible associations between insulin use and all-cause mortality, major adverse cardiovascular events (MACE), hospitalisation from heart failure, and cancer although with multiple confounding factors such as the amount of insulin exposed, glycaemic control, weight gain, and hypoglycaemic events. Fernandez and Radhakrishnan have concluded their review by providing some additional outlooks into the areas of uncertainty and emerging new therapeutic agents/devises to fight diabetes with insulins, the wonder drug molecule that revolutionised 20th-century diabetes care with its relentless battle now into the 21st century defeating DM related harm to the sufferers [10].

Metformin still remains the first-line drug of choice in patients with T2DM, and even a drug that can be used in obese patients with T1DM as pointed out by Rajagopal and Kochhar in their review "Efficacy and cardiovascular safety of metformin" in this special Journal issue [19]. Widely prescribed globally over the past 6 decades ever since its discovery, metformin has proven to be safe and effective in the management of DM with a reasonable tolerability profile, being the only drug molecule currently in use from the biguanide group of antidiabetic agents. Using up-to-date evidence, the authors depict the mechanisms of action of metformin with the details of its glycaemic lowering effects. Based on the data from RCTs and meta-analyses, it has been found that metformin use is associated with an HbA1c reduction of 1.1 – 1.2% as monotherapy, 0.6 – 0.83% as an add-on therapy to insulin, and 0.9 – 0.95% in combination therapy with other antidiabetic oral agents. The authors also give a detailed account of the appropriate use of metformin for weight management, gestational diabetes mellitus (GDM), T1DM, non-alcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), and the potential benefit in cancer prevention with relevant scientific data.

Although metformin was available for use in DM care much before the concept of CVOTs emerged in the 21st century, there are four CVOTs with metformin as portrayed by the authors in their review [19]. Three of these CVOTs [20-22] specifically address the parameters such as carotid intima-media thickness, reduction of left ventricular mass, systolic blood pressure, body weight, and oxidative stress while the ongoing fourth CVOT [23] assesses the time to MACEs such as non-fatal myocardial infarction, stroke, hospitalization for unstable angina, or symptom-driven coronary artery revascularization. None of these CVOTs showed any signals towards adverse cardiovascular profile. Rajagopal and Kochhar have further discussed the safety issues related to metformin use in pregnancy, children, and other medical conditions such as hepatic and renal failure, and demonstrated the safe use of this medication except in patients with advanced organ failure.

After the rosiglitazone controversy in 2007 and the introduction of newer antidiabetic molecules such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) in the early 21st century, the use of the thiazolidinedione (TZD) group of antidiabetic agents has markedly declined in the developed countries. This is not only because of the cardiovascular safety concerns about TZDs, but also due to the mechanisms of actions of DPP-4 inhibitors and GLP-1RAs, which grossly alter the metabolic and hormonal milieu of the individuals with T2DM and obesity. However, TZDs are still being used in developing countries owing to their economical pricing and reasonable efficacy for HbA1c reduction. In their article, Raveendran et al. have elaborated their mechanisms of action, efficacy in the management of various metabolic disorders, especially T2DM, and the cardiovascular safety of TZDs [24]. Based on the evidence from multiple RCTs and meta-analyses, the authors have demonstrated that monotherapy with pioglitazone and rosiglitazone results in HbA1c reduction of 1-1.5%, although associated with a weight gain potential of up to 3 kg. Lobeglitazone, the third molecule in the TZD class mainly

available in Southeast Asia, has shown to cause a mean HbA1c reduction of 0.6% and weight gain of 1.52 kg. Raveendran et al. have also provided a detailed account of the benefits of using TZDs in NAFLD, PCOS, prediabetes, and lipodystrophies [24].

As the cardiovascular safety issue was the main concern about TZD use a decade ago, Raveendran et al. analysed the currently available evidence on this hot topic in their extensive review. Although associated with a modest risk of heart failure in high-risk individuals, the authors have demonstrated that pioglitazone use is associated with improvement of cardiovascular outcomes such as MACE, including myocardial infarction and stroke. Even though there were no major evidence on the cardiovascular safety of rosiglitazone in several studies and the subsequent analysis of the controversial study data by Nissen *et al*.[7], the uncertainty persists even now as described by Wallach *et al*. [25] 54% higher risk of heart failure is another major safety concern about this drug molecule. There are no CVOTs with lobeglitazone though animal models showed anti-atherosclerotic potential. Augmented risk of hypoglycemia with insulin and insulin secretagogues, peripheral and macular oedema, reduction of bone mineral density, and fractures along with a signal towards an increased incidence of urinary bladder cancer with pioglitazone were the potential adverse effects of TZDs.

Sulfonylureas (SUs) are one of the earliest classes of oral antidiabetic agents available in the market over the past few decades with modest efficacy in the glycaemic management of patients with T2DM, especially in the early stages of the disease. These drugs augment insulin production from the pancreatic β cells, which results in the control of hyperglycemia. Thus, SUs may worsen diabesity (DM resulting from obesity) – the basic pathogenic mechanism; T2DM being a hyperinsulinaemic state, and insulin being an anabolic hormone [26]. However, considering the affordably low prices for most people, wide availability, and the reasonable safety profile make this medication class an attractive choice in the developing countries, if not in the economically affluent nations. In their article in this special issue, Fernandez et al. have provided an extensive review of the efficacy and safety issues of SUs, which enables readers to use these age-old medications scientifically for T2DM management.[27] Based on the currently available evidence from multiple RCTs and meta-analyses, the authors have proved that T2DM treated with SUs results in mean HbA1c reduction ranging from 0.97 – 1.5% with a modest risk of hypoglycemia, ranging from 3.6 – 13.9%, and with weight gain ranging from 2.3 – 2.8 kg, depending on the drug molecule in the subclass used [27-30]. Authors have also provided other uses of SUs apart from T2DM, such as treatment of gestational diabetes mellitus, permanent neonatal diabetes, and maturity-onset diabetes of the young (MODY).

Based on the evidence derived from various meta-analyses, Fernandez et al. have argued that SU use for the management of T2DM may be associated with a marginal increase in all-cause mortality and cardiovascular mortality, MACE, and stroke risk [27, 31-33]. However, most of these study data analysed were derived from observational studies with inherent methodological flaws that might skew the accuracy of the results. The recently published Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA) trial was a high-quality RCT that did not suggest a significant increase in CV risk with glimepiride [34]. The ongoing GRADE (Glycaemia Reduction Approaches in Diabetes: A Comparative Effectiveness) study is expected to shed more light on the gray area of the cardiovascular safety concerns surrounding SUs [35].

Meglitinides are the next class of oral antidiabetic agents used in the management of T2DM. The two molecules in this drug class, viz., repaglinide and nateglinide, act like SUs by stimulating the pancreatic β cells for insulin secretion. However, the duration of action is quite short in comparison to SUs, and these two molecules are used mainly to control postprandial hyperglycaemia in patients with T2DM and those with erratic eating patterns who are prone to develop hypoglycaemia with other long-acting antidiabetics. With extensive analysis of the currently available literature, Philip and Fernandez in this issue of the Journal have provided an up to date evidence-based review article on meglitinides [36]. The authors have described that the use of these molecules is associated with HbA1c reduction ranging from 0.2 – 1.5% depending on the baseline glycaemic control and the patient characteristics. Combination therapy with other antidiabetic medications except SUs is also associated with modest reductions in HbA1c. Hypoglycaemia and weight gain are the main problems with meglitinides, although less than that with SUs. Although there are no long-term well-designed CVOTs on the cardiovascular safety of these drugs, the currently available evidence does not suggest any signals towards major harm. However, being SU-like in their actions, hypoglycaemia may be a cardiovascular risk, especially in vulnerable populations such as the elderly and those with advanced renal disease.

Alpha-glucosidase inhibitors (AGIs) form a group of antidiabetic medications that reduce intestinal glucose absorption by inhibiting the breakdown of complex carbohydrates present in the diet into glucose molecules and thereby improve postprandial hyperglycaemia in T2DM cases. In their review "Efficacy and cardiovascular safety of alpha-glucosidase inhibitors," Ud Din and Arunagirinathan in this special issue of the Journal have identified that AGI use is associated with HbA1c reduction ranging from 0.56 – 0.93% depending on the baseline HbA1c [37]. Although not used widely in Europe and the Americas, AGIs such as acarbose, voglibose, and miglitol are still favored by many physicians in the developing countries, especially in the Far-East, where people have a diet with high carbohydrate content. With a reasonable back-up of scientific evidence, the authors propose that AGIs may be useful in NAFLD, PCOS, bodyweight management, prediabetic states, and GDM [37]. Though a meta-analysis of RCTs examining the CVOTs with AGIs did not show cardiovascular benefits, 23% reduction in incident T2DM was observed in those with IGT [38]. We can reach a conclusion that AGIs are safe to use in clinical practice as monotherapy as well as in combination with other antidiabetic agents.

DPP-4 inhibitors belong to the class of incretin enhancers of antidiabetic drugs available in the market for nearly one and a half decades and are moderately effective in the management of T2DM. Several molecules of this group are available across the world with slightly variable clinical efficacy and adverse effect profiles. In their article "Efficacy and cardiovascular safety of DPP-4 inhibitors," Subrahmanyan et al. have demonstrated that the use of this group of drugs is associated with modest reduc-

tions in HbA1c ranging from 0.5 to 1.0% when used as monotherapy and with similar benefits when used in combination with other antidiabetic agents [39]. The popular molecules in this group currently available are sitagliptin, linagliptin, saxagliptin, vildagliptin, alogliptin, anagliptin, teneligliptin, and gemigliptin, with several new agents under development. Apart from the management of T2DM, these drugs are also useful in NAFLD and PCOS. DPP-4 inhibitors are not safe during pregnancy, and there is insufficient data on their use among children. Four large CVOTs are available that examined the safety of sitagliptin, [40] linagliptin, [41] saxagliptin, [42], and alogliptin [43], which provide us the evidence for reasonable cardiovascular safety of DPP-4 inhibitors. However, hospitalization for heart failure is a potential issue in those with moderate to severe heart failure, where these drugs are better avoided.

Despite the availability of few different classes of antidiabetic medications and several drug molecules of each class in the global market over the past few decades, none was found to directly improve the cardiovascular or all-cause mortality in patients with T2DM until the GLP-1RAs were introduced in the early 21st century. The discovery of these agents revolutionized not only the management of T2DM but also our understanding of the pathobiology and long-term clinical behavior of this enigmatic disease. Being a multifaceted hormone with numerous metabolic effects, GLP-1 stimulates the glucose-dependent insulin secretion, slows down the gastric motility and emptying, suppresses appetite, enhances satiety, causes natriuresis, and modulates β-cell proliferation, and has cardio- and neuroprotective effects, anti-inflammatory and anti-apoptotic properties, and may modulate memory, learning, reward behaviour, and palatability [44, 45]. Therefore, GLP-1RAs not only alter the metabolic pathways of glucose homeostasis in the body but also possess diverse biological effects throughout the body which are not yet fully elucidated.

After the approval of exenatide for the management of T2DM in 2005, several molecules of GLP-1RAs were introduced into the global drug market, and newer agents are currently under development. Iqbal et al. in this issue of the Journal, have provided us a concise and critical review titled "Efficacy and cardiovascular safety of GLP-1 receptor analogues" that analyses the biopharmaceutical properties, efficacy, and cardiovascular safety issues surrounding the use of GLP-1RAs [46]. Based on the evidence from multiple large RCTs and meta-analyses, the authors have concluded that the use of GLP-1RAs is associated with HbA1c reduction of up to 1.8%, depending on the baseline HbA1c and baseline body weight/ diabesity. Apart from glycaemic control in patients with T2DM, GLP-1RAs are also beneficial in NAFLD, PCOS, treatment of obesity, T1DM with insulin resistance, and possibly in conditions such as Parkinson's disease.

Iqbal et al. have also elaborated the cardiovascular benefits associated with GLP-1RAs based on the extensive review of the 6 CVOTs using various molecules belonging to this drug class, such as lixisenatide liraglutide, exenatide, dulaglutide, and semaglutide [46, 47]. CVOTs showed mortality reduction with only liraglutide and possibly semaglutide, the other three agents in the class did not show this benefit. However, dulaglutide, liraglutide, and semaglutide showed reductions in MACE and stroke, whereas lixisenatide and exenatide did not show cardiovascular safety in these CVOTs. Overall, the results of these mega-RCTs transformed the entire pharmaco-therapeutic landscape of T2DM from a simple disease control approach to gross modifications in the health outcomes with treatment.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are another unique antidiabetic drug class that acts mainly through extra-pancreatic and extra-intestinal mechanisms of metabolic pathways by increasing the glucose excretion through the kidney. Several molecules of SGLT2 inhibitors are already available in the global drug market, and few newer ones are under development. Using the currently available evidence, Fernandez et al. in this issue of the Journal have updated the efficacy and cardiovascular safety of SGLT2 inhibitors to empower readers to use these molecules judiciously in their clinical practice [48]. Based on a meta-analysis of large RCTs, authors have proved that canagliflozin 300 mg daily is associated with maximum reduction HbA1c (mean: 0.80%; 95% CI 0.65 – 0.98%) compared to other available molecules of SGLT2 inhibitors. However, we need to bear in mind that at higher baseline levels, the HbA1c reduction achieved could be greater as observed with other antidiabetic agents. Modest reductions in body weight and blood pressure were the other observed benefits of this class of drugs. The reported major side effects from RCTs were urinary tract infections and fungal genital infections. Authors have also proved that SGLT2 inhibitors are useful in selected populations of T1DM (with obesity and high insulin requirements), NAFLD, heart failure, and diabetic nephropathy. This drug class is not safe in pregnancy and children with the currently available evidence.

Results of the recently published CVOTs with various SGLT2 inhibitors have evoked huge scientific enthusiasm not only among diabetologists but also in professionals from other branches of medicine such as cardiologists, nephrologists, and metabolic physicians. The first among these trials were the EMPA-REG OUTCOME trial with empagliflozin that showed marked reductions in MACE, stroke, and cardiovascular mortality [49]. Subsequent trials with other SGLT2 inhibitors also showed similar benefits of varying degrees. The overall results of the major CVOTs such as DECLARE-TIMI 58, CANVAS, EMPA-REG OUTCOME, and CREDENCE can be summarised as reduction in MACE by 7% (*HR: 0.93)*, 14% *(HR: 0.86)*, 14% *(HR: 0.86)*, and 20% *(HR: 0.80)*; reduction in hospitalisation for heart failure [HHF) by 27% *(HR: 0.73)*, 33% *(HR: 0.67)*, 35% *(HR: 0.65)*, and 29% *(HR: 0.71)*; composite HHF and CV-death by 17% *(HR: 0.83)*, 22% *(HR: 0.78)*, 34% *(HR: 0.66)*, and 31% *(HR: 0.69)*; and composite renal outcome by 47% *(HR: 0.53)*, 40% *(HR: 0.60)*, 46% *(HR: 0.54)* and 30% *(HR: 0.70)*, respectively [48, 50]. Fernandez *et al.* have also given us a very elaborate outline of all the current and ongoing CVOTs with the globally available SGLT2 inhibitors in their extensive review.

Last but not least among the antidiabetic group of medications is the amylin analogues. A neuroendocrine hormone, amylin, co-secreted with insulin at a ratio of 100:1 (insulin: amylin) from the pancreatic β cells in response to food intake, delays gastric emptying, suppresses postprandial hyperglucagonaemia, and enhances satiety [51, 52]. Absolute and relative amylin deficiency

occur in T1DM and T2DM, respectively, as in the case of insulin deficiency in these disorders [53]. Native amylin being therapeutically unstable and with a short half-life, experiments to develop synthetic amylin analogues, resulted in the successful invention of pramlintide useful in the management of DM as pointed out by Koshy *et al.* in their review article titled "Efficacy and cardiovascular safety of amylin analogues" in this Journal issue [52]. Significant reductions in HbA1c, insulin doses, body weight, and postprandial glucose levels were observed in patients with T1DM treated with pramlintide, though associated with a higher incidence of nausea, vomiting, anorexia, and hypoglycaemia compared to placebo [52, 54]. Pramlintide was also found to confer similar but modest beneficial effects in T2DM cases with similar side effects [52, 55]. Though approved by the FDA in 2005, pramlintide is not used in many countries except America.

Although there are no prospective CVOTs for the cardiovascular safety of pramlintide, few retrospective studies and pooled data from various RCTs do not suggest any safety concerns with these molecules as pointed out by Koshy *et al*. [52]. They also suggest that pramlintide may be useful in weight management especially in DM cases requiring high insulin doses for glycaemic control, in patients with PCOS and Alzheimer's disease. The safety of use of pramlintide in pregnancy and children is not established. Multiple daily injections administered apart from insulin increases the injection burden, although co-formulations are being developed now to address this issue. Koshy *et al.* have also proposed that current and future research may develop newer co-formulations and long-acting molecules, favouring increased use of pramlintide.

Overall, this special issue of the Journal provides the readers with a very elaborate and up-to-date analysis of the efficacy and cardiovascular safety of all the currently available antidiabetic medications. The evidence provided by each of the articles is based on large RCTs and meta-analyses, and therefore I am sure this special issue shall equip readers with the best and current evidence-based knowledge to develop dialectical thinking in the fight against diabetes, one of the most dreaded diseases with catastrophic complications that has already affected nearly 9% of the global population.

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