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Extended Abstract

Underuse and misuse of newer antidiabetic medications with established positive cardiovascular outcome

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Abstract

Diabetes is a growing problem globally despite all advances in its management strategy. In the last decade particularly there has been a plethora of newer anti diabetic medications that have been introduced in the market. Recent trials and studies have shown promising results in terms of cardiovascular event reduction using some newer classes of anti-diabetic medications such as GLP1 agonist and SGLT2 inhibitors. There are now well-established guidelines on use of these medications in certain group of patients. The pathophysiology of how they work, and their potential benefit are now well understood. Despite clear recent guidelines, a significant proportion of patients with established or risk of CVD are not on appropriate anti-diabetic medications. It is therefore needed that practicing physicians are educated and made aware of the use of these medications. At the same time, they also need to be aware of any side effects and contraindications and therefore use them judiciously. A wiser decision and choice of these agents should be made in partnership with the patient after they are adequately educated of the proposed new medication.

Recent trials suggested that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter-2 (SGLT-2) inhibitors reduced cardiovascular events. Comparative effectiveness of these new antidiabetic drug classes remains unclear. We therefore performed a network meta-analysis to compare the effect on cardiovascular outcomes among GLP-1 RAs, SGLT-2 and dipeptidyl peptidase-4 (DPP-4) inhibitors.

Introduction

Type 2 diabetes mellitus (T2DM) is rising in prevalence and is a major cause of morbidity and mortality worldwide. Cardiovascular disease, especially myocardial infarction (MI) and stroke, is the primary cause of complications and deaths in patients with T2DM. Prevention of cardiovascular disease is, therefore, a goal of treatment of T2DM as important as glycaemic control. Metformin is the first-line therapy according to the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) and the International Diabetes Federation. However, metformin is contraindicated or not tolerated in some patients. Rosiglitazone, another class of antidiabetic drug, was withdrawn due to increased cardiovascular events, which prompted the US Food and Drug Administration and the European Medicines Agency to require all new antidiabetic drugs to undergo large cardiovascular outcome trials (CVOTs) to rule out excess cardiovascular risk.

Methods

MEDLINE, EMBASE, Cochrane database, ClinicalTrials.gov, and congress proceedings from recent cardiology conferences were searched up to April 20, 2019. Cardiovascular outcome trials and renal outcome trials reporting cardiovascular outcomes on GLP-1 RAs, SGLT-2 and DPP-4 inhibitors in patients with type 2 diabetes mellitus were included. The primary outcome was major adverse cardiovascular events (MACE). Secondary outcomes were nonfatal myocardial infarction, nonfatal stroke, cardiovascular mortality, all-cause mortality, hospitalisation for heart failure (HF), and renal composite outcome. ORs and 95% CI were calculated using random-effects models.

Conclusion

Cardiovascular disease (CVD) is the leading cause of death in patients with diabetes mellitus, but not all patients with diabetes have the same risk of developing CVD. CV risk increases with diabetes duration and is affected by other comorbidities like hypertension, dyslipidemia, metabolic syndrome, and chronic kidney disease. Diabetic patients with existing CVD, as a function of pre-selection, have the highest risk of a subsequent CV event. Thus, secondary prevention of CV events may not be synonymous with cardio-protection in diabetes in general and evidence for the efficacy of anti-diabetic therapies should be evaluated in this light. Until recently there was a paucity of large prospective randomized clinical trials (RCTs) in diabetic patients with CVD. However, based on the 2008 Food and Drug Administration (FDA) mandate to demonstrate safety of all newer hypoglycemic agents prior to seeking approval, the scenario has changed. As

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a result, several new hypoglycemic medications have recently undergone randomized placebo-controlled CV outcome trials (CVOT) focused on patients with pre-existing CVD or are at high risk of developing CVD. The following review is a concise synthesis of these new trial data for the clinical cardiologist.

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