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Cardiovascular disease in patients with type 2 diabetes

Diabetes mellitus is treated pharmacologically, accompanied by lifestyle modifications, to achieve individualized glycemic goals. Reductions of acute hyperglycemic crises (diabetic ketoacidosis and hyperosmolar coma) are sought, as are the prevention or delay of chronic microvascular and macrovascular complications. There is no debate about whether glycemic control reduces the risk of microvascular complications[1]. However, there is limited clinical evidence that glycemic control reduces cardiovascular disease[2–4]. One in three type 2 diabetes patients has cardiovascular disease, which is the leading cause of death[5,6]. The mortality risk is twofold higher in patients with both diabetes and cardiovascular disease than in patients with diabetes alone[7]. Notably, patients with recently diagnosed type 2 diabetes already have higher risks of death and cardiovascular disease than do individuals without diabetes[8]. Thus, because morbidity and mortality in diabetes patients are generally attributable to cardiovascular disease, the prevention of such disease is a top priority in the treatment of diabetes. Along with glycemic control, several risk factors (hypertension, dyslipidemia, smoking and obesity) must be managed to prevent cardiovascular disease[9]. Recently, some antidiabetic agents have been shown to reduce cardiovascular disease; clinical guidelines have been changed to encourage the use of such drugs[9].

The standard approach toward prevention of cardiovascular events in diabetes patients includes the control of blood glucose and lipid levels, blood pressure, and weight; all are known cardiovascular risk factors. An association between ethnicity (a non-traditional risk factor) and a high risk of cardiovascular disease has been suggested[10]. In addition, hypoglycemic events should be avoided considering the increased risk of cardiovascular events, particularly in elderly individuals[11]. Recent works found that glycemic variability independently of hyperglycemia was a risk factor for both cardiovascular disease and microvascular complications[12–14]. Hyperglycemia-induced endothelial dysfunction and vascular damage are caused by oxidative stress and increased levels of pro-inflammatory cytokines; such problems are accentuated when glucose levels fluctuate[15].

Until recently, antidiabetic drugs initially were used to lower blood glucose levels and ultimately to prevent diabetic complications. A major change in this approach was triggered by the results of recent cardiovascular outcome trials, particularly in the participants of these studies (patients with type 2 diabetes and either established cardiovascular disease or a high risk of such disease). In patients with type 2 diabetes and established cardiovascular disease, heart failure or chronic kidney disease, the primary indications for sodium–glucose cotransporter 2 (SGLT2) inhibitors are evolving from targeted reduction of the glycated hemoglobin level to decreases in major atherosclerotic cardiovascular events, slower progression of renal failure and hospitalization for heart failure. The primary indications for glucagon-like peptide-1 receptor (GLP-1R) agonists are also changing; the current aim is to reduce major atherosclerotic cardiovascular events. In the cardiovascular outcome trials, despite being of the same class, they did not exert equivalent effects on cardiovascular disease[16]. Thus, it might not be simple to use these antidiabetic drugs in clinical practice, because the same class of drug cannot be grouped as equally effective in terms of preventing cardiovascular disease.

All SGLT2 inhibitors tested in the cardiovascular outcome trials reduced hospitalization for heart failure by 27–39% in diabetes patients, regardless of any history of heart failure[17]. The indications for dapagliflozin and empagliflozin have been broadened, because both drugs slow heart failure and cardiovascular death in patients with reduced ejection fractions irrespective of diabetes[18]. Empagliflozin and canagliflozin greatly reduce the incidences of major atherosclerotic cardiovascular events[9]. In real-world settings, SGLT2 inhibitors are more effective than dipeptidyl peptidase-4 inhibitors for cardiovascular disease treatment in patients with shorter durations of diabetes[19].

Five GLP-1R agonists (liraglutide, semaglutide, albiglutide, dulaglutide and efpeglenatide) significantly reduce the incidences of major atherosclerotic cardiovascular events in patients with type 2 diabetes who have established cardiovascular disease or a high risk of such disease; however, lixisenatide and extended-release exenatide do not reduce these incidences[20]. Such protective effects of GLP-1R agonists on cardiovascular disease might be associated with decreases in the various cardiovascular risks and direct effects on the heart and endothelium[21,22]. However, the GLP-1R agonists differ in terms of their effects on cardiovascular outcomes, perhaps reflecting differences in their durations of actions or extents of GLP-1R[21,22] downregulation. The effects of GLP-1R agonists on cardiovascular disease must be considered individually; it is inappropriate to group the results to derive class effects.

Inflammation caused by chronic hyperglycemia and diabetes-related dyslipidemia contributes to endothelial dysfunction and atherosclerosis progression. Patients with diabetes have shorter life expectancies because of increased

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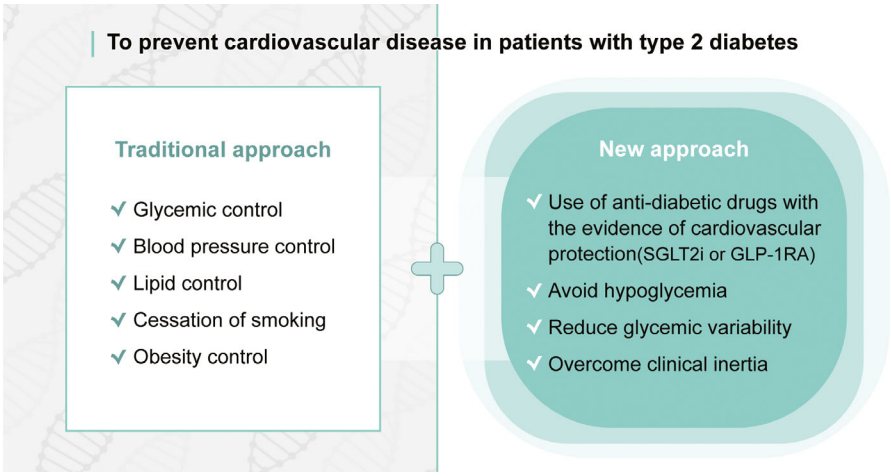

Figure 1 | Approach to prevent cardiovascular disease in patients with type 2 diabetes. This summarized multifaceted approaches to reducing the risk of cardiovascular disease in patients with type 2 diabetes.

mortality and cardiovascular disease[7]. Multifactorial risk management of cardiovascular disease should be a main part of diabetes care, commencing when diabetes is first diagnosed. Physicians should consider immediate prescription of SGLT2 inhibitors or GLP-1R agonists with clear benefits in type 2 diabetes with cardiovascular disease. The prescription rate of SGLT2 inhibitors increased from 1% in 2013 to 14% in 2019, and the prescription rate of GLP-1R agonists did not change from 10% in 2013 to 10% in 2019 (Hawkins Gay, 2020 unpublished data). Considering that one in three patients with type 2 diabetes has comorbid cardiovascular disease, clinical inertia might be in the use of SGLT2 inhibitors or GLP-1R agonists. Such inertia has been previously noted in the context of glycemic control[23]. In conclusion, it is essential to manage the cardiovascular risk factors of diabetes patients, and to select drugs indicated by recent research results and revised clinical guidelines (Figure 1).

DISCLOSURE

The authors declare no conflict of interest.
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