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Current trends in epidemiology of cardiovascular disease and cardiovascular risk management in type 2 diabetes

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ABSTRACT

With the advances in diabetes care, the trend of incident cardiovascular disease (CVD) in patients with type 2 diabetes mellitus (T2DM) has been decreasing over past decades. However, given that CVD is still a major cause of death in patients with diabetes and that the risk of CVD in patients with T2DM is more than twice that in those without DM, there are still considerable challenges to the prevention of CVD in diabetes. Accordingly, there have been several research efforts to decrease cardiovascular (CV) risk in T2DM. Large-scale genome-wide association studies (GWAS) and clinical cohort studies have investigated the effects of factors, such as genetic determinants, hypoglycaemia, and insulin resistance, on CVD and can account for the unexplained CV risk in T2DM. Lifestyle modification is a widely accepted cornerstone method to prevent CVD as the first-line strategy in T2DM. Recent reports from large CV outcome trials have proven the positive CV effects of sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with high CVD risk. Overall, current practice guidelines for the management of CVD in T2DM are moving from a glucocentric strategy to a more individualised patient-centred approach. This review will discuss the current epidemiologic trends of CVD in T2DM and the risk factors linking T2DM to CVD, including genetic contribution, hypoglycaemia, and insulin resistance, and proper care strategies, including lifestyle and therapeutic approaches.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by insufficient insulin production and/or insulin resistance resulting from both environmental and genetic components. DM is one of the fastest growing diseases worldwide and poses a major threat to global health. The number of people with DM has continued to increase from 151 million in 2000 to 425 million in 2017, and it is estimated to reach 629 million by 2045 [1]. Consequently, DM imposes a substantial social and economic burden on both patients and their families. In the United States (US), the estimated economic burden associated with DM in 2017 was $327 billion, and the estimated cost of DM averaged ~$9600 per patient per year, which is more than twice that of nondiabetic patients [2].

DM is strongly associated with cardiovascular disease (CVD). The prevalence rate of CVD is higher in adults with diabetes than in those without diabetes. This risk increases progressively with increasing fasting plasma glucose levels, even before it reaches sufficient levels for the diagnosis of diabetes [3,4]. CVD is one of the leading causes of mortality among individuals with DM. Approximately half of the deaths of individuals with DM are attributable to CVD, and individuals with type 2 diabetes mellitus (T2DM) have a two-fold increased risk of cardiovascular (CV) mortality than healthy individuals [5,6]. Therefore, one of the major goals of diabetes management is the early detection and provision of care for CV risks in patients with diabetes.

There is a need to understand the mechanisms of this trait-disease or disease-disease relationship to prevent devastating complications. One of the challenges related to the proper care of cardiometabolic risk factors in T2DM is the complex pathophysiologic mechanism of the link between T2DM and CVD. Traditional cardiometabolic risk factors, such as hypertension, dyslipidaemia, and obesity, which are common phenotypes in T2DM, synergistically increase the risk of CVD. In addition, many studies have reported several factors that are often present in patients with T2DM, including genetic predisposition, hypoglycaemia during treatment, and increased insulin resistance. These factors have been considered a major barrier in preventing CVD. Nonetheless, there are some effective strategies to prevent CVD in patients with T2DM. For instance, there is abundant evidence that lifestyle changes can effectively improve CV risk and prevent CVD events [7–10]. Furthermore, recent trials have shown that the use of newer antidiabetic medications can lead to a marked risk reduction of CVD in T2DM with high CVD risk [11–13].

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In this review, we focus on the current epidemiologic trends of CVD in T2DM and risk factors linking T2DM to CVD. We also evaluate the relevance of genetic variants, hypoglycaemia, insulin resistance, lifestyle changes and glucose-lowering agents for the prevention of CVD in T2DM.

2. Epidemiology of CVD

The increasing prevalence of obesity has led to significant increases in the prevalence and incidence of T2DM [14]. However, among patients with diabetes, there has been a contrasting decrease in the incidence of CVD or CV death within the last two decades [6,15–21]. Analysis of the Swedish nationwide registry data from 1998 to 2014 showed that there was a marked reduction of 20% in hospitalization for CVD and CV mortality among patients with T2DM [16]. The rate of CVD reduction was greater among patients with diabetes than among those without diabetes, resulting in a relative reduction in mortality associated with CVD. Other reports from the US, Canada, and the United Kingdom (UK) reported a similar declining pattern, with a 3–5% yearly decline in the rates of acute myocardial infarction (MI), stroke, and CV mortality among patients with diabetes since the early 1990s [17–19]. According to the US National Health Interview Survey, the excess all-cause mortality in patients with diabetes declined from 11.3% in 1988–1994 to 5.9% in 2010–2015 [18]. These trends of CVD prevalence in diabetes are consistent with those reported by Asian studies. Analyses using data from the National Health Insurance Service database of Korea indicated that the incidence of CVD in T2DM has been decreasing annually [20,21]. Although the overall incidence rate of CVD shows decreasing trends, there has been some evidence of a paradoxical increase in heart failure (HF) in adults with diabetes [21,22]. This finding may be due to ageing and advances in care and treatment that prolong survival after acute cardiac events, consequently increasing the number of patients with HF [22–24].

The reduction in CVD and its mortality in diabetes observed during recent decades is multifactorial and could be explained by several reasons. Considerable advances in diabetes management, such as better control of conventional CV risk factors with lifestyle modification or intensive pharmacologic therapies, emerging new drugs with favourable CV effects, and a declining frequency of hypoglycaemia events, may have led to the overall significant reduction in CV complications in this population [25–27]. Furthermore, increasing emphasis on the multidisciplinary approach for patients with DM and efforts to increase the quality of diabetes care with evidence-based clinical guidelines may have also contributed to the reduction in CVD in patients with T2DM [28–31]. Quality improvement strategies in diabetes care can effectively improve cardiometabolic risk factors compared with traditional approaches [32].

Despite advances in CV risk prevention and a trend of reduction in overall CVD risk, individuals with diabetes are still at high risk for CVD. A recent systematic review of 57 articles involving 4 million people with DM indicated that the overall prevalence of CVD in DM patients was 32.2%, with coronary artery disease (CAD) being the most frequent type of CVD reported [33]. A 7-year prospective study in China revealed that those with diabetes had an approximately two-fold increased risk of all-cause mortality than those without diabetes [34]. In contrast, patients with T2DM who had major risk factors for CVD within the target range had little or no excess risk of CVD and mortality [23]. Although the overall mortality rate from coronary heart disease (CHD) has steadily declined in the US, the rates of decline in CHD mortality in younger adults have slowed [35]. This finding indicates that there are still considerable challenges to the prevention of diabetes morbidity and mortality.

3. Factors associated with CVD and type 2 diabetes

3.1. Genetic contribution to T2DM and CVD

The individual risks of CVD and T2DM reflect the complex interaction of lifestyle behaviour acting on a backdrop of genetic predisposition [36]. Although estimates of the heritability of CVD and T2DM in the general population vary widely, approximately 30% of the genetic contribution to the variation in risk can be quantified for each individual [37]. It is largely unknown whether common risk factors predisposing to both diseases include shared genetic components or whether T2DM has a disruptive influence on pathways related to the pathogenesis of CVD. Although large-scale genome-wide association studies (GWAS) have attempted to identify shared genetic backgrounds, only a few robust shared loci between T2DM and CVD have been identified.

GWAS that were focused on identifying genetic determinants of CAD in individuals with T2DM have analysed important genes related to CAD stratified by diabetes status. Based on earlier GWAS for T2DM and CAD, there are robust shared loci between CAD and T2DM located at chromosome 9p21.3 near the *CDKN2A* and *CDKN2B* genes [38–40]. Previous GWAS have identified a group of single nucleotide polymorphisms (SNPs) in linkage disequilibrium near the *IRS1* locus, which is associated with T2DM, increased blood pressure, decreased body fat percentage, decreased waist-hip-ratio, and lower HDL cholesterol [40,41]. Shah et al. found two single nucleotide polymorphisms (rs57922 and rs9299870) that were significantly associated with CVD in the intensive glycaemic treatment group and that may interact with GLP-1. These variants can be used to identify subgroups that may derive greater benefit from intensive glycaemic control [42]. This identification can be done using the polygenic risk score, which represents an individual's burden of polygenic risk from common variants and is calculated by summing up the number of risk alleles weighted by an estimation of the impact of each allele on a disease. A previous study showed that the polygenic risk score for T2DM, which was calculated using millions of common genetic variants, was an independent predictive factor for CV mortality [43]. In this prospective nationwide cohort study from the UK Biobank dataset, individuals at very high genetic risk for T2DM had an over two times higher risk of CV mortality.

Whereas genetic correlation can reveal the shared genetic components of target diseases across all variants in a GWAS, Mendelian randomization (MR) analysis allows testing for causal relationships between traits or diseases. MR is less likely to be affected by confounding or reverse causation than conventional observation studies [44]. Ross et al. identified an association between glycated haemoglobin and CAD with MR analysis, although the study had limitations concerning heterogeneity and potential confounding by other cardiometabolic risk factors [45]. Ahmad et al. suggested that genetic variants for fasting glucose were associated with an increased risk of CAD in individuals without diabetes [46]. Merino et al. found that individuals with 12 variants associated with fasting glucose, but not T2DM, had a significantly higher risk for CAD [47]. As knowledge about the genetic correlation and causal relationship between T2DM and CVD begins to increase, improvement in prevention strategies and treatment methods for diseases is expected in the future.

3.2. Hypoglycaemia and CVD

Although the causal relationship of hyperglycaemia with the adverse cardiovascular outcome has been clearly established [45,48], some trials have failed to demonstrate that intensive glycaemic control in a certain group of patients with diabetes is helpful to improve the risk of cardiovascular disease [49–51]. One of the main reasons for the increased CV risk in these trials was thought to be the deleterious effect of hypoglycaemia. Post hoc analyses found that hypoglycaemic events were associated with increased subsequent CVD and mortality risks, especially in older patients with multiple comorbidities [51–55]. The lack of evidence for CV benefit from strict glycaemic control in T2DM patients at high risk of CVD has prompted guidelines to suggest relaxing individual glycaemic targets to prevent hypoglycaemia risk and associated risks of CVD and mortality [56,57].

The relationship between severe hypoglycaemia (SH) and CVD outcomes or mortality is supported by many previous studies

[51,52,54,55,58–67] (Table 1). In the post hoc analysis of the Veterans Affairs Diabetes Trial (VADT) with sub optimally controlled T2DM, SH events were associated with major adverse cardiovascular events (MACE) regardless of the assignment of the glycaemic control group [52]. Another post hoc analysis of the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial suggested a greater risk of SH after CV events and a greater risk of CV events after SH, indicating a possible bidirectional relationship [54]. We also investigated the association of SH with subsequent CVD and mortality events and found an increased risk of MI, stroke, heart failure and all-cause mortality in T2DM patients who experienced an SH event. The study demonstrated a dose-response, temporal relationship, and consistency of the relationship between SH and CVD outcomes for determining causality of the relationship in Asian populations [64]. This finding is in line with the results from the Atherosclerosis Risk in Communities cohort study [63].

Several reports have suggested pathophysiological mechanisms that explain the observed relationship between SH and CV outcomes. Sympathoadrenal activation in response to hypoglycaemia induces haemodynamic and electrophysiologic changes and promotes cardiac stress by increasing heart rate, blood pressure, myocardial contractility, and cardiac output [68]. Hypoglycaemia can cause an atherogenic state because of the increase in cell adhesion, blood viscosity, and platelet activation [69,70]. The long-term CV effect on hypoglycaemia can lead to increased endothelial dysfunction and a proinflammatory state, further contributing to the progression of atherosclerosis [71]. Additionally, there may be another potential link between hypoglycaemia and heart failure through subclinical myocardial damage because the myocardium may be directly damaged by low glucose levels [62]. These abnormalities contribute to a blood vessel condition that increases the risk of developing CVD by persisting for a long time after recovery to normoglycaemic levels (Fig. 1).

Importantly, SH is a cumulative consequence of antecedent hypoglycaemic events in high-risk patients who have attenuated defence mechanisms for hypoglycaemia [72]. Therefore, clinical guidelines recommend that the occurrence and risk of hypoglycaemia in patients with diabetes should be evaluated at every visit to a medical facility [73]. More attention and proper strategies for hypoglycaemia are needed to prevent CVD in patients at high risk for hypoglycaemia. Screening and stratifying high-risk patients for SH can be done with a prediction model, which can also be a useful tool for advanced care in patients with T2DM. Previously, we developed a prediction model to estimate the one-year risk for SH using a nationwide population database [74]. Fourteen variables, including age, sex, smoking, body mass index (BMI), previous history of SH, antidiabetic medication, comorbidities, and glycaemic status, were included, and they showed excellent discrimination and calibration for predicting future events of SH. This risk model can be helpful in determining treatment strategies or adjusting the type or dose of hypoglycaemic agents in routine clinical practice.

3.3. Insulin resistance and CVD

Insulin resistance, which is the major pathophysiology of T2DM, has been considered a strong predictor of atherosclerotic CVD [75–77]. Insulin resistance is defined as an inadequate response of insulin-sensitive target tissue to insulin-mediated cellular action, accompanied by hyperinsulinaemia as a compensatory response [78]. Insulin resistance is closely related to visceral adiposity and obesity, and it results in a wide range of deleterious metabolic derangements, including hyperglycaemia, hypertension, and dyslipidaemia. Persistent exposure to insulin resistance can lead to an increased risk of metabolic syndrome, T2DM, and CVD [79].

Obesity and dysfunctional adipose tissue promote insulin resistance. Excess calories and obesity cause hypertrophy of visceral adipocytes,

Table 1
Post hoc analyses of cardiovascular outcome trials for the association between hypoglycaemia and CV outcomes.

	Publication year	Sample size	Follow-up period	Definition of hypoglycaemia	Study outcome	Effect size (95% CI)
ACCORD [57]	2010	10,194	5.0 years	Severe hypoglycaemia	All-cause mortality	All-cause mortality, intensive arm HR 1.41 (1.03-1.93); standard arm HR 2.30 (1.46-3.65)
ADVANCE [50]	2010	11,140	5.0 years	Severe hypoglycaemia	All-cause mortality, CV mortality, CVD	All-cause mortality HR 3.27 (2.29–4.65) CV mortality HR 3.79 (2.36–6.08) CVD HR 3.53 (2.41–5.17)
ORIGIN [64]	2013	12,537	6.2 years	Non severe hypoglycaemia Severe hypoglycaemia	All-cause mortality, CV mortality, 3P MACE	Non severe hypoglycaemia: All-cause mortality HR 1.12 (0.99–1.26) CV mortality HR 1.03 (0.88–1.20) 3P MACE HR 1.00 (0.88–1.12) Severe hypoglycaemia: All-cause mortality HR 1.74 (1.39–2.19) CV mortality HR 1.71 (1.27–2.30) 3P MACE HR 1.58 (1.24–2.02)
EXAMINE [65]	2017	5380	1.5 years	Severe hypoglycaemia	CVD	CVD HR 2.42 (1.27–4.60)
VADT [51]	2018	1791	5.6 years	Severe hypoglycaemia	CVD	All-cause mortality HR 2.4 (1.1–5.1) CV mortality HR 3.7 (1.3–10.4) CVD HR 1.9 (1.06–3.52)
DEVOTE 3 [66]	2018	7637	2.0 years	Severe hypoglycaemia	All-cause mortality, CVD	All-cause mortality HR 2.51 (1.79–3.50) CVA HR 1.38 (0.96–1.96)
TECOS [53]	2018	14,671	3.0 years	Severe hypoglycaemia	4P MACE, all-cause mortality, CV mortality	4P MACE HR 1.57 (1.07–2.31) All-cause mortality HR 1.91 (1.27–2.88) CV mortality 1.81 (1.08–3.02)
LEADER [54]	2018	9340	3.8 years	Severe hypoglycaemia	3P MACE, all-cause mortality, CV mortality, non-CV mortality	3P MACE HR 1.9 (1.5–2.5) All-cause mortality HR 2.2 (1.7–3.0) CV mortality HR 2.2 (1.5–3.2) non-CV mortality HR 2.3 (1.4–3.6)
EXSCEL [53]	2019	14,752	3.2 years	Severe hypoglycaemia	All-cause mortality, CV mortality, hHF	3P MACE HR 1.19 (0.89–1.60) All-cause mortality HR 1.83 (1.38–2.42) CV mortality HR 1.60 (1.11–2.30) hHF HR 2.90 (1.37–3.17)

CV, cardiovascular; CVD, cardiovascular disease; 3P MACE, 3-point major adverse cardiovascular event; 4P MACE, 4-point major adverse cardiovascular event; hHF, hospitalization for heart failure.

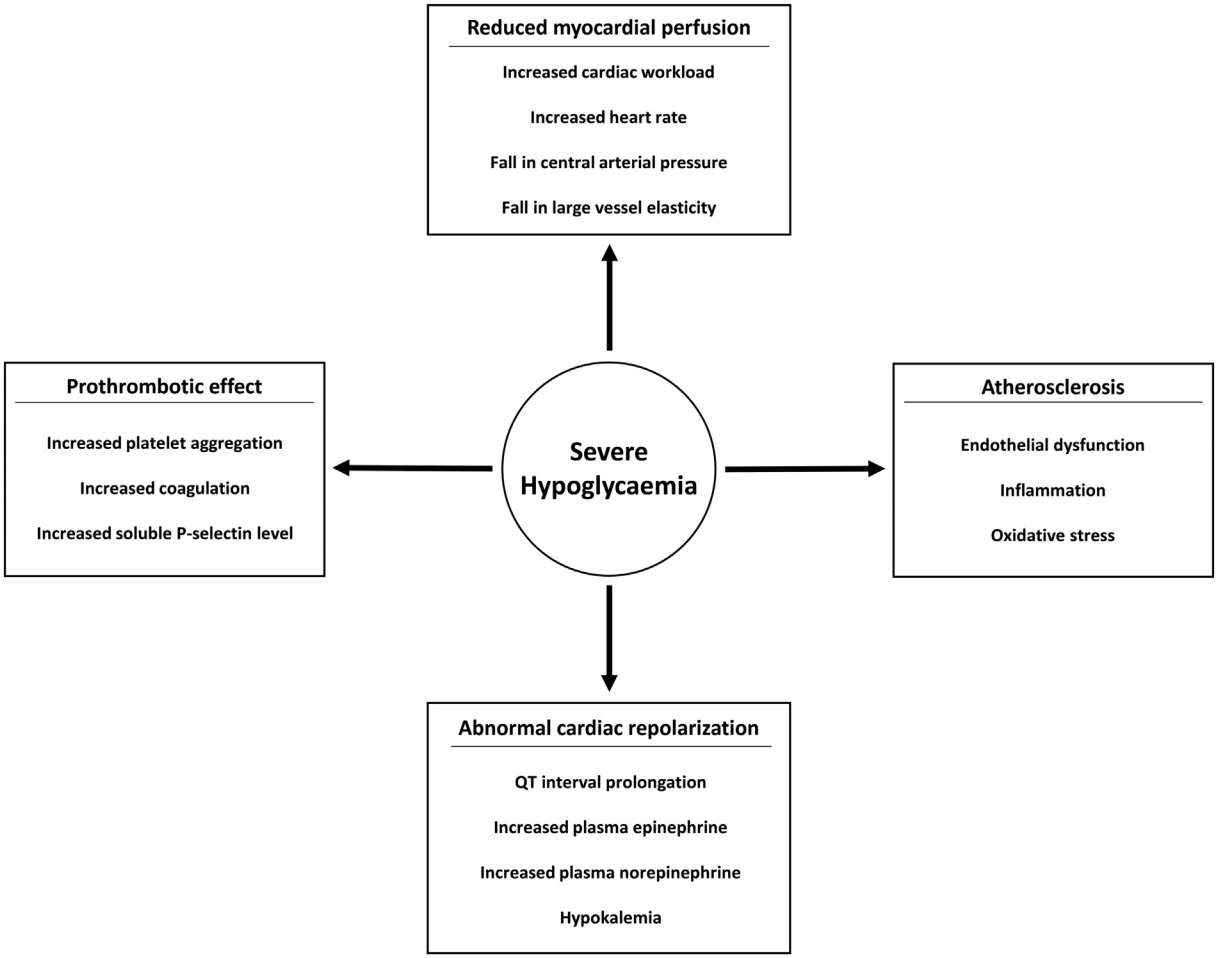

Fig. 1. Pathophysiological effect of hypoglycaemia on cardiovascular system.

which then become less sensitive to insulin's antilipolytic action, more susceptible to apoptosis, and infiltrated with macrophages [80,81]. Macrophages modulated by monocyte chemoattractant protein-1 (MCP-1) and tumour necrosis factor (TNF)-α play critical roles in the progression of atherosclerosis [82]. Defective insulin signalling in macrophages might contribute to the proliferation of vascular smooth muscle cells, macrophage apoptosis, plaque formation, necrosis, rupture, and thrombosis [83,84]. Increased influx of free fatty acids to ectopic adipose tissue results in the accumulation of ectopic lipid disposition, lipotoxicity, and systemic insulin resistance. Excess fatty acids and limited degradation of apolipoprotein B that are due to insulin resistance lead to potentially atherogenic lipids, including an increase in large very low density lipoprotein (VLDL), a greater proportion of small dense high density lipoprotein (HDL) and low density lipoprotein (LDL) particles [85]. The small dense HDL, by augmented activity of hepatic lipase in insulin-resistant states, leads to an increased catabolism of these particles [86]. Triglyceride (TG)-rich small dense LDL is more prone to arterial retention and oxidation and to forming atheroma in arterial walls [87]. Hypertension and hyperglycaemia in T2DM activate the renin-angiotensin-aldosterone system (RAAS) [88]. Increased RAAS activity and compensatory hyperinsulinaemia may synergistically contribute to vasoconstriction, inflammation, and sodium and fluid retention [89]. Insulin resistance also induces endothelial dysfunction and promotes atherosclerosis by reducing the PI3K-NO pathway and increasing MAPK-ET-1 pathway activation [90,91]. Insulin resistance in endothelial cells promotes vascular tissue inflammation, increases the levels of prothrombotic factors and reactive oxygen species (ROS), and selectively reduces nitric oxide synthesis stimulated by insulin [92,93].

Several prospective population-based studies have demonstrated an association between insulin resistance and the incidence of CV outcomes in individuals with normal glucose tolerance or prediabetes [76,94–98]. In early 2000, Hanley et al. suggested a significant association between the homeostatic model assessment for insulin resistance (HOMA-IR) and incident CVD events over an 8-year follow-up in their prospective San Antonio Heart study [76]. A meta-analysis of 65 studies including over 500,000 subjects demonstrated that the risk of CHD increased by 46% for an increase in HOMA-IR of 1 SD in individuals without diabetes [97]. The authors found that insulin resistance measured by HOMA-IR was a better predictor of CVD events than fasting glucose or fasting insulin levels in subjects without diabetes. Insulin resistance has also been associated with the development of subclinical atherosclerosis. Insulin resistance was independently associated with inflammatory cytokines and the coronary calcium score [99–101]. The clinical phenotypes of insulin resistance are components of metabolic syndrome, abdominal obesity, hypertension, abnormal glucose tolerance, and dyslipidaemia. Bigaard et al. reported that each 10% increase in waist circumference corresponded to a 48% increase in the risk of mortality after adjusting for BMI [102]. The recent China Cardiometabolic Disease and Cancer Cohort (4C) study comprehensively detected the contribution of metabolic components to CVD risk and showed that metabolic risk factors accounted for 37% of CVD events [103].

Obesity or central obesity is considered a major cause of insulin resistance. However, insulin resistance is associated with CVD or CV mortality, even after adjusting for BMI or waist circumference [104,105]. Studies have also shown that the relationship between insulin resistance and CVD or CV mortality was attenuated in individuals with

obesity or diabetes [96,106]. In addition, there was even a paradoxically beneficial effect of insulin resistance on CV mortality in obese subjects [98]. These findings support the hypothesis that the induction of insulin resistance can be a process of physiological adaptation to protect against excess nutrient entry into cells and insulin-mediated metabolic stress [107]. According to this hypothesis, it may be preferable to apply strategies of nutrient offloading, such as intensive lifestyle intervention and the use of GLP-1 agonists rather than high-dose insulin or sulfonylurea, to reduce the risk of CVD.

3.4. Lifestyle and CVD

Comprehensive management of lifestyle and metabolic risk factors has become an imperative issue for the prevention of diabetes and CVD. Prior studies have shown that unhealthy lifestyle factors, such as smoking [108], excess alcohol intake [109], lack of physical activity [110,111], and an unhealthy diet [9], are detrimentally related to an increased risk of diabetes, CVD, and premature death. Both lifestyle and metabolic health status interact in complex ways, and these factors are rationally outlined as preventive targets [10,103,112]. Primordial prevention, defined as preventing disease before there is any evidence of the condition by addressing the underlying clinical risk factors through a healthy lifestyle, can reduce the incidence of CHD. A previous study showed that more than 60% of the decline in CV mortality was attributable to primordial prevention [113]. Therefore, changes in unfavourable metabolic factors with lifestyle intervention can contribute to an improved long-term prognosis of CVD.

Several epidemiologic studies have demonstrated reliable associations between adherence to a favourable lifestyle and reduced risk of CV morbidity and mortality [9,114]. The China Kadoorie Biobank study has presented the contribution of a healthy diet, physical activity, and moderate alcohol intake to the prevention of T2DM and CVD as well as the greater effect of smoking on CVD than T2DM [8]. A recent prospective urban rural epidemiology study measured the effect of modifiable risk factors on CVD across 21 countries and reported that multiple modifiable lifestyle behaviours were associated with a lower risk of CV mortality [10]. The same study also found that 6.1% of CVDs can be attributed to poor diet and tobacco use, whereas low physical activity contributed a modest effect (1.5%) to the risk. A recent 4C study reported that a healthy lifestyle was important for preventing CHD in individuals who already had four or more metabolic risk factors [103]. Lifestyle status was shown to have robust effects on new-onset diabetes and MACEs, regardless of metabolic status; a graded increment of risk according to the combination of lifestyle and metabolic health highlighted the importance of lifestyle modification regardless of the present metabolic status. This association is also supported by previous studies in a T2DM cohort. Analysis from two large prospective cohorts indicated that adherence to a composite healthy lifestyle was associated with a substantially lower risk of CVD and mortality among adults with T2DM [7]. In addition, favourable lifestyle behaviour effectively reduced the risk of CVD and CV mortality, regardless of the individual's genetic risk [115,116]. In an analysis from a prospective population-based UK Biobank cohort, high-risk individuals who adhere to unfavourable lifestyles showed an approximately five- to eight-fold increased risk for CV mortality relative to those with low genetic risk and favourable lifestyles [43].

Previous studies have demonstrated that intensive lifestyle intervention can effectively modify CV risk and improve lifestyle behaviours. The 20-year follow-up of the Da Qing Prevention Study reported that lifestyle intervention reduced the incidence of all-cause or CV mortality in individuals with prediabetes (11.9% and 19.6% cumulative incidence of CV mortality in the intervention and control groups, respectively) [117]. In the recent PREvencion con Dieta MEDiterranea Plus trial, the effect of weight loss on long-term CV health was assessed based on composite lifestyle modification, which included an energy-restricted Mediterranean diet and increased physical activity [118]. In their study, participants allocated to the intensive lifestyle intervention group lost more weight and showed improvement in markers for proinflammation, insulin resistance (leptin, IL-18, and MCP-1), and glycaemic parameters (fasting glucose, insulin, and glycated haemoglobin) after 12 months of follow-up.

Although there is considerable evidence for the benefits of a favourable lifestyle, individuals may have difficulties changing their lifestyle and behaviour, as these are often based on longstanding behavioural patterns. To assist with behaviour changes, tools for the assessment of the individuals' risk for CVD according to lifestyle patterns can be used to provide practical clinical advice. Recently, several approaches that support lifestyle improvements using information technologies have been implemented and extensively evaluated. Unlike traditional self-reported measures, lifestyle care with newer technology, such as web- or app-based healthcare platforms or wearable devices, provides opportunities to assess lifestyle behaviour patterns in more accurate and ecologically valid ways [114]. A systematic literature review investigating information technology-based intervention studies reported that there was a significant improvement in diet, activity, smoking, weight, and drinking, although most of the research was short-term (<6 months) [119–123]. However, these new tools for evaluating and intervening in patients' lifestyles are not yet fully utilised by healthcare providers. Furthermore, several challenges still hinder their widespread adoption in CV care in clinical practice, including concerns regarding device accuracy, cost-effectiveness, patient privacy, and processing and utilization of actionable data. Therefore, more research is needed to understand the long-term effects of these interventions.

3.5. Glucose-lowering medication and CV outcomes in T2DM

Two classes of antihyperglycaemic medications, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter 2 (SGLT2) inhibitors, have demonstrated advantages in reducing MACE among individuals with T2DM and established CVD or those at high risk for CVD [124–138]. A recent meta-analysis of five CV outcome trials using SGLT2 inhibitors reported a significantly reduced risk of MACE (hazard ratio [HR] 0.90, 95% confidence interval [CI] 0.85–0.95), with benefits only seen in patients with atherosclerotic cardiovascular disease (ASCVD) (HR 0.89, 95% CI 0.84–0.95) and not in those without (HR 0.94, 95% CI 0.83–1.07, *P* for interaction = 0.63, Table 2) [26]. These results suggest that the prevention of MACE may be greater in patients with T2DM and diabetic kidney disease. In another study, patients with reduced renal function had a lower risk of MACE than those with preserved renal function (HR, 0.91 [95% CI 0.85–0.99] vs HR 0.77 [95% CI 0.65–0.90], p for heterogeneity between the two groups = 0.053) [139]. Recently, the beneficial effect of SGLT2 inhibitors in patients with T2DM and reduced kidney function (eGFR between 25 and 60 mL/min/1.73 m^2) was confirmed in the SCORED trial [131]. Sotagliflozin, an SGLT2 inhibitor, also provides some degree of SGLT1 inhibition, slowing intestinal glucose absorption and reducing postprandial glycaemia, which explains the additional improvement of glycaemic status in patients with renal dysfunction [140]. A previous MR study also showed that SGLT1 inhibition may be associated with decreased rates of CV events [141]. Most SGLT2 inhibitors have been shown to be beneficial, with a substantial risk reduction in hospitalization for heart failure (HF). All trials from the DAPA-HF with dapagliflozin, the EMPEROR-Reduced trial with empagliflozin, CANVAS with canagliflozin, the VERTIS-CV trial with ertugliflozin, and the SCORED trial with sotagliflozin consistently had a similar effect of the SGLT2 inhibitor on HF [125,126,129–131]. A meta-analysis of trials that evaluated the effect of SGLT2 inhibitors on HF showed a 32% reduction in the risk of hospitalization for HF in the group with SGLT2 inhibitors [11].

GLP-1RA has increasingly become one of the established therapeutic options for glucose lowering and weight loss in the management of T2DM (Table 3). To date, four GLP-1RAs (liraglutide, subcutaneous semaglutide, albiglutide, and dulaglutide) have shown significant reductions in MACE [133,134,136,137]. A meta-analysis of the first seven

Table 2
Cardiovascular outcome trials of SGLT2 inhibitor in type 2 diabetes.

	Publication year	Drug	Sample size	Follow-up period	Patients with established atherosclerotic CVD	Patients with a history of heart failure	Patients with eGFR < 60 mL/min per 1.73 m^2	Primary outcome	MACE	Hospital admission for heart failure	Cardiovascular death
EMPA-REG OUTCOME [123]	2015	Empagliflozin	7020	3.1 years	7020 (100%)	706 (10.1%)	1819 (25.9%)	3 point MACE	0.86 (0.74–0.99)	0.65 (0.50–0.85)	0.62 (0.49–0.77)
CANVAS Program [124]	2017	Canagliflozin	10,142	2.4 years	6656 (65.6%)	1461 (14.4%)	2039 (20.1%)	3 point MACE	0.86 (0.75–0.97)	0.67 (0.52–0.87)	0.87 (0.72–1.06)
CREDENCE [126]	2019	Canagliflozin	4401	2.6 years	2220 (50.4%)	652 (14.8%)	1769 (40.2%)	ESKD	0.80 (0.67–0.95)	0.61 (0.47–0.80)	0.78 (0.61–1.00)
DECLARE-TIMI 58 [127]	2019	Dapagliflozin	17,160	4.2 years	6974 (40.6%)	1724 (10.0%)	1265 (7.4%)	3 point MACE	0.93 (0.84–1.03)	0.73 (0.61–0.88)	0.98 (0.82–1.17)
DAPA-HF [125]	2019	Dapagliflozin	4744	1.5 years	–	4744 (100%)	1926 (40.6%)	Composite of worsening heart failure, death from cardiovascular causes	–	0.70 (0.59–0.83)	0.82 (0.69–0.98)
EMPEROR-R [129]	2020	Empagliflozin	3730	1.3 years	–	3730 (100%)	1799 (48.3%)	Composite of hospitalization for heart failure, cardiovascular death	–	0.69 (0.59–0.81)	0.92 (0.75–1.12)
VERTIS CV [128]	2020	Ertugliflozin	8238	3.5 years	Coronary artery disease 6256 (75.9%) Cerebrovascular disease 1889 (22.9%) Peripheral artery disease (18.7%)	672 (24.5%)	608 (22.1%)	3 point MACE	0.97 (0.85–1.11)	0.70 (0.54–0.90)	0.92 (0.77–1.11)
SCORED [130]	2021	Sotagliflozin (SGLT1/2 inhibitor)	10,584	1.3 years (Ended early due to loss of funding)	Myocardial infarction 2108 (20.0%) Coronary revascularization 2375 (22.4%) Stroke 946 (8.9%)	3283 (31.0%)	10,584 (100%)	Composite events of CVD, hospitalizations for heart failure, and urgent visits for heart failure	0.84 (0.72–0.99)	0.77 (0.66–0.91)	0.90 (0.73–1.12)

SGLT2, sodium-glucose cotransporter-2; MACE, major adverse cardiovascular event; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease.

Table 3
Cardiovascular outcome trials of GLP-1RA in type 2 diabetes.

	Publication year	Drug	Sample size	Follow-up period	Patients with established atherosclerotic CVD	Patients with a history of heart failure	Patients with eGFR < 60 mL/min per 1.73 m^2	Primary outcome	MACE	Hospital admission for heart failure	Cardiovascular death
ELIXA [131]	2015	Empagliflozin	6068	2.1 years	6068 (100%)	1358 (22%)	1407 (23.2%)	4 point MACE (non-inferiority)	1.02 (0.89–1.17)	0.96 (0.75–1.23)	0.98 (0.78–1.22)
LEADER [132]	2016	Liraglutide	9340	3.8 years	7598 (81%)	1667 (18%)	2158 (23.1%)	3 point MACE (non-inferiority)	0.87 (0.78–0.97)	0.87 (0.73–1.05)	0.78 (0.66–0.93)
SUSTAIN-6 [133]	2016	Semaglutide (Subcutaneous)	3297	2.1 years	2735 (83%)	777 (24%)	939 (28.4%)	3 point MACE (non-inferiority)	0.74 (0.58–0.95)	1.11 (0.77–1.61)	0.98 (0.65–1.48)
EXSCEL [134]	2017	Exenatide	14,752	3.2 years	10,782 (73%)	2389 (16%)	3191 (21.7%)	3 point MACE (superiority for efficacy)	0.91 (0.83–1.00)	0.94 (0.78–1.13)	0.88 (0.76–1.02)
Harmony Outcomes [135]	2018	Albiglutide	9463	1.5 years	9463 (100%)	1922 (20%)	Mean eGFR 79 mL/min per 1.73 m^2	3 point MACE (superiority)	0.78 (0.68–0.90)	0.71 (0.53–0.94)	0.93 (0.73–1.19)
REWIND [136]	2019	Dulaglutide	9901	5.4 years	3114 (31%)	853 (9%)	2199 (22.2%)	3 point MACE (non-inferiority)	0.88 (0.79–0.99)	0.93 (0.77–1.12)	0.91 (0.78–1.06)
PIONEER 6 [137]	2019	Semaglutide (oral)	3183	1.3 years	2695 (85%)	388 (12%)	856 (27.1%)	3 point MACE (superiority)	0.79 (0.57–1.11)	0.86 (0.48–1.44)	0.49 (0.27–0.92)

GLP-1RA, glucagon-like peptide-1 receptor agonists; MACE, major adverse cardiovascular event; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

GLP-1RA CV outcome trials with a combined total of 56,004 participants showed that GLP-1RA treatment reduced the risk of MACE by 12% (HR 0.88, 95% CI 0.82–0.94), CV death by 12% (HR 0.88, 95% CI 0.81–0.96), fatal or nonfatal MI by 9% (HR 0.91, 95% CI 0.83–0.99), and a 16% reduction in fatal or nonfatal stroke (HR 0.94 95% CI 0.76–0.93) [12]. GLP-1RA has shown a neutral effect on hospitalization for HF [142,143]. In addition, given the small increase in heart rate observed with GLP-1RA, the safety in patients with advanced HF remains uncertain [144]. Although a previous meta-analysis reported a significant benefit for hospital admission for HF, caution should be exercised when considering GLP-1RA use in patients with preexisting advanced HF [145].

In 2019, the American Diabetes Association and European Association for the Study of Diabetes (ADA-EASD) consensus report was published with strong recommendations on the management of hyperglycaemia in T2DM patients at high risk of established ASCVD [146]. This updated report highlighted the importance of treating high-risk T2DM patients with an SGLT2 inhibitor or GLP-1RA to reduce MACE, hypertensive HF, and CV death independent of the individual's glycaemic status. According to the updated ADA-EASD guidelines, for patients with T2DM and established ASCVD, the level of evidence for benefit with respect to MACE is greater for GLP-1 RA than for SGLT2 inhibitors. Patients with T2DM without established ASCVD but with indicators of high CV risk, such as patients aged ≥55 years with significant stenosis of major arteries, those with decreased kidney function, or those with albuminuria, should also preferentially receive GLP-1RA with demonstrated CV benefit independent of glycaemic control [146]. For patients with HF with or without established ASCVD, the level of evidence for benefit with respect to MACE is greater for SGLT2 inhibitors than for GLP-1 RA. In clinical practice, patient compliance, secondary benefits for weight reduction, and costs should also be considered.

4. Conclusion

Although the incidence of CVD in people with diabetes is decreasing, CVD remains the major cause of death in individuals with T2DM and is still one of the major complications of diabetes. The increased risk of CVD and CV mortality in diabetes cannot be fully explained by traditional CV risk factors. Considerable evidence suggests that genetic risk factors, insulin resistance, and hypoglycaemia can account for the unexplained CV risk in T2DM. Future studies are needed to advance our understanding of the shared genetic mechanisms between T2DM and CVD, the basic molecular aetiology of insulin resistance, and hypoglycaemia management to eliminate the risk of CVD in diabetes. Additionally, comprehensive lifestyle modifications can improve CV risk factors. Intensive lifestyle modification and other strategies for nutrient offloading could be more appropriate for specific situations, such as in obese T2DM patients with insulin resistance, rather than increasing doses of antidiabetic medications. Recent CV outcome trials have also led to remarkable advances in our understanding of the effectiveness of SGLT2 inhibitors or GLP-1RAs in improving CV risks. Accumulating evidence suggests that GLP-1RAs and SGLT2 inhibitors should be considered for hyperglycaemia treatment in patients with T2DM, particularly in those with established CVD, given that they reduce the risk of MACE and HF. Current practice guidelines for the management of CVD in diabetes are moving from a strict glucocentric strategy to a more patient-centred approach based on individual medical history, lifestyle behaviours, and CV and metabolic risk factors. Given the complex interaction of risk factors shared by T2DM and CVD, a comprehensive approach to T2DM management that includes modification of all CV risk factors should be applied.

CRediT authorship contribution statement

Jae-Seung Yun: Writing - original draft. **Seung-Hyun Ko:** Writing - review & editing.

Declaration of competing interest

Nothing to declare.

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