UNIT NO. 2

DIABETES MELLITUS AS A CARDIOMETABOLIC DISEASE

Dr Khoo Chin Meng

ABSTRACT

Diabetes mellitus is a global health crisis. It is associated with many disabling co-morbidities and could lead to premature cardiovascular disease and death. Chronic hyperglycaemia leads to many pathological changes that are atherogenic. Some studies have regarded diabetes mellitus as a coronary heart disease risk equivalent, especially patients with a long duration of disease. Diabetes mellitus is associated with other traditional cardiovascular risk factors such as hypertension and dyslipidaemia, which together increase the risk of cardiovascular disease manyfold. There are several strategies to improve the cardiovascular outcomes among people with diabetes mellitus, including the following: 1) early intensive glycaemic control (UKPDS); 2) optimal treatment of traditional cardiovascular risk factors (STENO-2); and 3) use of novel glucose-lowering therapies (sodium-glucose transporter 2 inhibitors or glucagon-like peptide 1 agonist) that have benefits on cardiovascular events or mortality.

Keywords: Diabetes Mellitus; Cardiovascular Disease; Glucagon-like Peptide-1; Sodium-Glucose Transporter 2.

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INTRODUCTION

We are facing a global epidemic of type 2 diabetes mellitus (DM).[1] The prevalence of DM among Singaporean adults is projected to rise from 13.7 percent in 2017 to 15 percent by 2050. This translates to an increase in the total cases of DM among Singaporean adults from 606,000 to 1,000,000 by 2050.[2,3] At present, DM accounts for 10 percent of disease burden in Singapore.

DM is not a benign condition. DM is associated with a higher risk of end-stage kidney disease, non-traumatic lower limb amputation, adult blindness, premature cardiovascular diseases (including ischaemic heart disease, stroke and heart failure) and death. In many instances, DM is likened to a slowly, progressive malignant disease that significantly affects all facets of life and quality of life. The cost burden from DM is expected to rise from $940 million in 2014 to $1.8 billion in 2050.[4] It is, therefore, timely that the Ministry of Health, Singapore declared the War on Diabetes in April 2017, outlining the strategies to prevent DM from occurring in the first place, and to prevent DM-associated complications among people with DM.

KHOO CHIN MENG
Head and Senior Consultant,
Division of Endocrinology, National University Hospital

DM AND CARDIOVASCULAR DISEASE

DM is an independent risk factor of heart disease. A large meta-analysis that included data of 698,782 people from 102 prospective studies found that DM was associated with about twice the rate for coronary heart disease (hazard ratio 2.0), ischaemic stroke (hazard ratio 2.3) and haemorrhagic stroke (hazard ratio 1.6).[5] In a Finnish population-based study, people with DM had 6- to 7-fold higher rates of 7-year incidence for myocardial infarction compared to those without DM. People with DM had the same risk for future myocardial infarction as adults with previous myocardial infarction and without DM **(Figure 1)**.[6]

The Asia Pacific Cohort Studies Collaboration (APCSC) combined data of over 600,000 participants from 44 cohort studies in the Asia-Pacific region.[7] In this report, Singapore, being a developed country, was projected to have the highest prevalence of DM by 2030 among other countries in the APCSC. The direct impact of DM on the burden of cardiovascular disease was estimated using population-attributable fractions, which ranged from 2 percent to 12 percent for coronary heart disease, 1 percent to 6 percent for haemorrhagic stroke, and 2 percent to 11 percent for ischaemic stroke. The Emerging Risk Factors Collaboration also analysed data for 689,300 people from 102 prospective studies and found that DM was associated with higher rates of coronary heart disease, ischaemic stroke and haemorrhagic stroke, even with adjustment for lipid, inflammatory or renal markers.[8] At an adult population-wide prevalence of 10 percent, DM was estimated to account for 11 percent of vascular deaths, and the risk of death was higher in people with multi-morbidity **(Figure 2)**.

Taken together, the epidemiological data suggest that DM is a coronary heart disease risk equivalent, although this concept has been challenged recently. In the United Kingdom Prospective Diabetes Study (UKPDS), the reduction in myocardial infarction did not reach statistical significance during the initial 10 years of intensive glycaemic control among newly diagnosed DM, but achieved a statistical significance in the reduction in myocardial infarction only with further 10-year follow up.[9] This suggests that DM is not a coronary heart disease risk equivalent in the early stage of the disease. Other studies have also shown that the coronary heart disease risk equivalence in DM depends on concomitant risk factors for coronary artery disease and that the duration of DM matters to coronary heart disease risk.[10] Typically it would take

a duration of 8 to 10 years for DM to reach a coronary heart disease risk equivalent state.[11]

Cardio-metabolic Abnormalities in Diabetes

The underlying mechanism contributing to the cardiovascular complications of DM is complex and multifactorial. Patients with DM usually have concomitant traditional risk factors for cardiovascular disease, such as hypertension, obesity and dyslipidaemia:[10]

- More than 60 percent of patients with DM have arterial hypertension. This is directly linked to activation of the sympathetic and renin-angiotensin-aldosterone system, as well as hyperinsulinaemia which increases renal reabsorption of sodium.

- Generalised obesity and abdominal obesity are prevalent in patients with DM, and are related to other cardiovascular risk factors. Obesity is associated with chronic inflammation and production of adipocytokines which are prothrombotic. Obesity is also associated with obstructive sleep apnoea which causes chronic hypoxia and activation of the sympathetic and renin-angiotensin-aldosterone system. Obstructive sleep apnoea increases the risk of heart failure, stroke and coronary heart disease.

- Diabetic dyslipidaemia is associated with changes in the levels of lipoproteins and in the structure of the lipoprotein themselves. The lipid profile of patients with DM is usually characterised by low high-density lipoprotein (HDL), high triglycerides (TG), increased apolipoprotein B-100 synthesis and small dense low-density lipoprotein (sdLDL) particles. sdLDL particles are prone to oxidation and poorly interact with LDL receptors. Patients with DM also have slower clearance of postprandial chylomicrons, and higher postprandial very-low density lipoproteins (VLDL) and TGs. Chronic hyperglycaemia compromises the anti-atherogenic properties of HDL and results in rapid catabolism of the HDL particles.

Inflammation seems to play a key role in the pathogenesis of cardiovascular disease in patients with DM.[10] The disease is associated with chronic low-grade inflammation, a common feature associated with obesity. Chronic inflammation may result in an unstable lipid plaque with a high risk of rupture and an acute occlusive event. Typically, the levels of pro-inflammatory cytokines such as C-reactive protein, tumour necrosis factor-α, interleukin 1β, interleukin 6 and plasminogen activator inhibitor 1 levels are elevated, with a decrease in the level of anti-inflammatory cytokine adiponectin.[10,11] Hypoadiponectinaemia in patients with DM is independently associated with endothelial dysfunction, increased carotid intima media thickness, and a higher risk of hypertension and coronary heart disease.[11]

Strategies in Reducing Cardiovascular Disease among People with DM

The cardiovascular risk mitigation among people with DM takes into account the direct deleterious effects of chronic hyperglycaemia and the associated risk factors for cardiovascular disease. The UKPDS showed that intensive glycaemic control (aiming for an HbA1c of 7 percent or below) in newly diagnosed diabetes led in statistically significant 25-percent risk reduction in microvascular complications and a trend toward 16-percent risk reduction in macrovascular complications over a median follow-up of 10 years from diagnosis.[12] During the subsequent 10-year post-trial monitoring, the differences in glycaemic control between the intensive and conventional treatment groups disappeared, but the effect of intensive glycaemic control on both micro- and macrovascular complications persisted in the intensive treatment group. This has led to the concept of legacy effect, where early intensive glycaemic control after diagnosis of DM confers better long-term micro- and macrovascular outcomes.[13]

Three landmark clinical trials have examined the effect of intensive glycaemic control on cardiovascular disease among patients with long-standing DM. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study showed that while intensive therapy reduced microvascular complications, cardiovascular risk and mortality was not significantly improved.[14] The Veterans Affairs Diabetes Trial (VADT) showed that intensive glycaemic control in patients with poorly controlled DM did not significantly reduce the rates of major cardiovascular events or death.[15] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was discontinued due to the finding of higher mortality in the intensive glycaemic control group compared to standard therapy.[16] It is noteworthy to mention that the three studies used high doses of sulphonylureas and insulin to achieve the aimed glycaemic target, and in the ACCORD study, the glycaemic target (HbA1c 6.0 percent or below) was achieved rather rapidly within 6 months of enrolment. The rates of hypoglycaemia and weight gain were also higher in the intensive group than the standard-treatment group. The findings of these 3 studies suggested then that intensive glycaemic control in people with long-standing DM could be harmful. Further analyses indicated that the presence of baseline cardiovascular disease and a higher severe hypoglycaemia rate from the intensive glycaemic control could lead to excess mortality. For these reasons, it has been suggested that the glycaemic control should be moderated in people with baseline cardiovascular disease; an HbA1c target of 7–8 percent would then be considered optimal. But this suggestion was made when glucose-lowering agents with lower risk of hypoglycaemia were not yet widely available in clinical practice.

As alluded above, people with DM would have other traditional cardiovascular risk factors and the optimal reduction of cardiovascular risk in people with DM requires a multi-pronged approach that addresses multiple cardiovascular risk factors. STENO-2 was a randomised controlled trial that compared the

effects of a stepwise implementation of behaviour modification and pharmacotherapy to reduce hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria compared to conventional guideline-directed therapy among people with DM. After a mean follow-up of 7.8 years, those in the intervention group had lower HbA1c, blood pressure, serum cholesterol and urinary albumin excretion rates compared to the conventional treatment group.[17] These were associated with a significant reduction in the risk of developing cardiovascular disease (HR 0.47), nephropathy (HR 0.39), retinopathy (HR 0.42) and autonomic neuropathy (HR 0.37).

ENTERING THE ERA OF NEW DM THERAPEUTICS

Over the past decade, several new glucose-lowering agents have been introduced into the armamentarium of DM therapeutics and have rapidly changed the way we manage people with DM. Since December 2008, the U.S. Food and Drug Administration (FDA) required the pharmaceutical industry to conduct cardiovascular outcomes trials (CVOT) to secure approval of new glucose-lowering agents. Each of these trials must demonstrate noninferiority of their respective drugs to placebo in terms of major adverse cardiac events (MACE) as the primary composite endpoint.[18]

The dipeptidyl peptidase-4 (DPPIV) inhibitors inhibit the DPPIV enzyme to increase the endogenous incretin hormones (i.e., glucose-dependent insulinotropic polypeptide [GIP] and glucagon-like peptide 1 [GLP-1]). The incretin hormones are glucose-dependent hormones and are secreted by the gut cells during meals to enhance endogenous insulin production. The DPPIV inhibitors have modest glucose-lowering effect (HbA1c lowering of 0.5-0.8 percent) and low risk of hypoglycaemia, are weight neutral and safe among people with chronic kidney disease. All the CVOTs for the DPPIV inhibitors (SAVOR-TIMI 53, EXAMINE, TECOS, CARMELINA) have demonstrated MACE safety profiles similar to placebo.[19-22]

In contrast, the CVOTs for GLP-1 receptor agonists have demonstrated cardiovascular benefits. GLP-1 receptor agonists are injectable agents, and given exogenously, have potent glucose-lowering effect (up to 1.5 percent decrease in HbA1c), while also reducing appetite and body weight. The risk of hypoglycaemia with these agents is relatively low. Gastrointestinal side effects appear to be common but tend to be transient with the continuation of therapy.

The Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) study showed that liraglutide significantly reduced the risk of cardiovascular events by 13 percent (p=0.01).[23] Additionally, the Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with type 2 Diabetes (SUSTAIN-6) found that semaglutide reduced the risk of cardiovascular events by 26 percent (p=0.02).[24] However, the benefit on cardiovascular events is not consistently seen with other GLP-1 receptor agonists such as lixisenatide and exenatide.[25,26] Nonetheless, a meta-analysis of the 4 mentioned CVOTs of GLP-1 receptor agonists showed a 13 percent reduction in cardiovascular death and 12 percent in all-cause mortality in patients who received GLP-1 receptor agonists compared to placebo.[27]

Lastly, the sodium-glucose cotransporter 2 (SGLT2) inhibitors are oral glucose-lowering agents that act at the proximal tubule of the kidney to inhibit the glucose reabsorption by SGLT2 receptors, leading to glycosuria. This reduces hyperglycaemia, and the calorie loss from glycosuria can lead to a reduction in body weight (up to 5% of baseline weight). Glycosuria is also associated with natriuresis with a significant reduction in blood pressure (average of 4/2 mmHg).[28] There are 3 SGLT2 inhibitors widely available: dapagliflozin, empagliflozin and canagliflozin. The CVOTs of the three SGLT2 inhibitors have been published. These were the Dapagliflozin Effect on CardiovascuLAR Events—Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) study, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study, and the CANagliflozin cardioVascular Assessment Study (CANVAS).[29-31] These 3 trials included people with DM with multiple risk factors for cardiovascular disease and/or those with established cardiovascular disease. SGLT2 inhibitors have demonstrated unprecedented cardiovascular and renal benefits, including diminished hospitalisation for heart failure and progression of renal disease. In a recent meta-analysis of data from the three CVOTs, SGLT2 inhibitors reduced MACE by 11 percent, with benefit mainly seen in patients with established cardiovascular disease. SGLT2 inhibitors also reduced the risk of cardiovascular death or hospitalisation for heart failure by 23 percent and the risk of progression of renal disease by 45 percent.[32] Real-world studies on these agents, such as the CVD-REAL studies, further corroborate the findings of the randomised studies.[33,34] Given the positive results and the multiple benefits of SGLT2 inhibitors beyond glycaemic control, the SGLT2 inhibitors have been recommended as agents of choice after metformin in the management of people with DM in many guidelines, especially among those with established cardiovascular disease and/or history of heart failure.[28]

CONCLUSIONS

Despite significant advances in cardiovascular therapeutics, cardiovascular diseases remain the main cause of death among people with DM. The disease contributes to the atherogenic processes directly and through multiple traditional risk factors of cardiovascular diseases. We have a better understanding of the strategies to mitigate the rate of cardiovascular diseases among people with DM: 1) early intensive glycaemic control among those newly diagnosed; 2) multifactorial approach targeting the three "H"s — hyperglycaemia, hypertension and hyperlipidaemia; and 3) use of novel glucose-lowering agents with cardiovascular and survival benefits.

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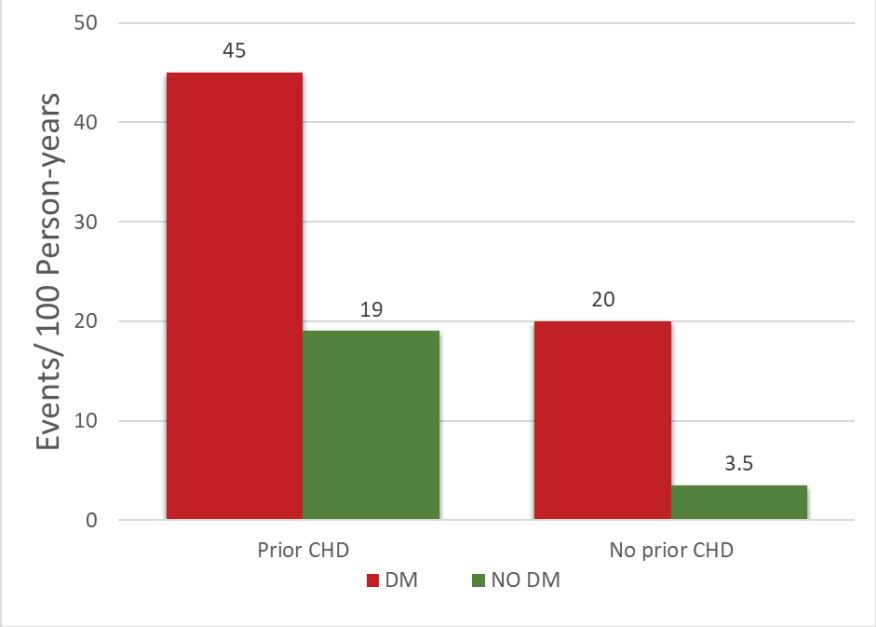
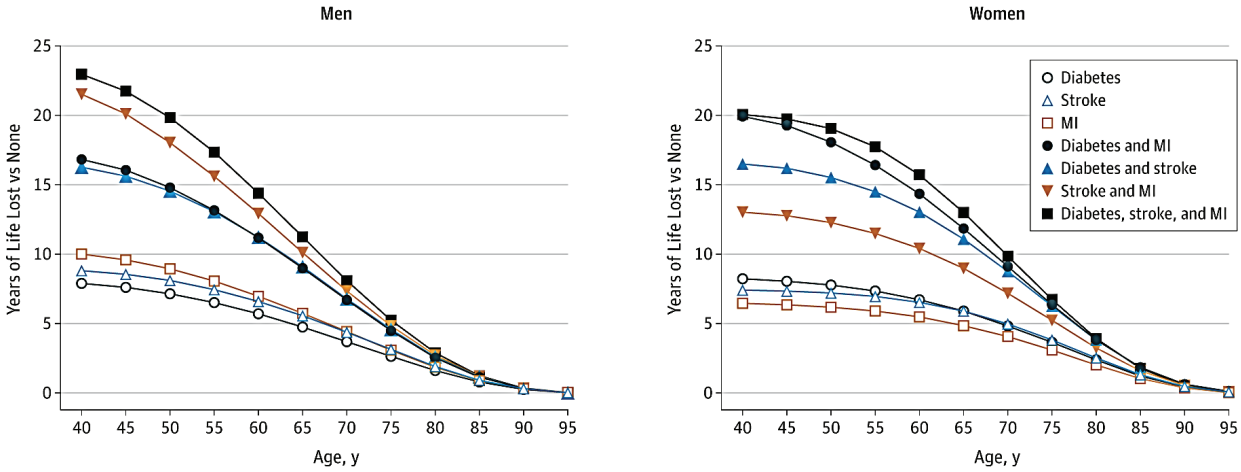
Figure 1: Seven-year incidence rates of myocardial infarction in a Finnish population-based study (n=2,432)[6]



CHD, coronary heart disease; DM, diabetes mellitus.

Figure 2: Years of life lost by disease status at baseline compared with those without diabetes, stroke or MI[8]



MI, myocardial infarction.

Table 1: Cardiovascular outcome RCTs evaluating SGLT2 inhibitors in patients with T2DM

Study (reference)	Patient population	Comparators	Key results
DECLARE-TIMI 58[29]	17,160 T2DM patients with who had or were at risk for atherosclerotic CVD	Dapagliflozin vs. placebo	• Similar rate of MACE (HR 0.93; 95% CI 0.84–1.03; p=0.17) • Lower rate of CVD death or HHF (HR 0.83; 95% CI 0.73–0.95; p=0.005) • Lower rate of renal events (HR 0.76; 95% CI 0.67 –0.87)
EMPA-REG[30]	7,020 T2DM patients aged ≥18 years at high CV risk	Empagliflozin vs. placebo	• Lower rate of 3-point MACE (HR 0.86; 95% CI 0.74–0.99; p=0.04 for superiority) • Lower rate of reduced HHF and all-cause death (RRR of 35% and 32%, respectively, vs placebo)
CANVAS, CANVAS-R[31]	10,142 T2DM patients aged ≥30 years with CVD or ≥50 years with CV risk factors	Canagliflozin vs. placebo	• Lower rate of 3-point MACE (HR, 0.86; 95% CI, 0.75–0.97; p=0.02 for superiority) • Lower rate of progression of albuminuria (HR, 0.73; 95% CI, 0.67–0.79)

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; CANVAS: Canagliflozin Cardiovascular Assessment Study; CANVAS-R: Canagliflozin Cardiovascular Assessment Study—Renal; DECLARE-TIMI 58, Dapagliflozin Effect on CardiovascuLAR Events—Thrombolysis in Myocardial Infarction 58; EMPA-REG: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial; HHF, hospitalisation for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events (3-point MACE includes CV mortality, nonfatal myocardial infarction and nonfatal stroke); RCT, randomised controlled trial; RRR, relative risk reduction; T2DM, type 2 diabetes mellitus.

LEARNING POINTS

- **DM is an independent risk factor of cardiovascular disease.**
- **People with DM often have other cardio-metabolic risk factors that heighten the risk of cardiovascular disease.**
- **Early intensive treatment and therapeutic strategy targeting multiple cardiovascular risk factors significantly lower the cardiovascular risk of people with diabetes.**
- **GLP-1 receptor agonists and SGLT2 inhibitors are new glucose-lowering agents that have demonstrated risk reductions on cardiovascular events and death, especially those with established cardiovascular disease.**