Paradigm shift in diabetes care: Glucose-centric to cardio-metabolic-renal approach

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Introduction

Type 2 diabetes is a growing global epidemic with 537 million adults living with diabetes worldwide which is projected to increase to 783 million in 2045 [1]. It is the ninth leading cause of death worldwide [2]. In addition to microvascular complications, diabetes is associated with atherogenic lipid profile, high blood pressure, endothelial dysfunction, low-grade inflammation, renal impairment and advanced glycation end products [3]. These factors collectively contribute to an elevated cardiovascular risk.

A pooled analysis of individual participant data from 22 prospective cohort studies conducted in Asia between 1963 and 2006 comprising over 1 million participants found that patients with diabetes had a 1.89-fold risk of all-cause death compared with patients without diabetes (hazard ratio [HR], 1.89; 95% CI, 1.74-2.04), with the highest relative risk of death due to diabetes itself (HR, 22.8; 95% CI, 18.5-28.1), followed by renal disease (HR, 3.08; 95% CI, 2.50-3.78), coronary heart disease (HR, 2.57; 95% CI, 2.19-3.02), and ischemic stroke (HR, 2.15; 95% CI, 1.85-2.51) [4]. A study done based on World Health Organization (WHO) mortality database showed an upward trend of diabetic vascular complications related deaths during the period of 2000-2016, mainly because of renal complication [5]. These findings highlight the importance of addressing the vascular complications to reduce the mortality and morbidity of diabetes.

Glucose-centric care

Glucose-centric care of diabetes has been the mainstay of diabetes care for decades and was further established after United Kingdom Prospective Diabetes Study (UKPDS) in 1998 where the intensive blood-glucose control to glycated haemoglobin (HbA1C) less than 7% compared to conventional treatment with HbA1C of 7.9% showed 25% risk reduction in the microvascular complications [6]. The 10-year follow up of these patients showed that there was a reduction in macrovascular complications as well in the intensive blood-glucose control group [7]. The 2003 American
Diabetes Association (ADA) standards of care focused on glycaemic control as the most essential component of diabetes management with the HbA1C target of <7% which was individualized according to the risk of hypoglycaemia and co-morbidities. The management of blood pressure and lipids were focused as a component of cardiovascular disease (CVD) risk reduction [8]. The first line oral hypoglycaemic medicines were metformin followed by sulphonylureas [9]. Meta-analysis of 13 trials involving 2079 patients comparing metformin with other medicines or placebo showed no statistically significant superiority in reducing the risk of all-cause mortality, cardiovascular death, myocardial infarction, stroke and peripheral vascular disease [10].

Based on the observation of linear relationship between HbA1C and cardiovascular events, Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial (VADT) were conducted subsequently to assess the further lowering of HbA1C to prevent CVD. The meta-analysis of 13 studies involving 34,533 patients comparing intensive vs conventional glucose control showed that the intensive treatment did not significantly affect all-cause mortality or cardiovascular death although there was a reduction in the risk of non-fatal myocardial infarction and microalbuminuria [11].

**CVD safe to CVD protective anti-diabetic medicines**

After the famous meta-analysis by Nissen et al which led to the withdrawal of rosiglitazone from clinical use in 2007 the FDA published “Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes” necessitating all new therapies type 2 diabetes to have cardiovascular outcome trials (CVOT) in their approval process in addition to demonstrating improvement in glycaemic control [12,13]. Up to 2022, 18 CVOTs were published for newer glucose lowering drugs including dipeptidyl peptidase-4 inhibitors, glucagon like peptide-1 receptor agonists (GLP1-RA), and sodium-glucose cotransporter-2 (SGLT-2) inhibitors [14].

The meta-analysis of 5 CVOTs of SGLT-2 inhibitors showed cardiovascular and renal benefits including reduction of cardiovascular death [15]. Accordingly for 1000 individuals with type 2 diabetes, most with established CVD, treated over 3.5 years, nine major adverse cardiac events (MACE), 11 cases of heart failure (HHF) and two cases of end stage renal failure (ESRD) are expected to be prevented at the expense of two diabetes ketoacidosis (DKA) events and 36 genital infections. They were separately shown to be beneficial in renal disease and heart failure by reducing cardiovascular death and hospitalization [16]. The beneficial effect of SGLT2-inhibitors were shown in multiethnic observational studies like Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) [17].

Meta-analysis of 8 trials GLP-1 RA showed reduction of MACE by 14% (HR=0.86, 95% CI, 0.79-0.94, P=0.006) compared with placebo, reduction of cardiovascular mortality by 13%, non-fatal stroke by 16% and nonsignificant decrease in non-fatal myocardial infarction. They also significantly reduced risk of hospitalization for heart failure, all-cause mortality and reduction of microalbuminuria [18].

The cardiorenal protection of both SGLT-2 inhibitors and GLP-1 RA is considered to be beyond the reduction of blood glucose and largely independent of the degree of HbA1c reduction and not seen with other drugs with potent glucose lowering effect [19].

**Control of blood pressure and lipids**

Dietary and lifestyle intervention with weight loss has been successful in achieving non-diabetic state without antidiabetic drugs (diabetes remission) as shown in DiRECT and DIADEM-1 studies [20,21]. In a patient register based study in Denmark, the 5-year risk of major adverse cardiovascular events was higher in patients achieving remission of type 2 diabetes (12.3%, CI 11.2-13.3) compared to patients who were well controlled on glucose lowering treatment (10.3%, CI 9.1-11.6). This has been attributed to lower initiation of statins and renin-angiotensin system inhibitors in the patients achieving remission of diabetes [22].

Prediabetes patients have high risk of all-cause mortality, CVD and coronary heart disease compared to those with normoglycaemia [23]. In a population cohort study, incidence of cardiovascular events was higher in prediabetes group compared to those with normoglycaemia (RR 1.54; CI 1.28-1.95) but it decreased and became nonsignificant (RR 1.17; CI 0.97-1.41) after adjustment for previous CVD, smoking, total cholesterol, HDL cholesterol, systolic blood pressure, and use of antihypertensive treatment [24].

The traditional approach primarily targets HbA1c levels which mainly addresses microvascular complications of diabetes, such as retinopathy and nephropathy. However, it may not effectively address the macrovascular complications and cardio-renal diseases associated with type 2 diabetes. By solely focusing on glycaemic control, other risk factors that contribute to cardio-renal diseases, such as hypertension, dyslipidaemia, and chronic kidney disease, may not receive adequate attention. Comprehensive management of these risk factors is crucial in preventing atherosclerotic cardiovascular diseases and end-stage renal disease in type 2 diabetes.
Based on the above evidence many international associations have changed their approach in the management of patients with type 2 diabetes in which cardio-renal protection and mortality reduction have become central pillars of care compared to traditional glucose-centric approach (Table 1).

Future potential therapies to reduce cardiovascular disease in diabetes include, antibodies to proprotein convertase subtilisin-kexin type 9 (PCSK9); RNA therapeutics; agents targeting distinct components of the immune/inflammatory response; and novel small molecules that block the actions of receptor for advanced glycation end products (RAGE) signalling [30].

Conclusion

Diabetes care has shifted from ‘glucose-centric concept’ that emphasized on blood glucose control, to the concept of ‘cardio-metabolic and renal safety’ to ensure the safety from CVDs, heart failure, chronic kidney disease, weight gain and hypoglycaemia. Current change is the paradigm of ‘organ protection’ related to heart and kidney diseases which are the major causes of mortality and morbidity in diabetes. It is crucial to adopt comprehensive and cost-effective strategies addressing hypertension, dyslipidaemia, and hyperglycaemia with cardiorenal protection. Selection of anti-diabetic medicines needs to factor in individualized glycaemic goals, hypoglycaemic risk, weight goals, co-morbidities and cardiorenal protection to effectively prevent cardiovascular morbidity and mortality.

References


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AACE, American Association of Clinical Endocrinology; ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; ESC, European Society of Cardiology; GIP, gastric inhibitor peptide; GLP1-RA, glucagon like peptide-1 receptor agonists; KDIGO, Kidney Disease: Improving Global Outcomes; SGLT-2, sodium-glucose cotransporter-2.
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