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Unit No. 3

ATTENTION TO CARDIOVASCULAR AND RENAL COMPLICATIONS IN DIABETES – HOW TO PREVENT THEM?

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ABSTRACT

It is a well-established fact that patients with diabetes mellitus are at high risk of cardiovascular and renal complications in the course of their lifetime. Much effort has been invested in understanding the pathobiology of this as well as in developing an effective strategy to reduce the morbidity and mortality associated with it. Metabolic control together with mitigating other known risk factors for the cardiovascular and renal disease has been the basis of improving the outcomes of all patients with diabetes. Ongoing scientific discoveries continue to provide physicians and patients with better means of treatment over the years. Each is a step forward, and with the addition of new classes of therapeutics, we will need to reconstruct the management pathway that is best for each patient given their risk profiles and characteristics.

Keywords: Prevention, Diabetes Mellitus, Complications

There is significant cardiovascular (CV) and renal disease burden associated with diabetes. Atherosclerotic cardiovascular disease (ASCVD) – coronary artery disease, stroke, and periphery vascular disease – is a major cause of mortality and morbidity in the diabetic population. Apart from diabetes, many of these patients have hypertension and dyslipidaemia as co-existing risk factors for CV disease. Heart failure is also a significant cause of mortality and morbidity in diabetics. Heart failure can result from coronary artery disease, long-standing, and poorly controlled hypertension, as well as a unique entity known as diabetic cardiomyopathy. The pathobiology of diabetic cardiomyopathy (a functional and structural heart disorder) is thought to be related to the combined presence of glucotoxicity, lipotoxicity, and hyperinsulinemia, and its downstream adverse effects. Chronic kidney disease (CKD) related to diabetes is another major concern, and it is reported that 20-40 percent of patients with diabetes will develop CKD. The most common form of CKD is diabetic kidney disease (DKD). Phenotypically, it presents first as urinary albumin leakage followed by a decline in glomerular filtration rate (GFR) as the disease progresses. DKD is presumably diabetic nephropathy (which is a distinct histological diagnosis requiring a kidney biopsy). CKD in diabetes may also be the result of hypertension (hypertensive or ischemic CKD), recurrent serious urinary tract infection (pyelonephritis), atonic bladder (incomplete emptying and obstructive uropathy) as well as other forms of glomerular and interstitial kidney diseases. The increase in end-stage renal failure (ESRF) worldwide is largely driven by CKD in diabetics.

Given the high healthcare cost (both human and monetary costs) associated with diabetes, the Ministry of Health Singapore launched a national campaign to reduce the incidence of diabetes as well as to screen, prevent and manage known diabetic complications more intensively. Primary care certainly has a very significant and indispensable role in this aspect of care. CV and renal complications can be prevented with a consistent and evidence-based systematic approach.

PRIMARY PREVENTION OF CVD IN DIABETES

The American College of Cardiology published their latest recommendations for prevention of CVD in type 2 diabetes mellitus (DM) last year (2019). Some of the key recommendations are summarised here.

1. Nutrition

It is imperative that all adults with type 2 DM should adopt a heart-healthy diet. This is targeted at improving glycaemic control, lowering blood pressure, correcting dyslipidaemia, and maintaining a healthy weight. In a prospective randomised study conducted in Spain, a supplemented Mediterranean Diet (with extra-virgin olive oil or nuts) led to a 30 percent reduction in major CV events or death from a CV cause. Study participants did not have established CVD at baseline. The dietary intervention is detailed in the Supplementary Appendix of the article (see reference section). About half of the participants in this study had type 2 DM. Some of the dietary patterns associated with CVD are sugar, high-carbohydrate diets, low-carbohydrate diets, refined grains, trans fat, saturated fat, sodium intake, red meat, and processed red meat. These should be avoided or reduced substantially as part of the healthy eating pattern. Calories also need to be adjusted to maintain the ideal body weight and prevent obesity.

2. Physical activities

The second lifestyle modification that can have a significant impact on CVD is physical activity. An active lifestyle is a key component of CVD prevention. There is a strong inverse dose-response relationship between the amount of moderate-to-vigorous physical activity and incident ASCVD events and mortality. Adults should engage in at least 150 minutes/week of moderate-intensity or 75 minutes/week of vigorous-intensity physical activity, including resistance exercise.

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3. Glycaemic and blood pressure control

Achieving target glycated haemoglobin A1c (HbA1c) is another crucial step in the prevention of diabetic complications including CVD. The HBA1c should be individualised depending on the goals of care (risk-benefit trade-off). Younger patients with longer life expectancy and lower pre-existing disease complications should generally have a target HBA1c of 6.5-7 percent. The use of metformin to achieve glycaemic control and to prevent CVD is well established. There is broad consensus across best practice guidelines by various professional bodies that metformin is the appropriate first-line therapy for type 2 DM (unless contraindicated).

Blood pressure (BP) lowering to the recommended appropriate target is an effective and necessary strategy to prevent CVD. For most, the recommended BP target should be < 130/80mmHg.

4. Statin and aspirin

Statin therapy has been the cornerstone of CVD management and prevention for many decades now. The use of moderate-intensity is advocated for diabetic patients age 40-75 years, with no known established CVD. In younger diabetic patients (age 20-39 years) with additional ASCVD risks, it is also reasonable to consider statin therapy.

Aspirin use as a primary preventive strategy is indicated only for those with additional or increased CVD risk. Patients are to be counselled for the possibility of an increased risk of bleeding.

5. Sodium-glucose transport protein 2 inhibitors or gliflozins

Sodium-glucose transport protein 2 inhibitors (SGLT2-I) is a new class of agents that is used for the treatment of type 2 DM. The SGLT2-I agents decrease the reabsorption of sodium and glucose in the tubules of the kidney resulting in lowering blood glucose, natriuresis (loss of sodium), and weight loss. The three major CV Outcome Trials published in this new class of DM therapy (EMPA-REG, CANVAS, DECLARE-TIMI) all showed a fairly consistent and robust results in reducing CV events. A meta-analysis evaluating data from these three trials found a reduction in the composite endpoint of CV death, myocardial infarction, and stroke by 11 percent in those given SGLT-2 inhibitors compared to placebo; however, the benefit was only observed in participants with a history of CVD. However, treatment with SGLT2-I reduced heart failure hospitalisation by 31 percent regardless of prior history of established CVD or heart failure.

The DAPA-HF trial (dapagliflozin being the intervention) mirrored the outcome of the three CVOT trials but differs in that the study population included non-diabetic patients and the fact that only patients with known reduced systolic heart function are enrolled. In the trial, when added to currently accepted treatments for heart failure, dapagliflozin produced a 26 percent reduction in the combined risk of cardiovascular death, hospitalisation for heart failure, or an urgent visit for worsening heart failure requiring intravenous therapy.

PRIMARY PREVENTION OF CKD / DKD IN DIABETES

In addition to optimal glycaemic control, which has been proven to delay the onset of microvascular complications of diabetes, other modifiable factors to prevent the development of DKD are BP, weight, dyslipidaemia, and smoking. Most of the recommendations given for CVD prevention related to these factors will also contribute towards preventing the onset of DKD or delay worsening of DKD if it does develop. However, there are two classes of therapeutic agents that are especially important in the management of a diabetic patient pertaining to DKD. These are also consistent with the latest recommendations by the American Diabetes Association. The final draft version of the Kidney Disease: Improving Global Outcomes (KDIGO) to be released soon (2020) on diabetes management in CKD has also incorporated the choice of DM medications from the perspective of renal disease in DM.

1. Renin-Angiotensin System (RAS) blockade

Investigators first established that angiotensin-converting enzyme inhibitors (ACEI) was useful in retarding the progression of DKD in patients with type 1 DM. This was further supported a few years later with two landmark studies of established DKD in type 2 DM using angiotensin receptor blocker - ARB (RENAAL and IDNT). Current guidelines suggest first-line use of ACEI or ARB for use in diabetics with elevated BP and albuminuria (unless contraindicated). In addition, RAS blockade is indicated in diabetic patients with albuminuria even if normotensive. However, one must be cautious not to cause excessive lowering of BP given that baseline BP in these patients are normal. The dose should be titrated gently and as tolerated. There is also a strong advisory against the use of combination ACEI and ARB for any category of patients for the purpose of renal protection. The dose of ACEI or ARB should be optimised; there is evidence to support further improvement in albuminuria reduction if a supra-maximal RAS blockade strategy is employed but no long-term study for more robust renal outcome (such as rate of doubling of serum creatinine or rate of ESRF). Given the higher risk of adverse events, especially hyperkalaemia, it is prudent not to attempt this in a primary care setting. Adding a mineralocorticoid receptor blocker (such as spironolactone) to ACEI or ARB also reduces albuminuria but again lacks compelling evidence that it truly retards the progression of DKD and can reduce the rate of ESRF.

The evidence available is conflicting, and consensus currently does not suggest starting ACEI or ARB for primary prevention in patients with DM (diabetic patients without albuminuria or other evidence of CKD) if they are normotensive and does not require BP lowering agent.

2. SGLT2-inhibitors

The unexpected favourable renal outcomes as reported in the three major CV Outcome Trials using SGLT2-I have certainly given the nephrology community plenty of optimism that after nearly 20 years since RAS blockade became standard of care for diabetic patients and renal protection, we now have another

class of drug that can be equally effective, if not perhaps more. Although the CVOTs were not designed primarily to test renal outcomes, the renal endpoints were prospectively determined and measured. Further, it is important to note that the renal endpoints were robust hard endpoints such as the rate of doubling of serum creatinine (a common measure of GFR decline over time), rate of reaching ESRF, and death related to renal disease.

The study population was quite different between the three CVOTs. EMPA-REG has a more defined (and smaller study population of just over 7000 patients). All patients (type 2 DM) enrolled had established CVD and the study accepted eGFR of at least 30ml/min/1.73m^2. CANVAS had a mixture of about 2/3 of the patients with established CVD but also included about 1/3 with no CVD but did have additional CV risks (again all are type 2 DM). CANVAS also dictated that eligible patients must have eGFR at least 30ml/min/1.73m^2. The study involved more than 10,000 patients. DECLARE was an even larger study with a longer follow-up period of over four years. Almost 2/3 of the patients (all type 2 DM) recruited were patients without established CVD. The study involved over 17,000 patients and involved patients with a creatinine clearance of at least 60ml/min/1.73m^2. All three CVOTs reported renal protection with hazard ratio ranging from 0.60 to 0.76 for almost similar composite renal outcome (rate of decline in GFR, ESRF, and renal death). What was also insightful and encouraging was the fact that renal protection was generally seen across all categories of albuminuria (including those with UACR < 30mg/g), across all eGFR (CKD 1-3) and across the population with and without established CVD.

Soon after, CREDENCE (with canagliflozin as the intervention) further supported the findings in the CVOTs. This is a study of established CKD patients in a type 2 DM cohort with the primary intent of comparing the renal outcome using SGLT2-I vs placebo. Key entry criteria included eGFR of between 30-90ml/min/1.73m^2; with significant albuminuria (UACR) of 34mg/mmol to 565mg/mmol (300-5000mg/g). It should be noted that almost 100 percent of the study population was already on RAS blockade. Hence, the study was not designed to test if SGLT2-I was better than RAS blockade in DKD but if the addition of SGLT2-I to a regimen consisting of ACEI or ARB adds value (protection) to a patient with DKD. The result was again very similar to the CVOTs outcome; the hazard ratio was 0.7 for the composite renal outcome (GFR decline, ESRF, and renal death).

DAPA-CKD (with dapagliflozin as intervention) was terminated prematurely a few months ago as the independent Data Monitoring Committee felt that the benefit of dapagliflozin was so apparent at that stage that the study should not continue. The results were recently presented at the recent European Society of Cardiology congress (end of August 2020). DAPA-CKD result has not been published formally at the time of writing – it should come soon. What is noteworthy is that DAPA-CKD was not an exclusive trial of patients with DKD but included about 30 percent of CKD patients who do not have diabetes. The study enrolled patient patients with eGFR in the range of 25-75ml/min/1.73m^2; extending the use of SGLT2-I for renal protection to patients with CKD stage 4.

There have not been any studies (completed or published) using SGLT2-I as primary prevention in the diabetic cohort. It is interesting to note that the results were seen in the CVOTs (especially DECLARE) seem to suggest that it is effective in patients with eGFR > 90ml/min/1.73m^2 and without significant albuminuria (UACR < 30mg/g) – a population that fits the definition of 'absence of renal disease or DKD'. This would suggest that perhaps SGLT2-I may be effective in altering the natural history of this much-feared diabetic complication and add to the primary prevention strategy for all diabetic patients.

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LEARNING POINTS

- **The prevention of CV and Renal complications requires a multi-prong approach, as there are many modifiable risk factors that can be attenuated to improve outcomes (or prevent the onset of complications). There is an absolute need to pay close attention to glycaemic control, BP targets, weight management amongst many of the recommended efforts as discussed.**
- **The use of aspirin, statin, and RAS blockade in the appropriate population is also crucial in the overall management strategy of diabetic patients. In particular, the use of RAS blockade in a diabetic patient with albuminuria is strongly advocated, and all efforts should be made to maintain these patients on the optimal doses of ACEI or ARB.**
- **SGLT2-I has certainly added to the therapeutic options to further improve CV and Renal Outcomes in diabetic patients; especially in preventing hospitalisation related to heart failure and progression of renal disease. These are two highly costly adverse endpoints in the lives journey of diabetic patients and effective therapy against these complications is very much a major step in the right direction.**