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CHRONIC KIDNEY DISEASE

CARDIOVASCULAR RISK IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is a major risk factor for coronary artery disease (CAD). As well as their high prevalence of traditional CAD risk factors, such as diabetes and hypertension, persons with CKD are also exposed to other nontraditional, uremia-related cardiovascular disease risk factors, including inflammation, oxidative stress, and abnormal calcium-phosphorus metabolism. This association has been demonstrated in both community-based populations (i.e. cohorts not selected specifically to enroll individuals with CKD or cardiovascular disease) and in patients with an elevated cardiovascular risk profile. As glomerular filtration rate (GFR) declines below 60 to 75 ml/min/1.73 m2 , the probability of developing CAD increases linearly (Figure 1) and patients with CKD stages G3a to G4 (15-60 ml/min/1.73 m2) have approximately double and triple the CVD mortality risk, respectively, relative to patients without CKD. [End stage kidney disease in patients dependent on dialysis, have a higher cardiovascular risk which is beyond the scope of this article]. Elevated plasma cystatin C concentration, another filtration marker may be a more accurate measure of cardiovascular risk than elevated plasma creatinine concentration. Cystatin C is not routinely used in clinical practice thereby limiting its usefulness.

Presentation of CAD

CKD modifies the clinical presentation and cardinal symptoms of CAD. Recognition of ischemia in CKD requires an appreciation that coronary syndromes present atypically, and a high index of suspicion is critical for anginal equivalents such as shortness of breath or fatigue. CKD patients are more likely to have an acute coronary syndrome (ACS) rather than stable exertional angina as their initial clinical manifestation of CAD. This ACS presentation may reflect a supply-demand mismatch, ischemic pre-conditioning, collateralization of blood vessels, and perhaps a higher prevalence of left ventricular hypertrophy rather than culprit plaque rupture.

Risk Assessment and Diagnosis

Standard clinical guidelines recognize CKD as a "modifying factor" to be considered in using the standard risk equations. However, they do not formally incorporate kidney-specific variables, even though eGFR is readily available. When eGFR and albumin-creatinine ratio is included with traditional cardiovascular risk factors, the ability to forecast cardiovascular events is increased. Other risk stratifying tests such as coronary calcium scoring may help to refine atherosclerotic CVD risk estimates when benefits and risks of treatment are uncertain. Coronary calcification is prevalent among patients with CKD, and although the prognostic value is likely similar to that in the general population, the progression of coronary calcification is faster with worsening CKD. Whereas atherosclerosis in early CKD is driven by traditional CAD risk factors, nontraditional risk factors play a predominant role as GFR declines, leading to fibrocalcific lesions. Modification of lipoproteins (e.g., low-density lipoprotein carbamylation, high-density lipoprotein dysfunction) in CKD likely contributes to accelerated progression of CAD, and risk factors for calcification include inflammation, senescence, mechanical factors (e.g., shear stress, elastin fatigue), and potentially accumulation of microbiomedependent metabolites such as trimethylamine N-oxide. The association of phosphorus, calcium, and parathyroid hormone with coronary artery calcification in patients with CKD is inconsistent.

Exercise testing and pharmacologic perfusion imaging have reduced accuracy for detecting CAD in CKD, with a higher rate of both false-negative and false-positive tests. There are several provisos to the use of functional testing in CKD. Exercise testing is frequently limited by an inability of CKD patients to reach diagnostic workloads. Second, exercise testing in the CKD population is often limited by baseline electrocardiographic abnormalities (e.g., LVH) that could limit ability to detect ST-segment changes during exercise. Non-invasive tests may have a low negative predictive value and may not exclude the presence of functionally significant or anatomically high-risk disease. Thus, maintaining a high index of suspicion is critical in evaluating noninvasive cardiac testing in CKD patients. Computed tomography angiography (CTA) may offer significant advantages over functional imaging modalities in the setting of CKD, but the risk of acute kidney injury needs to be considered, especially in late stage CKD.

Troponin

Cardiac troponins (cTn) are frequently elevated in advanced CKD in the absence of ACS or overload, but the mechanism of this remains unclear. Regardless of cause, cTnT and cTnI elevations (both in the presence and absence of ischemia) are associated with increased all-cause and CV mortality in CKD. It is also unknown whether elevations in baseline measurements should trigger additional investigation to assess cardiac structure or atherosclerosis. More data are needed to better understand whether a CKD-specific high-sensitivity cTn threshold for absolute cTn values or dynamic change could improve sensitivity and specificity of MI diagnosis.

Cardiovascular Risk Reduction

The evidence supports the following approach in CKD patients with traditional CV risk factors to reduce the atherosclerotic event risk:

- Smoking cessation, maintenance of an ideal body weight, an active lifestyle, and, in patients with diabetes, glycemic control
- Statin therapy
- Blockade of the renin-angiotensin axis, as part of the anti-hyperten sive regimen to achieve blood pressure goals in patients with proteinuric CKD
- Aspirin

The recently published ISCHEMIA-CKD (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches—Chronic Kidney Diseases) trial randomized CKD patients with moderate ischemia on a clinically indicated stress test to medical therapy with or without revascularization to clarify the value of revascularization in the setting of stress-induced ischemia. At a median of 2.2 years, patients with stable coronary artery disease and advanced kidney disease who were treated with an invasive strategy of coronary angiography with revascularization if indicated did not have a lower risk of death or MI than those who were treated with a conservative strategy of medical therapy alone.

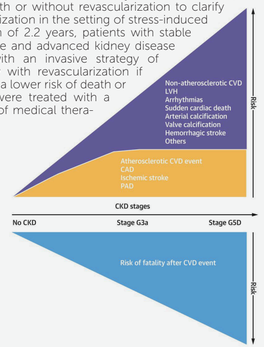

Figure 1

By **Dr. Rohit Khurana**
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HYPERTENSION

RENOVASCULAR DUPLEX SONOGRAPHY IN HYPERTENSION

Epidemiologic studies suggest that renovascular disease is responsible for hypertension in approximately 1 to 6% of the general hypertensive population and is the most common cause of secondary hypertension [1]. In patients whose hypertension acutely worsens, those with malignant hypertension or referred to specialty centres for difficult-to-control hypertension, the prevalence of renovascular disease is about 30% and may be as high as 45% in patients with both accelerated hypertension and renal failure.

Since renovascular hypertension is the most frequently encountered form of potentially curable hypertension it is important to identify patients with renal artery disease. Significant renal artery atherosclerotic stenosis (RAS) can be treated with renal artery angioplasty and possible stenting. Young women with fibromuscular dysplasia (FMD) on the other hand respond very well to an angioplasty, but stenting must be avoided as recurrences can occur. And in select cases with resistance to multiple drugs, renal nerve denervation offers a potentially effective alternative to excessive medication.

The diagnosis of renovascular hypertension or ischemic renal failure has two requirements: demonstration of a renal artery lesion (RAS or FMD); and proof that this lesion is functionally significant. In addition, an assessment that there is sufficient healthy renal cortical tissue left to salvage is also essential before contemplating intervention.

To date, the usual test for the demonstration of functional significance has been measurement of renin levels in both renal veins. Unfortunately, measurement of renal vein renin is expensive and invasive (requires renal angiography and selective sampling), cannot be used for the determination of functional significance of lesions in patients with bilateral disease, and is not infallible.

Ultrasound duplex scanning combines a B-mode ultrasound image with a pulsed Doppler unit to obtain flow velocity information from known locations along a visualized vessel. The non-invasive method has gained wide acceptance in the diagnosis of carotid artery occlusive disease and the evaluation of renal allografts. With the introduction of low frequency ultrasound scan probes which allow penetration of the ultrasound beam to greater depths, duplex scanning can now be applied to intra-abdominal vessels including the renal arteries. However, for the test to be reliable, it requires ultrasound machines with much computing software and scanning probes of high specification, as well as sonographers and physicians trained and skilled in its performance and interpretation.

At the Vascular diagnostic laboratory located at the Harley Street Heart and Vascular Centre, the renovascular duplex scan protocol allows for direct measurements of flow velocities in the aorta and renal arteries, as well as measurements of intra-renal waveforms that add to the diagnosis of significant renovascular disease. This is in addition to the standard ultrasound imaging of renal tissue for cysts, scarring and lesions.

Direct measurements are of the peak systolic velocity of flow (PSV) in the renal artery and increases in PSV across a stenosis define the significance of that lesion. PSV of the renal artery and the aorta are also used to calculate the ratio between the two (renal-aortic ratio, RAR), as a measure of renal artery ostial stenosis. An RAR of greater than 3.5 indicates a greater than 60% diameter reduction across the ostium.

An alternative method of identifying RAS indirectly is by using intrarenal waveforms, where the systolic upstroke is abnormal distal to a hemodynamically important stenosis. This phenomenon has been called the "tardus-parvus" effect, borrowing from the term used earlier to describe the delayed (tardus) and dampened (parvus) upstroke in the peripheral pulse distal to a stenosis of the aortic valve. A slowing of the systolic upstroke or the acceleration index (normal, >300 cm/s2), an increase in acceleration time (normal <70 milliseconds) and loss of the early systolic peak (ESP) are the most important parameters.

Another key parameter measured is the renal arterial resistive index (RI) which is a sonographic index of intrarenal arteries defined as (peak systolic velocity - end-diastolic velocity) / peak systolic velocity. The resistive index (RI) is measured using spectral Doppler at the arcuate arteries (at the corticomedullary junction) or interlobar arteries (adjacent to medullary pyramids). The normal range is 0.50-0.70.

The renal resistive index is a nonspecific but important prognostic marker in vascular diseases that affect the kidney. High resistive indices (>0.8) in native kidneys are associated with renal dysfunction and adverse cardiovascular events. In renal transplant recipients, high resistive indices (>0.8) are associated with increased risk of graft loss and death. Though there is little correlation between the resistive indices and the quantitative extent of renal dysfunction (measured by serum creatinine values), the RI is a key marker of salvageable renal cortical function. An RI >0.9 suggests to us that interventional therapy, be it renal angioplasty, stenting or renal denervation may no longer be worth it as too much cortical damage has occurred.

Normal indices and parameters used at our vascular lab[1] are shown in table 1, and duplex images in a healthy kidney in figure 1.

Who should have a renovascular duplex scan?

The AIUM[2] recommends assessment in the following groups of patients:

1. Hypertension with suspicion of a significant vascular lesion (young onset hypertension < 50 years of age, known coronary or peripheral arterial disease with HTN)
2. Vascular murmur in the epigastrium
3. Significant (>15 mm) asymmetry in kidney size
4. Evaluation of renal perfusion in patients with known aortic dissection, post trauma, and other diseases known to affect renal perfusion
5. Hypertensive patients with deterioration of renal function
6. Monitoring of patients with previously diagnosed renovascular hypertension
7. Poorly controlled HTN despite 3 drug therapy

Renovascular duplex scanning is an important diagnostic and monitoring tool in patients with hypertension. Early diagnosis and treatments and/ or intervention can prevent deterioration of renal function and other cardiovascular complications of poorly controlled hypertension in our patients.

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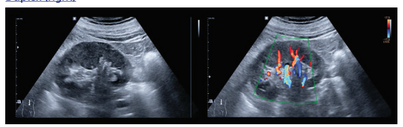
2. American Institute of Ultrasound in Medicine, American College of Radiology, Society for Pediatric Radiology, Society of Radiologists in Ultrasound . AIUM practice guideline for the performance of native renal artery duplex sonography. J Ultrasound Med 2013; 32: 1331–1340.

Table 1. Renovascular Duplex parameters at The Harley Street Heart and Vascular Centre

Peak systolic velocity	Condition	Renal Aortic ratio
PSV <180 cm/s	Normal	< 3.5
PSV <180 cm/s	Stenosis < 60%	< 3.5
PSV <180 cm/s	Stenosis > 60%	> 3.5
PSV absent	Obstruction	-
Indirect intra-renal parameters		
Renal Resistive index (RI)	< 0.7	
ΔRI (right – left)	< 0.05	
Acceleration time (AT)	< 0.07	

Figure 1. Renal ultrasound (left) with corresponding Renovascular Duplex (right)



By **Dr. Sriram Narayanan**
Senior Consultant Vascular Surgeon
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SGLT2 INHIBITORS

HEART FAILURE-EXPANDING INDICATIONS FOR SGLT2 INHIBITORS

Diabetes and heart failure, although seemingly very different conditions, they both form part of the cardiometabolic spectrum. Patients with heart failure commonly develop diabetes, with a recent study in Singapore showing that in patients hospitalized with HF, 59% had diabetes. Similarly, patients with diabetes are at much greater risk of getting heart failure. Diabetes increases the risk of developing HF partly through increased risk of coronary artery disease and hypertension but also because diabetes has a direct effect on the myocardium that leads to myocardial dysfunction. Despite all the available treatments for heart failure, it still has a very poor prognosis with around half of patients dying within 5 year of diagnosis. It is therefore not surprising that a drug that has created a paradigm shift in the management of diabetes is also now the being used to treat heart failure in patients with and WITHOUT diabetes!

The Sodium Glucose Co-transporter 2 (SGLT2) protein promotes glucose reabsorption from the glomerulus back into the circulation and is responsible for approximately 90% of the kidney's glucose reabsorption. The SGLT2 inhibitors block this protein from reabsorbing glucose, causing it to be passed out in the urine. There are currently 3 SGLT2's licensed for the treatment of diabetes in Singapore, Canagliflozin (Invokana), dapagliflozin (Forxiga), and empagliflozin (Jardiance).

SGLT2 inhibitors are an established treatment for diabetes, with 4 major cardiovascular outcome trials examining their ability to improve outcomes in patients with diabetes. Whilst these trials are difficult to directly compare due to the heterogeneous populations examined, they all showed significant reductions in hospitalization for heart failure, in the region of 30%. The benefits are seen very quickly following the initiation of these drugs. Interestingly, most of these trials only enrolled around 10-15% of patients with known heart failure.

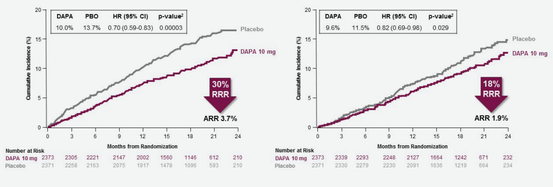
Given the significant improvements in hospitalization for heart failure in patients with diabetes, trials examining these drugs in patients with heart failure were commenced. The first trial to publish its results was the DAPA-HF trial in November 2019. This trial enrolled 4744 patients with heart failure and reduced ejection fraction both with and without diabetes. To be enrolled in the trial, patients had to have symptomatic HF with an LVEF ≤ 40%, an NTproBNP≥600 pg/ml and an eGFR above 30 ml/minute/1.73 m2. They were randomized to dapagliflozin 10mg versus placebo, on top of standard heart failure therapy. The primary composite outcome was CV death/ HF hospitalisation and urgent HF visit. Mean age was 66 and most had NYHA 2 heart failure. Only 45% had diabetes at baseline. Patients were well treated with around 94% being on ACE/ARB/Entresto and 71% an MRA. The results were striking! The primary endpoint was reduced by 26% with a number needed to treat of just 21 over 2 years. The primary outcome occurred in 16.3% of the Dapagliflozin group and 21.2% of those in the placebo group. The event curves began separating in the first month demonstrating that patients began to benefit very quickly. Every component of the primary endpoint was reduced significantly, including CV death. Most remarkable of all was that these benefits were seen in both diabetics and non diabetics.

There are a number of other trials on the horizon in heart failure patients with both preserved and reduced ejection fraction. In the last month, we have had an announcement from Boehringer that their trial EMPEROR-Reduced using empagliflozin has also met its primary outcome. However, this paper has not been published yet and we will need to review the data when it is available, and wait for approval from HSA prior to promoting its use in heart failure patients. Forxiga (dapagliflozin) already has HSA approval for its use in HFrEF patients with and without diabetes, when given in addition to standard therapies.

These drugs are clearly effective treatments in multiple patient groups and some have likened them to ACE/ARB where they provide CV protection in multiple subsets of patients of patients at high CV risk. But what are the potential side-effects of SGLT2s? The most common side effects are genital yeast infections. They are usually mild and don't recur once treated. Urinary tract infections are also slightly more common. Ketoacidosis has also been described but it is rare. In the CANVAS program, Canagliflozin was associated with a slightly greater risk of bone fractures and lower limb amputations.

In summary, dapagliflozin is now part of the standard of care in HFrEF patients both with and without diabetes. There are a number of other exciting trials on the horizon, and the trials I am particularly interested in seeing are the SGLT2 trials in HFpEF. HFpEF continues to be a disease that we do not yet have any satisfactory treatment for.

Components of the Primary Endpoint[1,2] — **Published**



*Worsening HF includes hHF or urgent HF visit.
† ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; PBO = placebo; RRR = relative risk reduction.

1. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008. 2. McMurray J. Presented at: ESC Congress; August 31-September 4, 2019; Paris, France.

By **Dr. Michael MacDonald**
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SGLT2 INHIBITORS

A SAFE EARLY TERM DIP IN THE GFR WITH A LONG TERM KIDNEY PRESERVATION

The lifetime risk of diabetic nephropathy averages 40% in the diabetic population, higher in some populations (eg extremely high in native americans). Malays certainly have an aggravated risk of developing this complication. Nephropathy reduces life expectancy and amplifies severity and frequency of concurrent macrovascular complications. Renin angiotensin blockers or ACE inhibitors reduce nephropathy progression in both microalbuminuria and macroalbuminuria patients. These effects are partial, with relative risk reduction of at best 25% in the historical trials.

The sodium / glucose co-transporter 2 inhibitors ((SGLT2)) are newer hypoglycemic agents which reduce average hba1c , but directly reduce GFR decline and MACE, likely independent of glucose control. They selectively block the sodium dependent glucose transporter receptors that are expressed almost entirely in the renal proximal tubules. Selective inhibition of this protein leads to renal glucosuria and reduction of plasma glucose. They do so without causing weight gain, (but weight loss instead) and contribute to small reductions of the blood pressure as well.

EMPA REG OUTCOME trial (Empaglifozin vs placebo) demonstrated the superiority of these drugs over placebo in lowering serum glucose, but added gains were seen in both reduced MACE and renal events beyond that accounted for by glucose lowering. Since then other trials focusing primarily on adverse CVD outcomes had convergently demonstrated the effects in major adverse cardiovascular events. This was not the only benefit; secondary renal endpoints were most encouraging. CANVAS (Canaglifozin Cardiovascular Assessment Study) with a study population of 10 000) showed a relative reduction of 27% in progression of albuminuria, with a relative risk reduction of 40% renal replacement or death from renal causes; DECLARE (Dapaglifozin Effect on Cardiovascular Events -Thrombolysis in Myocardial Infarction 58 with 17 000 studied) demonstrated a 24% relative risk reduction in ESRD or death from renal or CV causes.

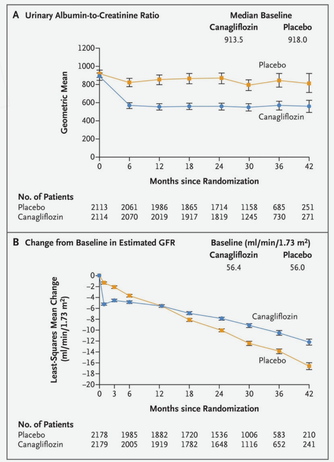
The CREDENCE (Canaglifozin versus placebo) study with a study population of 4401 patients studied as primary end point ESRD, sustained eGFR of less of 15ml/min, or death from renal or cardiovascular causes against a placebo in patients who were already on standard therapy with an ACE inhibitor or an ARB. Importantly they studied patients with a GFR of between 30 to 90ml per minute with established macrovascular disease. The positive results were exciting. There was a relative risk reduction of 30% in renal endpoints at the end of 2.6 years of therapy. The trial was stopped prematurely because of these excellent results. The addition of these drugs would reduce 47 ESRD or ESRD deaths in 1000 treated patients, and reduce hospital events (less 22 hospitalisations for every 1000 treated patients). The beneficial effects of reduced renal events were present in patients across all GFR groups, from as low as 30 up to 90ml/min. This bring fresh hope to patients with already established and advanced diabetic nephropathy.

There were safety concerns. Similar to the effects of introducing an ACE inhibitor, there is an initial dip in the GFR. Nevertheless, there was a non significant difference in acute kidney injury in both the treated and placebo groups (86/2200 vs 98/2197); The initial GFR dip which is seen as early as 2 to 4 weeks stabilizes by then, and the slope of further decline of GFR flattens considerably compared to the continuous decline seen in the placebo group.* An enhanced osmotic diuresis with the treatment group may cause this until there is a compensatory increased intake of fluids in patients. The GFR initial decline however also reflects the likely effect of reduced renal hyperfiltration. The enhanced sodium delivery to the macula densa with glycosuria enhances a tubular glomerular feedback, increasing afferent arteriolar tone to compensate for enhanced natriuresis, an effect that eventually stabilities, and translates to a reduction in the intraglomerular pressure that is protective to the kidneys in the long term.. The enhanced natriuresis and volume contraction may be contributory also to its effect on lowering blood pressure and cardiovascular protection.

There are concerns of increased urinary tract infections or balanitis because of the persistent glycosuria, reversible on stopping the drug. In May 2013 to 2018 there reports of Fournier's gangrene in the May 2018 in 12 patients in whom hospitalization and treatment required. No cases of Fourniers were reported in the clinical trials earlier. Invokana had carried a black box warning for amputation, but not so for the other SGLT; this was just recently removed by the FDA in 26/8/2020. Finally the SGLTs are only for use in the Type2 DM and there are ongoing concerns of its precipitating ketoacidosis in the type 1 patient.

The SGLT2 antagonists are currently approved for use in patients with a GFR>60 mL/min/1.73 m 2 for dapagliflozin and a GFR>45 mL/min/1.73 m 2 for empagliflozin and canagliflozin.They provide end organ protection, despite a visible but not dramatic reduction in glucose control. Already they are recommended for early use in diabetic patients,The threshold of their use may lower, with permissible use at a lower GFR .It is after all it is the end points that matter eventually.

***Renal Indices in Credence (June 13, 2019; N Engl J Med 2019; 380:2295-2306)**



By **Dr. Stephen Chew**

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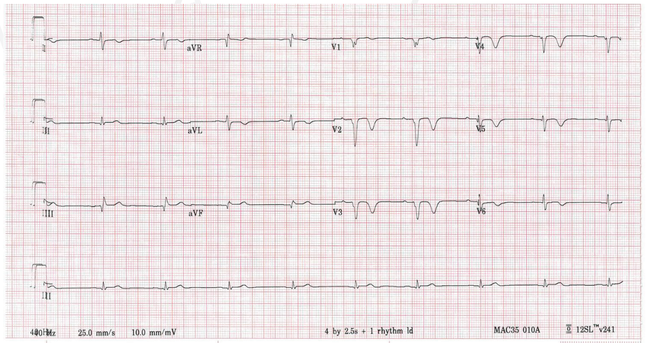
QUIZ

A 47-year-old man, who was previously fit and well, developed a non – ST elevation myocardial infarction whilst skiing in the USA earlier this year which was treated with percutaneous coronary intervention. He came to see me one week later after he returned to Singapore and felt well with no chest pain or breathlessness. His ECG (Figure A) and 4-chamber view of his echocardiogram (Figure B) when seen in clinic are shown below. His left ventricular (LV) ejection fraction measured 47% with anteroseptal regional wall motion abnormalities. What does the ECG and echo image show? How would you manage his condition?

(a)



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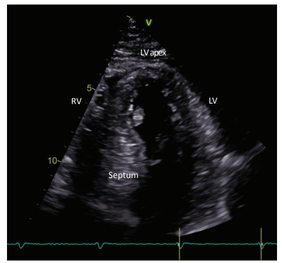

Answer is available on our website: ***http://www.harleystreet.sg/quiz-answers/medbulletin-Sept-2020/***

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THE HARLEY STREET HEART & VASCULAR CENTRE

MEDBULLETIN SEPTEMBER2020

THE HARLEY STREET HEART & VASCULAR CENTRE

From left to right:
Dr. Sriram Narayanan, Dr. Reginald Liew
Dr. Michael MacDonald, Dr. Rohit Khurana

INTRODUCTION

Greetings from the Harley Street Heart and Vascular Centre! Despite these difficult and uncertain times, we are keen to provide our primary care colleagues with the most up-to-date information and practical tips in helping you manage your patients with cardiovascular disease. The focus of our second newsletter of 2020 is to provide a succinct update on the management and treatment of patients with increased cardiac risk, diabetes and renovascular disease. As more people in Singapore lead stressful and unhealthy lifestyles, especially during the current pandemic, healthcare providers are diagnosing more patients with diabetes and heart disease. There have been a lot of recent changes and new drugs approved in Singapore which the busy clinician managing such patients should be aware of and comfortable to prescribe.

In this edition, Dr Rohit Khurana provides a summary of cardiovascular risk in patients with chronic kidney disease. His article describes how the presentation may differ in such patients and what practical measures doctors can take to reduce their cardiac risk. Dr. Sriram Narayanan explains how the renovascular duplex ultrasound scan, which is offered at the Harley Street Heart and Vascular Centre, can be used to detect secondary causes of hypertension and which patients should be considered for the scan. He describes the important parameters that should be measured which may signify a need for further assessment and intervention for renovascular disease in patients with hypertension. Dr Michael MacDonald introduces the newer class of anti-diabetic drugs, SGLT2 inhibitors, that were initially developed to treat patients with type II diabetes, but are now also indicated in the treatment of patients with heart failure with reduced ejection fraction, even in non-diabetic patients. We are delighted to have Dr Stephen Chew, consultant nephrologist, as our guest editor in this newsletter. Dr Chew's article gives an overview on how SGLT2 inhibitors can confer further renal protection in diabetic patients, despite an early dip in the GFR, as well as what safety concerns doctors prescribing this newer class of medication should be aware of.

As usual, the newsletter ends with an interesting and challenging medical quiz. Dr. Reginald Liew presents a case study of a patient with an acute myocardial infarction and an interesting finding on his echocardiogram. The answer to the quiz will be posted on our website (www.harleystreet.sg) within a week of the newsletter being sent out.

We hope these articles are useful in your daily practice and help challenge and improve your management of patients with diabetes and cardiovascular disease. Please feel free to contact us (at enquiries@harleystreet.sg) if you would like to provide any feedback or request a specific topic in future editions.

From The Harley Street Heart and Vascular Centre

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