UNIT NO. 6

RENOVASCULAR COMPLICATIONS

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ABSTRACT

Hypertension is an important risk factor for cardiovascular morbidity and mortality and can lead to chronic kidney disease (CKD) as manifested by proteinuria, renal dysfunction (eGFR <60 ml/min/1.73 m^2) and end stage renal failure. From the results of a survey in the US general population, over 17% were demonstrated to have proteinuria or renal dysfunction. On the other hand, hypertension was present in a significant proportion of those with underlying CKD: among survey participants, 51% of those with proteinuria and over 60% of those with eGFR < 60 ml/min/1.73 m^2, had hypertension. From the National Health Survey Singapore, 2004, the prevalence of hypertension in adults was 24.9%. Thus there is a strong association between hypertension and CKD and a significant proportion of the Singapore population is at risk for CKD. Regardless of whether hypertension is the cause or the result of CKD, one of the most difficult problems in managing patients with CKD is the achievement of blood pressure (BP) targets recommended by guidelines. Management of hypertension in CKD includes lifestyle measures such as sodium restriction as well as pharmacologic measures. A treatment regimen that optimises BP control while reducing proteinuria is necessary to reduce progression of kidney disease while minimising the risks of heart disease and stroke.

Keywords: chronic kidney disease, eGFR, microalbuminuria, end stage renal failure, Singapore Renal Registry, hypertension.

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PREVALENCE OF HYPERTENSION IN THE SINGAPORE POPULATION

According to the last National Health Survey (NHS), Singapore, 2004 [1], the prevalence of hypertension in adults aged 30 to 69 years in 2004 was 24.9%. Hypertension was more prevalent in males (29.5%) than females (20.4%) and more prevalent among Chinese (25.6%), compared with Malays (22.7%) and Indians (21.6%). The age specific prevalence of hypertension rose dramatically above the age of 40 years (prevalence of 8.8%, 21.6%, 36.2% and 56.1%, for those of 30-39 years, 40-49 years, 50-59 years and 60-69 years respectively). However, among those found to have hypertension, only 61.5% had been previously diagnosed, with 49.5% of these having good blood pressure control, as defined by systolic blood pressure < 140 mm Hg and diastolic blood pressure < 90 mm Hg.

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RENAL EFFECTS OF HYPERTENSION

Hypertension is a risk factor for atherosclerosis and its attendant complications and is an independent risk factor for heart failure, coronary artery disease, stroke, kidney disease and peripheral arterial disease. It is the most important risk factor for cardiovascular morbidity and mortality. Given the high prevalence of hypertension in the population and the wide range of end organ damage associated with hypertension, it would be useful to quantitate the impact of hypertension on these co-morbidities in the Singapore population.

However the NHS, Singapore was not intended to evaluate the systemic effects of hypertension; contrariwise, similar surveys in the United States have evaluated the impact of hypertension on various organs including the kidney. The National Health and Nutrition Examination Survey (NHANES) III [2], is a cross-sectional examination survey of the US civilian non-institutionalised population. For those surveyed between 2005 and 2008, approximately 68 million (31%) US adults aged ≥18 years had hypertension. The prevalence of hypertension was 30% and 31.7% among males and females respectively and as with the Singapore population, the prevalence of hypertension was higher among those 40 years and older. Among those aged 18-39 years, 40-64 years and >65 years, the prevalence of hypertension was 7.4%, 35.6% and 69.7% respectively. Of these, 70% were receiving pharmacologic treatment and 46% had good control of blood pressure. The many similarities between hypertension in the Singapore and US populations permit extrapolation of renal complications from one population to the other.

NHANES survey participants were evaluated for evidence of chronic kidney disease (CKD) by determining urinary protein and renal function[3]. Urine albumin (mg/l) and urinary creatinine (mg/dl) were measured and the urinary albumin/creatinine ratio (ACR) calculated. Participants with ACR > 30 mg/g were classified as having microalbuminuria. Renal function as estimated with the glomerular filtration rate (ml/min/1.73 m^2, eGFR) utilised the stan¬dardised creatinine and the MDRD formula described by Levey et al. Presence of chronic kidney disease (CKD) was defined as an eGFR < 60 ml/min/1.73m^2, or an eGFR ≥ 60 in the presence of

microalbuminuria. CKD stages were defined as follows:

Stage 1	ACR ≥ 30 and eGFR ≥ 90
Stage 2	ACR ≥ 30 and 60 ≤ eGFR ≤ 89
Stage 3	30 ≤ eGFR < 60
Stage 4	15 ≤ eGFR < 30
Stage 5	eGFR < 15

Among those with self reported hypertension in the survey, 17.2% had eGFR < 60 ml/min/1.73 m^2 while 17.3% had ACR > 30 mg/g, in contrast to the prevalence of these findings of 7.8% and 9.9% in the non-hypertensive population. In comparison to those without hypertension, the Odds ratio for reduced eGFR and microalbuminuria among hypertensives were 1.9 and 1.6 respectively. Thus the overall prevalence of CKD was significantly increased in the hypertensive population.

Indeed, on the other side of the spectrum of relationship between hypertension and CKD, the prevalence of hypertension was higher among those with proteinuria or reduced eGFR. Hypertension was present in 24% of par¬ticipants with an ACR < 10 mg/g, compared to 51% of those with an ACR > 30 mg/g. Among NHANES participants with eGFR < 60 ml/min/1.73 m^2, approximately 64% to 68% had hypertension, compared to 26% of those with an eGFR > 60 ml/min/1.73m^2. The prevalence of hypertension also rose with increasing CKD severity. In participants with eGFR < 30 ml/min/1.73 m^2, 84 to 85 percent had hypertension, compared to 5% of participants with eGFR > 60 ml/min/1.73 m^2. Renal dysfunction further conferred mortality risk in this survey population: deaths per 1,000 patient years were 45, 7 and 4 respectively for those with eGFR <60, 60-89 and > 90 ml/min/1.73 m^2. Thus the overall prevalence of hypertension was significantly increased in the population with either reduced eGFR or proteinuria.

This survey data is clear evidence of the strong association of CKD with hypertension in the general population. In this context, hypertension has been described as both a "victim" and a "villain". As a villain, atherosclerotic, hypertension-related vascular lesions in the kidney primarily affect the afferent arterioles resulting in ischemic changes in the glomeruli. Glomerular hyperperfusion and hyperfiltration from hypertension may also cause glomerular injury by direct damage to the glomerular capillaries. Glomerular injury progresses to glomerulosclerosis and eventually to renal tubular ischemia and atrophy. These glomerular changes lead to renal abnormalities including proteinuria and renal dysfunction as demonstrated above. In cases of malignant hypertension, fibrinoid necrosis of the afferent arterioles sometimes extending into the glomerulus occurs and may result in focal necrosis of the glomerular tuft, eventually progressing to renal damage.

Apart from the effects of hypertension on the kidney as described above, CKD itself increases the prevalence and severity of hypertension as described above. Extracellular fluid expansion in CKD may contribute to exacerbation of hypertension, leading to accelerated glomerular injury. Other mechanisms of exacerbation of hypertension in CKD include

- Renin-angiotensin aldosterone system activation
- Renovascular disease
- Increased sympathetic activity
- Alteration in endothelium-derived factors (nitric oxide/endothelin).

Hypertension as a cause of end stage renal failure (ESRF) is estimated at 27% in the US, with the proportion being particularly high among African Americans. Hypertension as a cause of ESRF is however less common in Singapore, with its estimated contribution approximately 10% of ESRF from data from the Singapore Renal Registry[4].

MANAGEMENT OF HYPERTENSION

Regardless of whether hypertension is the cause or the result of CKD, one of the most difficult problems in managing patients with CKD is the achievement of blood pressure (BP) targets recommended by guidelines[5]. Post hoc analyses of randomised clinical trials in patients with proteinuria > 300 mg/day have demonstrated slower declines in kidney function with lower BP levels. Thus, international guidelines for treatment of hypertension published since 2003, including the Seventh Report of the Joint National Committee on Prevention,Detection, Evaluation, and Treatment of High Blood Pressure (JNC7), recommend BP targets below 130/80 mm Hg for those with CKD so as to reduce progression of kidney damage. Furthermore, based on post hoc analyses of several studies demonstrating maximal slowing of nephropathy only when proteinuria was reduced to at least 30% below baseline values, and in conjunction with BP reduction, therapy to reduce proteinuria has become a recommendation in the management of hypertension and CKD.

Management of hypertension in CKD includes lifestyle measures such as sodium restriction as well as pharmacologic measures. For the latter, first line therapy comprising of Renin Angiotensin Aldosterone Blockers (RAAS), Angiotensin Converting Enzyme Inhibitors (ACEi) or Angiotensin Receptor Blockers (ARB), together with diuretics and Calcium Channel blockers (CCB) so as to control blood pressure and reduce proteinuria is recommended (Table 1). Beta blockers may be substituted for CCBs if the patient has angina, heart failure or arrhythmia. Agents such as hydralazine, methyldopa or clonidine can be used as adjunctive agents to achieve BP goals. Apart from these, aldosterone antagonists may be useful in treating hypertension in those with hypertension and advanced heart failure and for reducing proteinuria in those with significant proteinuric kidney diseases. On the basis of several studies, multiple agents are often required to achieve satisfactory blood pressures (3.3 agents at maximally tolerated doses).

Table 1: Guidelines for Management of Hypertension in Chronic Kidney Disease

	Antihypertensive Drug Class
Preferred Initial Antihypertensive	Angiotensin Converting Enzyme Inhibitors, Or Angiotensin Receptor Blockers
Adjunctive Antihypertensives	
2nd Line	Thiazide Diuretics for GFR ≥ 30 mL/min
	Loop Diuretics for GFR< 30 mL/min
3rd Line	Beta Blockers, Or Calcium Channel Blockers
Target Blood Pressure	< 130/80 mm Hg
Precautions	
ACEI / ARB	- Hyperkalemia, K^+ > 5.5 mmol/L - GFR Decline ≥ 30% from Baseline Value - Renal Artery Stenosis - Pregnancy
Aldosterone Antagonists	- Chronic Kidney Disease - Hyperkalemia, K^+ > 5.5 mmol/L
Diuretics	- Gout
Beta Blockers	- Bradycardia - Heart Failure - Heart Block - Asthma, Chronic Obstructive Lung Disease - In combination with Non-Dihydropyridine Calcium Channel Blockers
Calcium Channel Blockers	- Heart Block
Special Indications for Adjunctive Antihypertensives	
Heart Failure with Systolic Dysfunction	- Thiazide or Loop Diuretics - Aldosterone antagonists - Selected Beta Blockers[a]
Post Myocardial Infarction	- Beta Blockers
Chronic Stable Angina	- Beta Blockers - Calcium Channel Blockers
Coronary Artery Disease	- Thiazide or Loop Diuretics - Beta Blockers - Calcium Channel Blockers
Stroke prevention	- Thiazide or Loop Diuretics
Supraventricular tachycardia	- Beta Blockers - Non Dihydropyridine Calcium Channel Blockers

[a] Selected beta blockers such as Carvedilol, bisoprolol, metoprolol
Adapted from Guidelines from the Joint National Commission on the Prevention, Detection, Evaluation, Treatment of Hypertension and National Kidney Foundation Kidney Disease Outcomes Initiative and American Society of Hypertension position paper[5,6].

CONCLUSIONS

A treatment regimen that optimises BP control while reducing proteinuria is necessary to reduce progression of kidney disease while minimising the risks of heart disease and stroke.

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LEARNING POINTS

- **Hypertension is an important risk factor for cardiovascular morbidity and mortality and is associated with renal complications.**
- **The prevalence of hypertension in adults aged 30 to 69 years in 2004 in the Singapore population was 24.9%, indicating a large burden of disease.**
- **Only 61.5% had been previously diagnosed and only 49.5% of those diagnosed with hypertension having good blood pressure control, as defined by systolic blood pressure < 140 mm Hg and diastolic blood pressure < 90 mm Hg.**
- **One of the most difficult problems in managing patients with CKD is the achievement of blood pressure (BP) targets recommended by guidelines.**
- **A treatment regimen that optimises BP control while reducing proteinuria is necessary to reduce progression of kidney disease while minimising the risks of heart disease and stroke.**