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Prescribing adherence of antihypertensive agents in Chronic Kidney Disease (CKD) patients and its relationship with clinical outcomes

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***Abstract*---**Objectives This study was conducted to evaluate the utilisation of antihypertensive agents, assess prescribing adherence and determine the relationship between guideline adherence indicator (GAI) and clinical outcomes among hypertensive CKD patients. Methods This was a retrospective cohort study involving newly diagnosed CKD patients undergoing follow-up between January to December 2018 at a tertiary Malaysian hospital. The study subjects were screened and recruited using simple random sampling according to inclusion and exclusion criteria. Clinical data was retrieved from the online medical record (eHis system) using a pre-prepared data collection form. Results A total of 74 patients were included in this study with mean (SD) age of 66.86 (10.86) years old. The majority were male (n= 39, 52.7%) and Malay (n= 34, 45.9%). The study results showed that CCB was the drug of choice prescribed, while the most commonly prescribed combination therapy was ACEI + beta-blocker + CCB and ACEI + CCB. The overall adherence to the guideline was moderate (mean (SD) GAI score of 76.25 (17.56) %). There was a significant difference in mean GAI score between subjects with controlled and uncontrolled BP (92.86 (11.11) vs 69.23 (14.88), P <0.05). There was also a weak positive linear correlation between GAI and number of CV events at 1-year (r= 0.26, P= 0.025) although

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correlation with length of hospital stay (LoS) was insignificant. Conclusion This study suggests that since guideline adherence led to better BP control and correlates with lower number of CV events, strategies to improve prescribers' adherence to guideline should be intensified to optimise positive clinical outcomes among hypertensive CKD patients.

Keywords---*Prescribing adherence, Antihypertensive agents, CKD, Clinical outcomes.*

Introduction

Chronic kidney disease (CKD) is growing rapidly and is now causing a huge burden on the global healthcare system. The prevalence in Asia is reported to range between 7.0%–34.3% and in Malaysia, the reported prevalence was 15.48% (95% CI: 12.30, 19.31) in the year 2018 [1,2]. While high prevalence is in part due to the ageing population, it is also associated with increase in prevalence of hypertension [3]. CKD and hypertension are closely interlinked pathophysiologic states such that progressive decline in kidney function can lead to worsening BP control and sustained hypertension can conversely lead to worsening kidney function [4]. The extremely high prevalence of hypertension in CKD is an expected consequence of the central role played by the kidneys in the regulation of body fluid volumes and BP homeostasis. Nevertheless, although there is variability in the contribution of individual hypertensive pathways and the severity of resulting hypertension in different disease states associated with CKD, the pathways usually converge in sodium retention and/or an inadequate suppression of renin-angiotensin system (RAS) [5].

The 2018 Malaysian clinical practice guideline (CPG) for the management of CKD recommended a target BP of ≤130/80 mmHg for those with diabetic kidney disease (DKD) regardless of proteinuria [6]. Those with non-diabetic kidney disease (N-DKD), A target BP of ≤140/90 mmHg was adopted for those with proteinuria <1 g/day while a target of ≤130/80 mmHg was reserved for those with proteinuria ≥1 g/day. The CPG also recommended that any class of antihypertensive agents can be used to control BP in CKD. However, some antihypertensive agents are generally preferable due to their additional antiproteinuric effect. Angiotensin-Converting Enzyme Inhibitor (ACE inhibitor)/Angiotensin Receptor Blocker (ARB) should be the first-line therapy in DKD as they have additional renoprotective effect apart from BP reduction. ACEI inhibitors/ARB is also the preferred antihypertensive agent in non-diabetic hypertensive CKD patients with proteinuria. However, in the absence of significant proteinuria, there is no preferred class of antihypertensive agent, as long as the target BP is achieved.

Adherence to treatment guideline is important for optimising BP control, hence, improving clinical outcomes. However, a prospective observational cohort study conducted to assess BP control in CKD patients with atleast 1-year of follow-up under nephrology specialist care in Germany reported that only 49.3% of the patients had controlled BP [7]. Although the success of BP control may be

multifactorial, adherence to clinical guideline may play a role. Therefore, this study was conducted to evaluate the utilisation of antihypertensive agents, to assess prescribing adherence according to guideline and to determine the relationship between guideline adherence indicator (GAI) score and clinical outcomes among hypertensive CKD patients.

Methods

This was a retrospective cohort study utilising simple random sampling conducted at Serdang Hospital, a large government hospital that provides secondary and tertiary services. The study involved adult patients (age ≥ 18 years) with newly diagnosed CKD with existing hypertension seen at cardiology out-patient clinic between January to December 2018, were prescribed with antihypertensive agents and had a minimum of 1-year follow-up at the clinic from the date of CKD diagnosis. Patients with incomplete medical profile, pregnant women and referral cases where their main hypertension management were at their original hospitals were excluded. A sample size of 74 subjects were calculated for the study.

Data was collected from electronic medical records known as eHIS Live System. A pre-prepared data collection form (DCF) was developed and tested during a pilot study prior to actual data collection to ensure its relevance and ease of use. The DCF contained several sections including demographic and clinical characteristics, clinical and laboratory parameters, prescribed antihypertensives, guideline adherence assessment and clinical outcomes. The term 'adherence' in this study solely refers to physicians prescribing according to guidelines and not referring to patient compliance. A total of 8 relevant important statements from the 2018 Malaysian CPG for the management of CKD were identified and used as the guideline adherence indicator (GAI). Calculation for GAI was adopted and adapted from previous study where the number of adhered statements was divided by total statements and multiplied by 100 (8). GAI was divided into 3 categories, good adherence (80-100%), moderate adherence (50-79%) and poor adherence (0-49%). Clinical outcomes in this study were defined as BP control, number of CV events characterised by episodes of acute coronary syndromes (ACS), acute heart failure (HF) and acute stroke and length of hospital stay (LoS) within the 1-year follow-up period.

Results

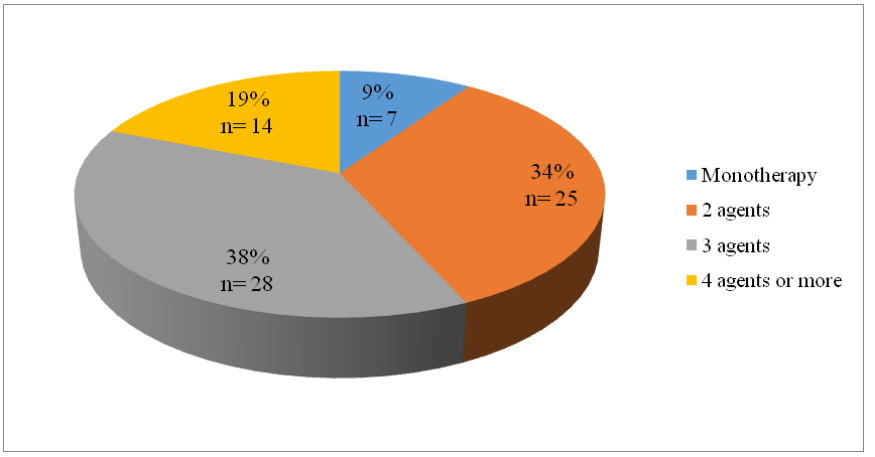
A total of 90 subjects were screened at the beginning of the study and 16 subjected were excluded for not fulfilling the study criteria, leaving a final number of subjects of 74. The mean (SD) age of subjects was 66.86 (10.86) years and majority were ≥ 65 years old, male and of Malay race (Table 1.0). At diagnosis, majority of the subjects were in Stage 3 of CKD (n=49, 66.2%) and the least were in stage 2 (n=9, 12%). In terms of BP, there were no difference in both systolic and diastolic BP at diagnosis and at 1-year follow-up (P> 0.05).

Table 1.0 Demographic and clinical characteristics of study subjects

[a]Paired t-test

As shown in Figure 1.0, the highest proportion of subjects were on 3 antihypertensive agents (n = 28, 38%) followed by 2 agents (n=25, 34%). Only 7 subjects (9%) were on monotherapy. Table 2.0 shows that calcium channel blockers (CCBs) were the most prescribed (n=60, 81.1%) followed by beta blockers (n=44, 59.5%) and loop diuretics (n=38, 51.4%). Meanwhile, combination of ACEI, CCBs and beta blockers were the most used followed by ACEI and CCBs (Figure 2.0).

Figure 1.0 Utilisation of antihypertensive agents in the study subjects

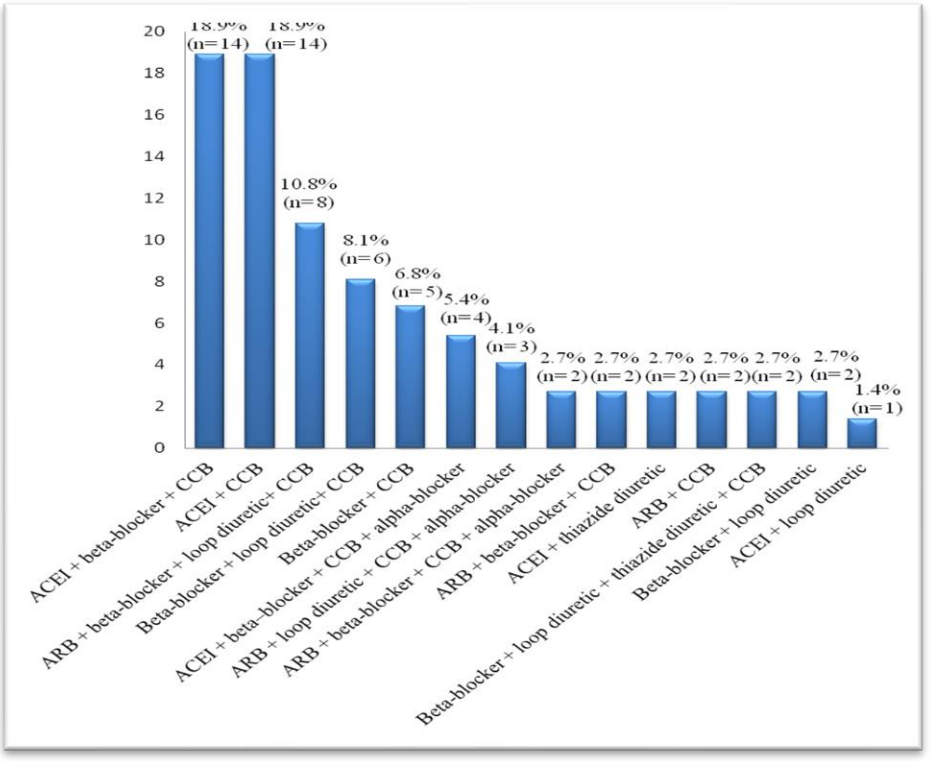


Class of antihypertensive agents	Frequency (N= 74)	(%)
Calcium channel blockers (CCBs)	60 (81.1)	
Beta-blockers	44 (59.5)	
Loop diuretics	38 (51.4)	

Table 2.0 Class of antihypertensive agents prescribed for study subjects

ACE inhibitors	33 (44.6)
Angiotensin receptor blockers (ARBs)	25 (33.8)
Alpha-blockers	13 (17.6)
Thiazide diuretics	10 (13.5)
Mineralocorticoid receptor antagonists (MRAs)	2 (2.7)

Figure 2.0 Combination of antihypertensive agesnts prescribed for study subjects



Analysis of hypertension management and prescribed antihypertensive agents in study subjects as compared to evidence-based recommendations by the 2018 Malaysian CPG for the management of CKD revealed that the mean (SD) GAI score was 76.25 (17.56) % (moderate adherence). Majority of the subjects (n=41, 55.4%) were found to be on antihypertensive treatment that were of good

adherence to the guideline while only 3 (4.1%) subjects were found to received treatment which are of poor adherence to the guideline (Table 3.0).

Table 3.0 Guideline adherence indicator (GAI) score among studied subjects

Guideline adherence	Frequency (%) (N= 74)	Mean (SD)
GAI score (%)		76.25 (17.56)
Good adherence (80-100%)	41(55.4)	
Moderate adherence (50-79%)	30 (40.5)	
Poor adherence (0-49%)	3 (4.1)	

Table 4.0 illustrates the comparison of GAI score according to BP control at 1-year. This study found that those with controlled BP had a significantly higher mean GAI score compared to those with uncontrolled BP (mean (SD) GAI score of 92.86 (11.11) versus 69.23 (14.88); P < 0.001). This indicates that good adherence to guideline led to better BP control among CKD patients.

Table 4.0 Comparison of GAI score (%) according to BP control

Variable	Controlled BP (N = 22) Mean (SD)	Uncontrolled BP (N = 52) Mean (SD)	Mean difference (95% CI)	P-value[b]
GAI score (%)	92.86 (11.11)	69.23(14.88)	23.63 (16.58, 30.67)	**<0.001***

[b] Independent t-test

*P value <0.05 is statistically significant

Correlation between GAI score and clinical outcomes represented by number of CV events at 1-year and length of hospital stay related to these events are shown in Table 5.0. This study found that there was a weak and statistically significant correlation between GAI score and number of CV events at 1-year (r=0.260, P = 0.025). Similar correlation trend was also seen in length of hospital stay although the finding was not statistically significant.

Table 5.0 Correlation between GAI score and clinical outcomes

Discussion

This study found that the mean (SD) age of the studied patients was 66.86 (10.86) years with more than half of the patients were elderly. With aging, there is a progressive loss of the visco-elastic properties of vessels, increased atherosclerosis and amplified SBP wave generated with each heartbeat, resulting in an increase in SBP and a fall in DBP. Furthermore, the ability of the kidneys to effectively excrete salt loads is gradually decreasing, leading to higher BP [9]. This study consisted of a higher number of male subjects than female subjects. Although many studies have reported that CKD is more prevalent in women compared to men, kidney function declines have been found to be faster in men than women [10]. This is possibly due to unhealthier lifestyles in men and the protective effects of oestrogens or the damaging effects of testosterone. Therefore, result of this current study was expected since it recruited newly diagnosed CKD subjects. Meanwhile, there were more Malay and Indian subjects compared to Chinese and this can be attributed to co-morbidities and lifestyles differences between the races. For example, previous studies have described high prevalence of obesity among Malays and metabolic syndrome among Indians which are both predisposing factors for CKD [11,12]. There were more CKD stage 3 subjects in this study compared to other stages which is supported by a prevalence of CKD in Malaysia study conducted in the year 2020 [13].

	GAI score (%) Correlation coefficient (r)	**P-value**
No. of CV events at 1-year	0.260 [c]	**0.025***
Length of stay (LoS)(days)	0.215[c]	0.066

[c] Spearman correlation test

*P value < 0.05 is statistically significant

This study established that more than one-third of the subjects were on ≥ 4 antihypertensive agents which suggests that resistant hypertension may be prevalent among the study subjects. A previous study has reported that the prevalence of resistant hypertension was 2–3 times higher in patients with CKD than in the general hypertensive population [14]. This study showed that CCB was the drug of choice prescribed among the subjects (81.1%), followed by beta-blockers (59.5%), while MRA (2.7%) was the least common class being prescribed. Although ACEI should be used more in CKD, this finding was supported by a multi-centre observational cohort study that showed ACEIs use plateaued during CKD stage 3 (75%) and declined to 37% by stage 5. Meanwhile, betablocker, CCB and diuretic use increased steadily with CKD (15). This study also showed that the most commonly prescribed combination therapies were triple and dual combinations which included ACEI + beta–blocker + CCB and ACEI + CCB respectively with the same percentage (14.9%). Although CCB displayed weaker renoprotective effect compared to ACEI or ARB, it did not increase all-cause mortality incidence in patients with CKD. The combination of a CCB and an ACEI

or ARB should be the preferable antihypertensive therapy in most patients with CKD, considering their higher effect in decreasing BP and fewer adverse metabolic problems caused [16].

This study showed that more than half of the subjects (55.4%) received antihypertensive therapies which were in good adherence to the 2018 Malaysian CPG for the management of CKD. However, this is of a lower percentage compared to those reported by a cross-sectional study conducted among 313 hypertensive patients in the cardiology outpatient clinic of Penang General Hospital, Malaysia. The study reported up to 82% of prescribing adherence although the percentage decreased with coexisting diseases, especially DM [17].

This study also found a significantly higher GAI score in study subjects with controlled BP compared to those with uncontrolled BP ($P < 0.001$) which emphasised the importance of guideline adherence in achieving clinical targets. Similarly, this study also demonstrated that there was a statistically significant positive linear correlation between GAI and number of CV outcomes among studied subjects. Although, the correlation is weak hence suggesting that CV events among CKD may be multifactorial, this study suggests that improving adherence to guideline for the management of hypertension may be able to reduce the number of CV outcomes among CKD patients.

Conclusion

This study established that significant number of subjects with controlled BP were prescribed with therapies that were adhering to the guideline compared to those with uncontrolled BP and there was a weak positive linear correlation between guideline adherence and number of CV outcomes. Hence, strategies to improve guideline adherence among prescribers such as continuous professional education series and regular prescribing audits are recommended to optimise clinical outcomes among hypertensive CKD patients.

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None to declare
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Conflict of interest

None to declare.

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