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Original Article

Evaluation of Medication Use in Malaysian Predialysis Patients

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ABSTRACT. Chronic kidney disease (CKD) patients suffer from multiple comorbidities and complications as a cause or consequence of kidney disease. Information regarding medication-prescribing patterns in predialysis patients is sparse. We conducted a retrospective study to evaluate the medication prescription patterns among predialysis patients. Medical records (both paper based and computerized) of patients at CKD Resource Centre, Hospital Universiti Sains Malaysia, were reviewed. A total of 615 eligible cases were included in the study. The mean number of medications prescribed per patient was 8.22 ± 2.81, and medication use was correlated to the renal function (stage 3a < stage 3b < stage 4 < stage 5; P <0.001). The top three prescribed medication groups were found to be lipid-lowering agents, calcium channel blockers, and antiplatelet agents. Some medication classes such as nonaluminum/noncalcium phosphate binders, erythropoietin-stimulating agents, and renin-angiotensin-aldosterone system blockers, particularly in advanced stage, were found to be underutilized. In conclusion, predialysis patients are prescribed a large number of medications. Our findings highlight the need for assessing the impact of current medication-prescribing patterns on morbidity and mortality rates in Malaysian predialysis population.

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Introduction

Chronic kidney disease (CKD) is an escalating medical problem worldwide, affecting the socioeconomic conditions of patient's family and country. End-stage renal disease (ESRD, also known as stage 5 of CKD), the most

advanced form of kidney disease,[1] is merely the tip of "CKD iceberg."

CKD stage 5D patients are known to suffer from numerous comorbidities and complications.[2-4] As a result, the treatment needs a large number and variety of drugs,[2-8] which are linked to a number of drug-related problems,[2-4] high cost,[6] and short-term mortality.[7] Despite a high prevalence of predialysis patients worldwide, little is known regarding the patterns of medication use to treat such patients. The majority of the published data only describe the medication use in CKD stage 5D, particularly hemodialysis (HD) population. Previous reports have shown that evaluation of medication-prescribing patterns is a valid tool to identify appropriate and questionable prescribing patterns.[6,9] Therefore, the aim of this study is to determine the patterns of medication use in Malaysian predialysis patients and identify any questionable prescribing.

Patients and Methods

This retrospective study was carried out at CKD Resource Centre, Hospital Universiti Sains Malaysia (HUSM), a tertiary referral institute in northeastern Peninsular Malaysia. Adult predialysis patients (≥18 years old), receiving treatment at CKD Resource Center, HUSM, from January 2010 to December 2013, were qualified for inclusion in the study. Patients suffering from acute renal impairment, age <18 years, and those receiving renal replacement therapy were excluded from the study. Medical records (paper based, hospitals' online prescription and laboratory results' software) were reviewed, and data regarding patient's demographics, CKD stage, comorbidities, laboratory findings, and medications were recorded, using a data collection form. The Human Research Ethics Committee, Universiti Sains Malaysia, reviewed and approved the protocol of this study.

Patients' kidney function was estimated by using the CKD Epidemiology Collaboration equation.[10] The CKD was classified based on the estimated glomerular filtration rate as per the criterion of the Kidney Disease: Improving Global Outcomes.[11] Comorbidities were assessed by physician- or nephrologist-based diagnosis in the medical record of the patient.

Data of all the prescribed medications were recorded, and individual drugs were classified into major classes of drugs according to the Anatomical Therapeutic Chemical Classification recommended by the World Health Organization.[12]

Continuous variables were presented as mean ± standard deviation while categorical variables were expressed in numbers or percentages. Data were analyzed by age categories (≤65 vs. >65 years old), gender, and stages of CKD. The comparison of continuous variables was made by ANOVA or *t*-test where applicable. Categorical variables were compared by using Chi-square test. All statistical tests were two sided, and statistical significance was identified as P <0.05. Analyses were performed using Statistical Package for the Social Science (SPSS) software version 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The general characteristics of the patients are shown in Table 1. There were 7045 drug orders noted in all the patients. The mean number of prescribed medications per patient was 8.22 ± 2.81. Moreover, the number of prescribed medication significantly increased with declining glomerular filtration rate (GFR) with a hierarchy as 7.24 ± 2.39 in stage 3a, <7.70 ± 2.52 stage 3b, <8.58 ± 2.93 stage 4, and <8.98 ± 2.96 stage 5. Patient's gender had no impact on the number of medication prescribed (8.17 ± 2.84 in males vs. 8.31 ± 2.78 in females; P = 0.548). However, the patient's age had a significant influence on the number of prescribed medications (8.01 ± 3.01 in patients ≤65 years old vs. 8.46 ± 2.57 in patients >65 years old; P = 0.048).

The overall proportion of patients utilizing medications with cardioprotective effects is presented in Table 2. The frequency of patients on renin-angiotensin-aldosterone system (RAAS) inhibitors was 50.6%, and percentage of patients on RAAS inhibitors significantly

Table 1. General characteristics of the patients.

Characteristics (%)	Total (*n* = 615)	CKD stage 3a (*n* = 74)	CKD stage 3b (*n* = 186)	CKD stage 4 (*n* = 240)	CKD stage 5 (*n* = 115)	*P**
Age (years)						
≤30	2.0	1.4	1.6	0.8	5.2	0.012
31–45	4.2	6.8	3.2	3.3	6.1	
46–65	46.0	56.8	44.1	42.1	50.4	
>65	47.8	35.1	51.1	50.4	38.3	
Gender						
Male	64.1	75.7	71.0	58.8	56.5	0.003
Female	35.9	24.3	29.0	41.3	43.5	
Smoking status						
Current smokers	7.0	6.8	8.6	6.7	5.2	0.103
Former smokers	31.9	35.1	38.7	26.3	30.4	
Nonsmokers	61.1	58.1	52.7	67.1	64.3	
Comorbidities						
Diabetes	68.0	68.9	65.6	69.6	67.8	0.849
Hypertension	94.1	94.6	90.6	96.3	94.8	0.128
Dyslipidemia	83.3	83.8	88.2	84.2	73.0	0.007
Cardiovascular disease	68.1	67.6	69.9	69.2	63.5	0.673

*Chi-square test, CKD: Chronic kidney disease.

decreased with declining kidney function. On the other hand, the percentage of CKD patients on calcium channel blockers (CCB), diuretics, and α-blockers increased significantly with declining kidney function. Lipid-lowering drugs were prescribed for 78.2% of the patients, and statins were the predominantly prescribed lipid-lowering agents. Moreover, atorvastatin was the

Table 2. Prevalence of medications with cardioprotective effects.

Characteristics (%)	Total	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5	*P*
Agents acting on renin-angiotensin system	50.6	73.0	62.4	49.2	20.0	
ACEIs	28.9	51.4	39.2	25.0	6.1	<0.001*
ARBs	23.6	25.7	25.8	25.8	13.9	0.062*
Diuretics	55.6	44.6	50.5	54.6	73.0	<0.001*
Beta-blockers	42.3	48.6	39.8	42.9	40.9	0.607*
CCB	64.2	48.6	49.5	72.1	81.7	<0.001*
Alpha-blockers	8.8	1.4	4.3	10.8	16.5	<0.001*
Cardiac therapy	44.1	45.9	51.6	35.8	47.8	0.009*
Nitrates	33.0	35.1	38.7	26.3	36.5	0.037*
Antiarrhythmic agents	2.0	5.4	2.2	1.3	0.9	0.113**
Digoxin	2.8	5.4	3.2	2.5	0.9	0.300**
Other drugs of cardiac therapy	26.0	24.3	28.5	25.4	24.3	0.822*
Anticoagulants	4.7	9.5	4.8	4.2	2.6	0.171*
Lipid-reducing agents	78.2	83.8	82.2	78.3	68.7	0.032*
Statins	76.7	82.4	80.1	77.5	66.1	0.019*
Fibrates	4.1	6.8	1.1	5.4	4.3	0.079*
Others	8.6	10.8	8.6	9.6	5.2	0.489*
Antiplatelet therapy	60.5	62.2	64.0	59.6	55.7	0.524*

*Chi-square test, **Fisher's exact test, ACEIs: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin receptor blockers, CCB: Calcium channel blockers.

most frequently prescribed whereas other statins (simvastatin, lovastatin, rosuvastatin, and pravastatin) were seldom prescribed. All of the patients were prescribed warfarin, and none of the newer anticoagulants were prescribed to the patients in the current study. About 38% of the patients were prescribed oral iron therapy, and their use was significantly higher in stage 5 CKD patients than in earlier CKD stages. None of the patients was on intravenous iron therapy and erythropoietin-stimulating agents. The mean phosphorus, calcium, and calcium-phosphorus (Ca-P) product levels were 1.28 ± 0.38 mmol/L, 2.26 ± 0.38 mmol/L, and 2.28 ± 0.86 $mmol^2/L^2$, respectively. The mean phosphorus and Ca-P product levels were significantly higher in CKD stage 5 patients as compared to the rest of CKD stages. About 71.2% of all patients had phosphorus levels within the Kidney Disease Outcomes Quality Initiative (K-DOQI)[13] target (0.90–1.49 mmol/L), and 47.8% of the patients had calcium levels within K-DOQI target (50.7%). Moreover, 96.1% of our study population had mean Ca-P product as per K-DOQI recommendations. The composite goal for all the three parameters as per K-DOQI guidelines was achieved in 39% of all the patients. We observed that the monitoring of parathyroid hormone level (PTH) in predialysis patients was very infrequent, and PTH level was available in only 5% of the patients. Vitamin D analogs were prescribed to 32 (5.2%) patients, and the predominantly prescribed Vitamin D analog was calcitriol. None of the patients was prescribed intravenous Vitamin D. The most frequently prescribed phosphate binder (PB) was calcium carbonate (31.2%) whereas sevelamer hydrochloride and lanthanum carbonate were not prescribed to any of the patients. The use of PBs and Vitamin D analogs increased significantly with declining kidney function (P <0.001).

Of the study patients, 56.1% were prescribed antidiabetic drugs. Insulin was prescribed in 37.6% of the patients while 31.1% of the patients were on oral hypoglycemic agents. No statistically significant difference was found in the percentage of patients prescribed insulin by CKD staging. Sulfonylureas (26.7%) were the predominantly prescribed oral hypoglycemic agents while biguanides (metformin) and alpha-glucosidase inhibitors (acarbose) were prescribed to only 7.3% and 3.9% of the patients, respectively. None of the patients was prescribed any incretin-based therapy and SGLT2 inhibitors for the management of diabetes. Among sulfonylureas prescriptions, gliclazide (second-generation sulfonylureas) was the most frequently prescribed medication in our study sample. None of the patients with CKD stage 5 was prescribed biguanides/metformin. The percentage of patients on oral antidiabetic agents decreased significantly with the declining kidney function.

As shown in Table 3, vitamins and analgesics were prescribed to 37.6% and 26.3% of the study participants, respectively, and their use

Table 3. Medication prevalence for the management of other coexisting diseases and complications.

Medications (%)	Total	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5	*P*
Vitamins	37.6	18.9	21.5	44.2	61.7	<0.001*
Analgesics	26.3	28.4	26.3	25.8	26.1	0.979*
Anti-inflammatory drugs	5.2	8.1	4.8	5.0	4.3	0.681*
Drugs for acid-related disorders	51.5	40.5	47.8	52.5	62.6	0.016*
PPI	48.6	37.8	44.6	50.0	59.1	0.019*
H2-receptor antagonists	4.4	5.4	3.2	2.9	8.7	0.069*
Antacids	2.3	1.4	3.2	2.5	0.9	0.549**
Drugs for functional gastrointestinal disorders	6.7	12.2	4.8	5.4	8.7	0.114*
Anti-gout	15.0	16.2	20.4	18.3	5.5	<0.001*
Urologicals	7.8	5.4	8.1	7.9	8.7	0.864*

*Chi Square, **Fisher's exact test; PPI: Proton-pump inhibitor.

was significantly increased with declining GFR. Nonsteroidal anti-inflammatory drugs (NSAIDs) were prescribed to 5.2%. More than half of the patients were taking drugs for the management of acid-related disorders. Of them, the vast majority were prescribed proton-pump inhibitors for the management of gastroesophageal reflux disease or peptic ulcer disease.

Discussion

The major findings of the present study were that predialysis patients were prescribed multiple drugs to manage the comorbidities and complications associated with kidney disease. Patients' gender did not affect the number of prescribed medications whereas age had a significant influence on the medication use. Moreover, we found that the numbers of prescribed medications increased with declining kidney function.

The mean number of medications prescribed per patient in our study was comparable to the findings of previous reports.[9,14] We observed that the number of drugs used per patient increased significantly with declining renal function. The interpretation for this could be the increase in complications, sequelae, infections, and comorbidities associated to deteriorating renal function. Contrary to the findings of a previous study conducted on ESRD patients,[6] we found that patient's age had an influence on the number of medications used.

Angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) slows down the progression of kidney disease[15] and are sometimes used in patients without hypertension to delay CKD progression.[16] The percentage of our patients prescribed ACEIs and ARBs was less than that reported in Spain.[17] However, the use of RAAS blockers (ACEIs/ARBs) had increased in Malaysia compared to that reported earlier (50.6 vs. 29.3%).[14] The use of ACEIs/ARBs decreased significantly with declining renal function despite the significantly higher prevalence of proteinuria by CKD staging (results not shown). The possible reasons for the underuse of ACEIs/ARBs in this study were hyperkalemia (19.7%) and/or patients with history of sudden reduction in GFR due to ACEIs/ARBs. The use of CCB in the present study was higher as compared to the previous studies.[9,14,17] The percentage of patients on diuretics was greater than previously reported in Malaysia.[14] However, it was less than that reported by Martínez-Castelao et al.[17] Furosemide was the most commonly prescribed diuretic and its use significantly increased with declining renal function (stage 3a < stage 3b < stage 4 < stage 5). Thiazide diuretics and spironolactone were less frequently used. The use of beta-blockers was less than the reported earlier.[9] The percentage of the patients on cardiac therapy in the current study was greater when compared to that noted previously.[14] The lesser use of cardiac therapy in the preceding study was due to the low prevalence of cardiovascular disease in their study population. We observed the change of prescribing patterns of cardiac therapy drugs as compared to the studies of the US involving HD patients.[6] The percentage of patients prescribed lipid-lowering agents was higher than that of the previous study,[9] and this was due to the fact that our sample had significantly high prevalence of hyperlipidemia (83.3% vs. 13.3%). The percentage of our study participants prescribed antiplatelet agents was also higher as compared to that described by Bailie et al.[9] It was encouraging to observe that the use of antiplatelet/aspirin and lipid-modifying agents has increased as compared to the earlier reports.[9,14] It has been reported that beta-blockers and aspirin[18] use are associated with reduced cardiovascular mortality. Moreover, recent clinical trial (Study of Heart and Renal Protection) demonstrated that lipid-lowering agents safely reduce the incidence of major atherosclerotic events in patients suffering from advanced CKD.[19]

Consistent with the findings of an earlier study,[9] we also observed that the monitoring of iron indices in the predialysis patients was infrequent. Underutilization of erythropoietin-stimulating agents noted might be due to the clinical inertia or high cost. Nevertheless, the use of iron supplementation in the current

study was significantly higher as compared to previously reported 13%.[9] We observed discrepancy between the number of patients suffering from anemia and those who were prescribed antianemic preparations. Therefore, there seems to be a room for improvement in the treatment of anemia since the published data advocate that anemia is an independent predictor of adverse cardiovascular outcomes,[20] and the combination of CKD and anemia was associated with significantly higher risk of stroke.[21]

Regarding the medication for the management of CKD-mineral and bone disorder, calcium carbonate was the most frequently prescribed PB. These findings are comparable to the results of another study conducted in a developing country.[22] The underprescription of lanthanum carbonate and sevelamer hydrochloride might be attributable to their prohibitive cost or physician inertia.

Consistent with an earlier study,[6] there was a mismatch between the number of diabetic patients and number of patients prescribed drugs to control glucose. Nevertheless, this prescribing pattern can be appropriate as some of the patients only need diet control. The pattern of oral hypoglycemic agents' use (31%) needs further investigations as some of these drugs are contraindicated in CKD or require dosage adjustments.[23] Nonetheless, less prescribing of metformin was an encouraging pattern. Moreover, lesser reliance on NSAIDs was also an appropriate prescription practice since these drugs are nephrotoxic. Regarding the use of drugs for acid-related disorders, our results were higher than that reported by Al-Ramahi.[14] Contrary to the findings of a previous study,[22] we observed that the majority of medications were prescribed by generic name rather than the brand name which is encouraging.

Even though the objectives of the study were achieved, there were few of limitations. First, our findings might not be easily generalizable because this study was carried out in a single northeast peninsular Malaysian tertiary care hospital. Second, this was a retrospective study, so we were not able to acquire some information (e.g., Income/revenue status and dietary habits of the patient, use of over-the-counter drugs, etc.). Revenue status and dietary habits of the patient might play a contributory role in the underutilization of some medication classes, for example, erythropoietin-stimulating agents, nonaluminum/noncalcium PBs, and ACEIs/ARBs. However, these prescribing patterns need further investigations. Third, we did not record the frequency and causes of drug-related hospital admission, and finally, we did not follow-up the patients, so we could not assess the impact of currently prescribed medication on drug-related hospital admissions.

Conclusion

Predialysis patients are prescribed a high number and variety of medications to manage comorbidities and complications associated with renal impairment. Moreover, the number of medications significantly increases with declining kidney function. Our findings highlight the need for assessing the impact of medication-prescribing patterns on morbidity and mortality rates in predialysis population.

Conflict of interest: None declared.

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