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Original Article

Retrospective Drug Utilization of Cardiovascular Drugs in A Tertiary Healthcare Setting in Malaysia

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ABSTRACT

Objective: The general objective of this study was to analyse the utilization patterns of cardiovascular drugs among a sample of patients in a tertiary healthcare setting during the preceding two years. **Methodology:** This study design was exploratory, descriptive and retrospective. Data were extracted from the case sheets pertaining to patients who had been admitted to the study site and administered CV drugs during the preceding two years, into customized data collection format. A total of 100 patient data were obtained, based on the inclusion criteria. The data collected were then analyzed by SPSS v22. **Results:** A total of 29 males (28.4%) and 73 females (71.6%) data were analysed. The majority of the patients were in the age range 50-55 years. Among the ethnic groups, the Malays (72.5%) were the highest, followed by Indians (14.7%) and the Chinese (11.8%). The co-morbidities observed among the sample are depicted in Table 1 with $p < 0.001$ (Chi-square test). It was noted that the combination of HTN +DM was the most observed (18.6%). Among the CV medications, statins (54.9%), antiplatelets (39.2%), anticoagulants (26.5%) and beta-blockers (33.3%) were more commonly used for these patients. **Conclusion:** The usage of all these medications was in accordance with the national guidelines in Malaysia. The mean CV drug count was 3.16, which though optimal might be indicative of potential non-compliance among patients.

Key words: Drug Utilization, Cardiovascular drugs, National Health and Morbidity Surveys, Angiotensin Converting Enzyme Inhibitors.

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INTRODUCTION

Cardiovascular diseases (CVDs) are one among the non-communicable diseases, associated with the heart and blood vessels. Some of the common CVDs are: coronary artery diseases, congestive heart failure, hypertension, peripheral artery diseases and arrhythmias. CVDs have contributed to the higher incidences of morbidity and mortality among Malaysians. According to the statistics provided by the Department of Statistics Malaysia, the primary cause of death in Malaysia in 2016 was ischemic heart disease, whereas cerebrovascular disease was the third major cause of death in Malaysia.[1] The National Health and Morbidity Surveys (NHMS) in Malaysia stated that cardiovascular (CV) risk factors such as high blood pressure, obesity, hypercholesterolemia and high blood sugar show a high and increasing prevalence in Malaysia.[2] At least 63% of the Malaysian population ≥18 years are inadvertently associated with at least one CV risk factor.[3] For the prophylaxis and treatment of CVDs, cardiovascular drugs are used to minimise complications and improve the quality of life of the patients. Various CV drugs of different classes such as anti-anginals, antihypertensives, antiplatelets and diuretics are commonly prescribed in Malaysia. The Ministry of Health Medicines Formulary (MoHMF) is available for reference of physicians and pharmacists in prescribing medications.[4] Drug utilisation (DU) refers to the drugs usage pattern by the healthcare personnel as well as the patients. It depends on the personality, belief and decision-making of the physician, pharmacists and patients. The pattern of drug utilisation may be influenced by various factors, such as: religious reasons, economical status of the patients, medical needs and health demands, physical state of the patients, demographic and geographical factors and drug allergy of the patients.[5] Retrospective DU studies evaluate the drug utilisation pattern in medical cases which have already occurred before the research studies is carried out, by referring the past medical records of the patients.[6] Data collection is obtained from the available records or databases which match the criteria of study. Retrospective studies consume less time when compared to other types of studies. The disadvantage of retrospective studies is the inability to obtain accurate and exact data for certain information such as risk factors, side effects and adverse drug reactions. Retrospective study was utilized in this research to evaluate the drug utilisation pattern of cardiovascular drugs in tertiary healthcare setting.

Malaysia has been witnessing a rapidly rising trend in the morbidity and mortality due to CVDs with high incidences of CV risk factors. The utilisation of CV drugs in various healthcare settings is continuously increasing in the prophylaxis and treatment of CVDs. It is essential to evaluate the CV drugs' utilisation pattern to study the pattern of drug use, processes of drug use and its treatment outcomes. This will aid to facilitate the rational drug usage in healthcare setting and improve the safety and therapeutic effectiveness of CV drugs in the future. The objective of this study was to analyse the utilization patterns of cardiovascular drugs in tertiary healthcare setting during the preceding two years.

METHODOLOGY

This study design was an exploratory, descriptive and retrospective study conducted over a period of one year. The study was divided into two main phases: (phase-I and phase-II). Phase-I comprised of data collection by means of a customized data collection format, in which the patients' demographic details, chief complaint, past medical history, past medication history, diagnosis, cardiovascular drugs utilised among the in-patients were reviewed and recorded. Based on the objectives in the context of this research, the dependent variable is the drug utilisation pattern; while the independent variables are gender, age and ethnicity. Phase-II

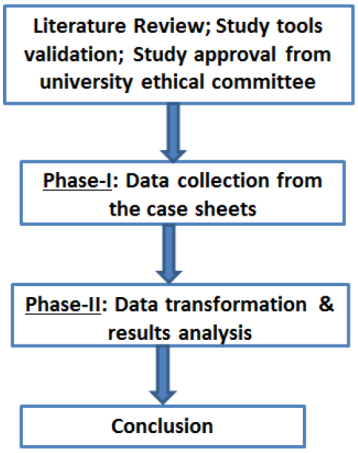

Figure 1: Study flow during the two phases.

comprised the results analyses of the data collected. Figure 1 depicts the study flow during the phases.

The ethical approval for the conduct of this study was also obtained from the AIMST University Human and Animal Ethics Committee (AUHEC/FOP/2018/24). Patients admitted to inpatient ward between years Jan. 2016 and Dec. 2017, patients who had received at least one cardiovascular drug during their treatments were included in the study. Patients below 18 years of age were excluded from the study.

Due to the retrospective nature of the study, the estimated sample size was 100 (95% CI, 5% margin of error), as calculated by the Raosoft and PASS sample size calculator softwares.[7] The data collection tool utilized in this study was a customized data collection format comprising of general demographic data section, followed by the pertinent data of cardiovascular drugs utilized for each patient. Data were extracted from the case sheets pertaining to patients who had been admitted to the study site and administered CV drugs during the preceding two years. These data were then coded for result analysis using SPSS v22 software (SPSS Inc., Chicago, USA).

RESULTS

A total of 29 males (28.4%) and 73 females (71.6%) data were analysed. The majority of the patients were in the age range 50-55 years. Among the ethnic groups, the Malays (72.5%) were the highest, followed by Indians (14.7%) and the Chinese (11.8%). The co-morbidities observed among the sample are depicted in Table 1 with $p < 0.001$ (Chi-square test). It was noted that the combination of HTN +DM was the most observed (18.6%).

Table 2 depicts the utilization pattern of the CV drugs by class. The top five commonly utilized drug classes were: antiplatelets (39.2%), anticoagulants (26.5%), statins (54.9%), beta-blockers (33.3%) and dihydropyridine CCBs (46.1%). Table 3 depicts the utilization frequencies of the individual drugs inclusive of the combinations, under each drug class. The utilization pattern of all these were deemed statistically significant ($p < 0.001$) by the Chi-square test.

Table 1: Descriptive data of co-morbidities.

Co-morbidity	Frequency	%	p-value
HTN	7	6.9	
DM	9	8.8	
Dyslipidemia	1	1.0	
IHD	2	2.0	
HTN + Diabetes	19	18.6	
HTN + Dyslipidemia	2	2.0	
HTN + DM + Dyslipidemia	8	7.8	
HTN + DM + Dyslipidemia + IHD	3	2.9	
HTN + DM + Dyslipidemia + IHD + CKD	1	1.0	< .001 *
HTN + DM + IHD	6	5.9	
HTN + DM + CKD	10	9.8	
HTN + DM + IHD + CKD	2	2.0	
DM + IHD + CKD	3	2.9	
DM + Dyslipidemia	2	2.0	
HTN + IHD	2	2.0	
HTN + CKD	1	1.0	
HTN + Dyslipidemia + CKD	1	1.0	

*Chi-square test

Table 2: CV drugs utilization by drug categories.

CV Drug Class	Frequency	%
Antiplatelets	40	39.2
Anticoagulants	27	26.5
Statins	56	54.9
Fibrates	4	3.9
Alpha-Blocker	8	7.8
Beta-Blocker	34	33.3
Central Alpha Agonist	9	8.8
ACEIs	20	19.6
ARBs	0	0.0
Dihydropyridine CCBs	47	46.1
Non Dihydropyridine CCBs	6	5.9
Nitrates	12	11.8
Antianginal	5	4.9
Antianginal	5	4.9
Anticholinergics	1	1.0
Cardiac Glycosides	1	1.0
Diuretics	24	23.5
Haemostatics	2	2.0
Combination	3	2.9

DISCUSSION

In the current study, antiplatelets were found to be the second most commonly prescribed CV drugs. The frequency of antiplatelet drugs used was 40 (39.2%). This is dissimilar to a study done by Kerkar *et al.* 2017, which was a prospective, observational study of 180 patients with CVDs admitted in medicine and cardiology wards of a tertiary care hospital, conducted through case records and patients' interviews. In that study, the incidence of cardiovascular diseases was more in males (56.67%) than the females (43.33%). Average number of drugs prescribed per patient was 9.16 and that of cardiovascular drugs was 5.08 ± 2.15. Antiplatelets (88.88%) were the most commonly prescribed cardiovascular drugs followed by hypolipidemics (82.22%). Among other findings, the researchers concluded that antiplatelets were an integral component of

Table 3: DU pattern of the drugs under each class observed.

S. No.	CV Drug Class	Drugs	Frequency	%	*p*-value
1	Antiplatelets	Aspirin	7	6.9	
		Dipyridamole	1	1.0	
		Glyprin	22	21.6	
		Glyprin + Clopidogrel	6	5.9	
		Aspirin + Clopidogrel	1	1.0	< 0.001*
		Aspirin + Glyprin	1	1.0	
		Aspirin + Clopidogrel + Glyprin	2	2.0	
2	Statins	Lovastatin	1	1.0	
		Simvastatin	40	39.2	
		Pravastatin	1	1.0	
		Atorvastatin	14	13.7	
3	Beta-blockers	Atenolol	2	2.0	
		Bisoprolol	12	11.8	
		Metoprolol	6	5.9	
		Propranolol	1	1.0	
		Labetalol	13	12.7	
4	ACEIs	Perindopril	19	18.6	
		Captopril + Perindopril	1	1.0	
5	Dihydropyridine CCBs	Nifedipine	5	4.9	
		Amlodipine	28	27.5	
		Felodipine	9	8.8	
		Amlodipine + Felodipine	5	4.9	
6	Nitrates	GTN	9	8.8	
		Isordil	1	1.0	
		GTN + Isordil	2	2.0	
7	Diuretics	Lasix	23	22.5	
		Lasix + Spironolactone	1	1.0	

*Chi-square test

treatment of certain CVDs.[8] The current study also indicated a high and significant usage of antiplatelet medications.

In the current study, statins (56; 54.9%) were found to be the most predominantly used CV drugs among the patients. This observation is similar to a cohort study conducted by George *et al.* Retrospectively assessing cardiovascular drug use determinants among coronary artery disease (CAD) patients in the coronary care unit (CCU). The clinical characteristics of the patients and cardiovascular drug utilization patterns among them were evaluated. Two cohorts of patients were analyzed: those with and without CAD. The results in this study revealed that statins were among the most commonly used. The five commonly prescribed drug classes were platelet inhibitors (88.7%), statins (76.3%), ACE-inhibitors/ARBs (72%), beta-blockers (58%) and heparin (57%). Poly-pharmacy (>5 drugs) was noticed in 71% of patients. A majority of patients diagnosed with CAD (72.6%), received significantly higher median number of drugs and had longer duration of CCU stay ($p < 0.0001$). The researchers concluded that antithrombotics, statins, ACE-inhibitors/ARBs and beta-blockers were the most frequently prescribed drugs in the sample studied. Clinical co-morbidities (renal dysfunction, arrhythmias) decreased the utilization of ACE-inhibitors, beta-blockers among CAD patients.[9]

In the current study, nitrates were prescribed in 11.8% of CVD patients. Nitrates were utilized primarily in the treatment of angina pectoris, with GTN (91.7%) and ISDN (8.3%). A similar prescribing trend of nitrates was observed by Thomas *et al.* in a prospective observational study conducted in a tertiary care hospital to assess the prescribing pattern of drugs in cardiovascular diseases (n = 123), where the cardiovascular diseases' incidence was common in males (84%) and more prevalent in the age group 51-60 years. The following drug classes were most commonly prescribed: antiplatelets (90.24%), anticoagulants (55.28%), thrombolytics (4.87%), antianginals (68.29%), antihyperlipidemics (81.3%), antihypertensives (87.80%) and ionotropes (22.76%). Antianginal drugs prescribed include nitrates (44.8%), trimetazidine (17.6%), among others. The nitrates used were ISMN (34.6%), ISDN (16%) and GTN (49.3%), in which GTN the most prescribed.[10] The similar trend in the above study with the current study can lead to the inference that the prescribing of nitrates are also in accordance to the guidelines, for the specific CV disease conditions stated. It can be observed that the nitrate class of CV drugs is highly preferred as treatment for certain CV conditions, primarily angina pectoris. The current study and the corroborative studies fortify that observation.

In the present study, antihypertensives of various drugs classes were prescribed to the patients having CVD. Among all the antihypertensives, the usage of dihydropyridine-calcium channel blockers (DHP-CCBs), beta-blockers, diuretics and ACEis were proven to be statistically significant. The most commonly utilized antihypertensives were DHP-CCBs (46.1%) and beta-blockers (33.33%), followed by diuretics (23.5%) and ACEIs (19.6%). This is similar to a six-months pilot study by Tiwari *et al.* to establish drug-prescribing trends of anti-hypertensives among outpatients. In monotherapy, four classes of drugs used were CCBs (48.1%), beta-blockers (46.2%), ACEIs (3.9%) and diuretics (1.9%). In combination therapy, 92.1% received two drugs, 7.9% received three drugs. The two-drug combination (beta-blockers-CCBs) was given to the majority of patients. 57.8% patients were treated with a single anti-hypertensive drug and 42.2% were treated with combination therapy. The usage pattern however, in a study by Singh *et al.* revealed dissimilar antihypertensives utilization patterns, with ACEIs (46.2%), followed by diuretics (45.5%), CCBs (45.4%), beta-blockers (34.5%) and α-blockers (20.0%).[11]

Total CV drug count observed in this study was 322. The mean CV drug count was 3.16, indicating that on average a CV patient consumed 3.16 drugs specific to their condition(s). While this number might not seem too burdensome, there however, are certain issues. Cardiovascular diseases are chronic conditions that necessitate long term treatment. A retrospective review of patient compliance with OD antihypertensive medications and the impact of partial compliance on healthcare outcomes were studied by Cramer *et al.*, wherein they concluded that persistence with treatment is necessary for reduction of long-term consequences of hypertension. They also stated that enhancing compliance with antihypertensive medications can profoundly impact the health outcomes of compliant patients in a positive manner. Once-daily dosing coupled with selection of a drug with long duration of action to overcome problems of missed doses is crucial. Widespread adoption of simple compliance enhancement methods could lead to decreased morbidity and mortality from cardiovascular disease and stroke.[12] A study by Moname *et al.* revealed that prescriptions for antihypertensive and lipid lowering medications are given assuming that patients reluctant to participate in lifestyle modification will be willing to take medication(s). However, that is not entirely the case as even once daily medications are not taken regularly. When blood pressure and lipids have been maintained at target levels for a long time, patients might feel that

the medication is no longer necessary.[13] A study of elderly patients newly treated for hypertension revealed that they filled prescriptions covering only 49% of days during the first year.[14] A retrospective cross-sectional study of 432 patients by Toh *et al.* investigated the association between number of doses per day, medications and readmissions into hospital. The researchers found that the number of readmissions was significantly associated with the number of medications ($p = 0.002$) and number of doses per day ($p = 0.003$) after adjusting for non-compliance, concluding that complex medication regimen is a statistically significant predictor of number of readmissions. Simplifying therapeutic regimens with alternatives such as longer-acting or fixed-dose combination drugs may facilitate better patient adherence and reduce costly readmissions.[15] In our study, the CV mean drug count of 3.16 could pose the issue of complex therapeutic regimen when considering the medications for comorbidities. The number of dosing times per day of all prescribed medications has an impact on the patient's compliance. This was illustrated in certain studies where the compliance rate decreased with an increase in the number of daily doses.[16-22] Simplifying the medication dosing frequency could improve compliance markedly.

Study Limitations

Being a retrospective study, the data collection was entirely dependent on the case sheets' information only. The possibility to accurately explore the incidences of drug interactions (drug-drug, drug-food) was also limited. Due to logistical issues only 100 case sheets were able to be assessed by the researcher. A more incisive result could be obtained with higher number of samples.

CONCLUSION

The retrospective drug utilization mode was utilized for this study to re-evaluate the cardiovascular drug usage pattern during the preceding two years among a sample of patients. The medications were prescribed in accordance with the standard guidelines issued by the Ministry of Health, Malaysia. Overall, the corroborative studies discussed indicate that the prescribing trends with regard to cardiovascular drugs (by class or individual drugs) might be highly dependent on the physician's prescribing choices and medications' availability. However, the prescribing (and administration) trends of the medications might also be hugely influenced by their pharmacological efficiency in terms of alleviating the patients' cardiovascular conditions and associated symptoms, while having relatively manageable side effects.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ACEIs: Angiotensin Converting Enzyme inhibitors; **ARBs:** Angiotensin Receptor Blockers; **CV:** Cardiovascular; **CVDs:** Cardiovascular diseases; **DM:** Diabetes Mellitus; **DU:** Drug Utilization; **HTN:** Hypertension; **IHD:** Ischemic Heart Disease; **MoHMF:** Ministry of Health Medicines Formulary; **NHMS:** National Health and Morbidity Surveys.

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