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Evaluation of utilised doses of Heart Failure (HF) medications between genders and its association with clinical status among Heart Failure (HF) patients at hospital Serdang

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***Abstract*---**Objective This study aimed to evaluate the utilised doses of HF medications between genders among HF patients in local setting. Methods This study was conducted as retrospective study involving data collection from medical records of patients with documented HF in Hospital Serdang, Selangor. A total of 131 patients (74 males versus 57 females) were conveniently recruited from patients undergoing follow-ups at cardiology outpatient clinic, Hospital Serdang, Selangor with matched age, different ethnics, baseline and current EF and comorbidities. Utilised doses of HF medications were categorised as percentage of recommended doses or usual daily doses, which were 0%, <50%, ≥50% and ≥100%.Results No significant difference was observed in utilised doses of HF medications between genders in study population which proved that the utilised doses of HF medications were not influenced by gender differences. However, Malay and Indian were found to utilise higher MRA doses compared to Chinese and indigenous people (P < 0.05). This study also found that

baseline (r = -0.386; P < 0.001) and current (r = -0.265; P < 0.01) ejection fraction were weakly and inversely correlated with MRA utilised doses. Higher ACEI/ARB utilised doses were used in subjects with hypertension (P < 0.01). Patients with ischaemic heart disease (IHD) and chronic kidney disease (CKD) had lower MRA utilised doses (P < 0.001; P < 0.01) while patients with atrial fibrillation (AF) earlier had higher MRA utilised doses (P < 0.01). Patients' current EF were significantly found higher than their baseline EF with treatment (P < 0.001). Conclusion Gender differences did not affect the dose utilisation of HF medications. Therefore, the dosage of HF medications is recommended to be evidence-based with reference to current guideline with individualised dosing regimen. However, there was significant association in doses of HF medications in relation with concomitant diseases. Overall, patients on HF medications had significant improvement in EF.

Keywords---heart failure, utilised doses, genders, clinical status.

Introduction

HF is one of the CVDs which results from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood [1]. A systematic review by Khatibzadeh *et al.* (2013) has stated that worldwide, an estimated 23 million people is affected by HF [2]. A review of previous studies on prospective, observational and cohort study at hospital of European countries (n = 1710) and Asian regions (n = 4500) showed that lowest hazards of death or hospitalisation for heart failure (HF) occurred at 100% of the recommended dose of ACE inhibitors or ARBs, and β-blockers in men but women showed approximately 30% lower risk at only 50% of the recommended doses, with no further decrease in risk at higher dose levels. This review concluded that females with HFrEF might need lower doses of ACE inhibitors or ARBs and β-blockers than males [3]. Apart from previous studies, an article stated among general population the pharmacodynamic differences in women which included greater sensitivity to and enhanced effectiveness of β-blockers, opioids, selective serotonin reuptake inhibitors and typical antipsychotics. In pharmacokinetic difference, women are affected by lower body weight, slower gastrointestinal motility, less intestinal enzymatic activity and slower glomerular filtration compared to men. These physiological differences between genders affect drug activity as well as drug dosages, additionally women are 50% to 75% more likely than men to experience adverse drug reaction [4]. A review recommended evidence-based dose reductions for women as it mentioned the common practice of prescribing equal drug doses to women and men risks overmedication of women and contributes to female-biased adverse drug reactions in relation with sex differences in pharmacokinetics and dimorphisms in body weight [5]. The review paper by Santema *et al.* (2019) have shown that women might have best outcomes with lower doses of ACE inhibitors or ARBs and β-blockers than men which bring into question on the true optimal medical therapy for women versus men with heart failure with reduced ejection fraction (HFrEF) [3]. However, the data on sex-specific outcome in relation to the prescribed dose levels of

medications for heart failure is still scarce. This study will assist healthcare providers to be able to determine the dosage of HF medications between different genders. Hence, dose regimen of HF medications can be prescribed accordingly which is more beneficial to HF patients of different genders. The general objective of this study is to evaluate the utilised doses of HF medications between genders and its association with clinical status among HF patients undergoing follow-up at Hospital Serdang.

Methods

This study was conducted as retrospective study from Jan 2020 to July 2020, using convenient sampling involving HF patients undergoing follow-up at the cardiology outpatient clinic at Hospital Serdang. Data collection was conducted using data collection form to access patients' details from medical records from year of 2018 to 2019 using eHIS system in Hospital Serdang. Data collection forms were used to collect information on demographic and clinical background of patients as well as the details of HF medications received by patients. This study compared the utilised doses of HF medications between male and female among HF patients undergoing follow-up at the cardiology outpatient clinic at Hospital Serdang. A minimum of 30 patients were recruited for each studied group. At the commencement of this study, patients are screened for inclusion and exclusion criteria from patients' medical profile. Adults, aged above 18 years old, with documented heart failure (left ventricular ejection fraction (LVEF) ≤40%) undergoing follow-up at Hospital Serdang were recruited in this study. Patients should be on maintenance phase for at least 6 months. Data were excluded if patient had incomplete medical records required for this study or was pregnant.

Sample size was calculated according to $[Z^2 \times (p) \times (q) / e^2]$ where Z is the statistic for level of confidence = 1.96 at 95% confidence interval; p is the expected prevalence of HF which was 0.067 [6] and C is margin of error of 0.05. Sample sizes were then corrected according to the number of HF patients undergoing follow-up at cardiology outpatient clinic in Hospital Serdang.

This study was registered under National Medical Research Register (NMRR) and application for ethical approval to conduct this study was submitted to Medical Research and Ethics Committee (MREC). The Clinical Research Committee of Hospital Serdang was also notified via NMRR. Approval to conduct this research was obtained (NMRR-20-118-52899) together with verbal permission to interact with patients at the mentioned study site. Permission to access the medical records of patients was also granted. When conducting this study, patient consent was first obtained and all information of patients were kept private and confidential in hardcopy and softcopy. Besides, all data collected will be kept in locked storage for 2 years solely for the purpose of data analysis and publication and will be completely destroyed after that. All data collected from respondents were analysed using SPSS version 24.0.

Results

There was a total of 131 HF patients in this study, including 74 male and 57 female HF patients. Table 1 shows the analysis of demographic characteristics of

the studied subjects. The mean (SD) age of male HF patients was similar to the mean age of female HF patients. In male group, majority of studied subjects was non-Malay (n = 42, 56.8%). Meanwhile, majority of HF patients in female group was Malay (n = 32, 56.1%). The association of ethnicity and genders was insignificant (P = 0.143). As shown in table 1, the mean (SD) baseline EF of male HF patients was observed similar to the mean (SD) baseline EF of female patient. Majority of HF patients had underlying of hypertension (63.5% versus 52.6%), followed by diabetes mellitus (DM) (50% versus 61.4%) and ischaemic heart disease (IHD) (52.7% versus 57.9%) in both male and female group. However, the association between comorbidities and genders was not significant (P = 0.085). In addition, table 1 showed that male and female group had matched clinical characteristics as there was no significance difference in the clinical characteristics between males and female patients (P > 0.05).

Table 2 demonstrates the utilisation of HF medications among studied subjects. The most commonly used HF medication at baseline and at follow-up was β-blockers followed by ACE inhibitors or ARB. There was no association between the use of HF medications and genders (P > 0.05). The most commonly used ACEIs/ARBs was perindopril in both male (67.6%) and female (70.2%) groups, followed by valsartan (29.7% in males versus 24.6% in females). Majority of male and female studied subjects was treated with β-blockers and the most common choice was bisoprolol (91.9% versus 96.5%). Study results showed that spironolactone was the most commonly used MRA among studied subjects and frusemide was the only diuretic used among studied subjects. However, there was no association between the utilisation of HF medications and genders (P > 0.05).

The comparison of ACEI/ARB utilised doses between genders was shown in table 3. Female group had higher mean (SD) ACEI/ARB utilised doses compared to mean (SD) ACEI/ARB utilised doses of male group. However, there was no significant difference in the ACEI/ARB utilised doses between the studied groups (P > 0.05). Higher proportion of male studied subjects was treated with 1 – 49% and 50 – 99% of ACEI/ARB recommended doses when compared to female studied subjects. Meanwhile, lower proportion of male studied subjects was treated with 100% and above of the recommended doses as female studied subjects.

Comparison of β-blockers utilised doses between genders in table 4 showed that female group had equal median (IQR) β-blockers utilised doses to the median (IQR) β-blockers utilised doses of male group which was 25.00 (25.00). There was no significant difference in β-blockers utilised doses between genders (P > 0.05). Most of the studied subjects was treated with β-blockers, in both male and female groups. Higher proportion of male studied subjects was treated with 1 – 49% of recommended doses when compared to female group. Higher proportion of female group was treated with 50 – 99%, and 100% and above of the recommended doses.

As shown in table 5, the mean (SD) MRA utilised doses of male group was higher than that of female group. However, there was no significant difference in MRA utilised doses between genders (P > 0.05). Majority of the studied subjects was treated with MRA, in both male (60.8%) and female (61.4%) groups. Higher

proportion of female studied subjects was treated with 50 – 99% of usual daily dose when compared to male studied subjects (35.1% versus 28.4%). Male group had higher proportion treated with 1 – 49%, and 100% and above of usual daily dose than female group.

For diuretic, utilised doses between genders showed that male studied subjects had equal median (IQR) diuretic utilised doses to female (table 6). There was no significant difference in the diuretic utilised doses between genders ($P > 0.05$). The utilised doses of diuretics in most of male (37.8%) and female (42.1%) studied subjects were 50 – 99% of usual daily dose. Less proportion in male group was with the use of 1 – 49% of usual daily diuretic dose when compared to female group (17.6% versus 19.3%). Male group had higher proportion with 100% and above of usual daily diuretic dose than female group.

Table 7 shows the correlation between age and the utilised doses of HF medications among studied subjects. Weak correlation was shown between age with the utilised doses of ACEIs/ARBs, β-blockers, MRA and diuretics ($r = 0.025$, $r = -0.087$, $r = -0.117$, $r = 0.008$). Among studied subjects, age was weakly and inversely correlated with the utilised doses of β-blockers and MRA ($r = -0.087$, $r = -0.117$). However, these correlations were statistically insignificant ($P > 0.05$).

Comparison of utilised doses of HF medications among different ethnicities (table 8) showed that in ACEIs/ARB domain, the median (IQR) of utilised doses of Indian was the highest compared to other ethnicities, while Malay and Chinese had equal median (IQR) ACEI/ARB utilised doses. In β-blocker use, there was no significance difference in median utilised doses among different ethnicities ($P > 0.05$). Malay and Indian had similar median (IQR) MRA utilised doses. Meanwhile, Chinese and other ethnicities had relatively lower median MRA utilised doses compared to Malay and Indian. This finding was statistically significant ($P = 0.031$). Similarly, there was no significant difference in diuretics domain, Malay, Indian and Chinese had similar median utilised doses.

Table 9 demonstrates the correlation between baseline and current EF with utilised doses of HF medications. There was weak correlation between baseline and current EF with utilised doses of ACEIs/ARBs ($r = 0.046$, $r = 0.073$). This finding was statistically insignificant ($P > 0.05$). Pearson correlation test revealed that utilised doses of MRA was weakly and inversely correlated to the baseline and current EF of studied subjects. This suggested that as the utilised doses of MRA decreases, baseline and current EF increase. These correlations were statistically significant ($P < 0.001$, $P = 0.002$). For β-blockers and diuretics, Spearman correlation test found that there was weak correlation between baseline and current EF with utilised doses of β-blockers ($r = 0.007$, $r = -0.07$) and diuretics ($r = -0.104$, $r = -0.265$) and statistically insignificant ($P > 0.05$).

Table 10 showed the comparison of utilised doses of HF medications between studied subjects with and without hypertension. The mean (SD) utilised doses of ACEIs/ARBs among studied subjects with hypertension was higher than the mean (SD) ACEI/ARB utilised doses in studied subjects without hypertension. This finding was statistically significant ($P = 0.007$). Studied subjects with or without hypertension had similar mean (SD) MRA utilised doses and was

statistically insignificant (P > 0.05). Among studied subjects with hypertension, the median (IQR) β-blocker utilised doses was lower than the median (IQR) β-blocker utilised doses in studied subjects without hypertension and was statistically insignificant (P > 0.05). The median (IQR) diuretic utilised doses among studied subjects with or without hypertension were equal and it was statistically insignificant (P > 0.05).

Table 11 demonstrated the comparison of utilised doses of HF medications between studied subjects with and without IHD. The mean (SD) ACEI/ARB utilised doses of studied subjects with IHD was lower than the mean (SD) ACEI/ARB utilised doses of studied subjects without IHD, however this finding was statistically insignificant (P > 0.05). Studied subjects with IHD had lower mean (SD) MRA utilised doses compared to mean (SD) MRA utilised doses in studied subjects without IHD and was statistically significant (P < 0.001). The median (IQR) β-blocker utilised doses in studied subjects with IHD and without IHD were the same. Furthermore, the median (IQR) diuretic utilised doses in studied subjects with IHD and without IHD were equal. These findings were not statistically significant (P > 0.05).

Table 12 demonstrated the comparison of utilised doses of HF medications between studied subjects with and without DM. The mean (SD) ACEI/ARB utilised doses of studied subjects with DM was lower compared to studied subjects without DM and this finding was statistically insignificant (P > 0.05). Studied subjects with DM had lower mean (SD) MRA utilised doses compared to studied subjects without DM. However, it was statistically not significant (P > 0.05). The median (IQR) β-blocker utilised doses in studied subjects with DM was similar to subjects without IHD. Furthermore, the median (IQR) diuretic utilised doses in studied subjects with DM was higher compared to subjects without DM. These findings were not statistically significant (P > 0.05).

Comparison of utilised doses of HF medications between studied subjects with and without CKD was shown in table 13. Mean (SD) ACEI/ARB utilised doses in studied subjects with CKD was lower than the mean (SD) ACEI/ARB utilised doses in those without CKD. However, this finding was not statistically significant (P > 0.05). Studied subjects without CKD had higher mean MRA utilised doses than those with CKD and it was statistically significant (P = 0.003). The median (IQR) β-blocker utilised doses in studied subjects with CKD and without CKD were the same. Furthermore, the median (IQR) diuretic utilised doses in studied subjects with CKD and without CKD were equal. These findings were not statistically significant (P > 0.05).

Table 14 demonstrates the comparison of utilised doses of HF medications between studied subjects with and without AF. Median (IQR) ACEI/ARB utilised doses in studied subjects with AF was lower than the median (IQR) ACEI/ARB utilised doses in those without AF. However, this finding was not statistically significant (P > 0.05). Studied subjects with AF had higher median MRA utilised doses than those without AF and it was statistically significant (P = 0.007). The median (IQR) β-blocker utilised doses in studied subjects with AF was higher than those without AF. Furthermore, the median (IQR) diuretic utilised doses in

studied subjects with AF and without AF were equal. However, these findings were not statistically significant (P > 0.05).

Table 15 shows the comparison between baseline and current EF of studied subjects. The mean (SD) current EF of studied subjects was found to be significantly higher (P < 0.001) than the mean (SD) baseline EF. Table 16 demonstrates the correlation between current EF with the utilised doses of HF medications. There was no significant correlation between the current EF and the utilised doses of ACEIs/ARBs, β-blockers and diuretics (P > 0.05). Weak and inverse correlation was found between current EF and utilised doses of MRAs (r = -0.265). As current EF increases, MRA utilised dose decreases. This finding was statistically significant (P = 0.002).

Discussion

The mean age of HF patients in this study was relatively younger as compared to a study in HF across 11 Asia regions which showed a higher mean age of 61.6 years old [7]. Besides, a HF study in multi-ethnic population in Kuala Lumpur, Malaysia also had shown a higher mean age of 63.6 years old when compared to that of HF patients in this study (58.23 ± 12.35 years) [8]. Furthermore, the incidence of hypertension and CAD was reported at younger age and this may indicate that the mean age of HF is also becoming younger as hypertension and CAD remain as risk factors of HF [9],[10]. In terms of racial difference, almost half of the HF patients in this study were Malays although statistically insignificant. A study of HF in Asia showed that Malays had higher prevalence of risk factors which were CAD, hypertension and DM as compared to Chinese, Indians and indigenous people [11].

This study showed that male and female studied subjects had mean baseline EF below 40% and this result is true as the inclusion criteria of this study was EF equal to or less than 40% for recruitment of the HF patients. Majority of HF patients in this study had associated comorbidities such as hypertension, followed by IHD, diabetes, CKD and AF. This data may be supported by a retrospective cohort study demonstrating that HF was highly associated with comorbidities and the studied comorbidities were hypertension, diabetes and renal function disorder [12]. A study of HF epidemiology in Asia had shown that as the underlying etiology of HF, CAD had the highest prevalence ranging from 28.2% to 53.1% [13].

ACEIs was shown to be used higher than ARBs in this study. Similar data was reported in Malaysia Statistics Medicines 2015-2016 with the highest use of perindopril compared to other ACEIs. A meta-analysis of randomised controlled trials showed that ACEIs reduced all-cause mortality by 11% and CV mortality by 14% in HF patients, however ARBs had no beneficial effect on reducing all-cause mortality and CV mortality [14]. Hence, ACEIs are considered as first line therapy in HF population.

In this study, among the ARBs, valsartan was more commonly used, compared to other ARBs. However, according to Malaysia Statistics Medicines 2015-2016, losartan was the highest used among ARBs. A review concluded that with ACEI

intolerance, valsartan was the first choice for patients having HF (15). This could be explained as valsartan improved NYHA class and EF significantly, leading to reduction in rate of hospitalization among HF patients. Likewise, valsartan was associated with reduction of all-cause mortality by 33% and composite mortality and morbidity risk by 44% in HF patients not receiving ACEIs. For patients having comorbidities of myocardial infarction or AF, ARBs may help to improve cardiac volume and EF as well as reduce the recurrence rates [15].

Majority of HF patients in this study used β-blockers and bisoprolol was highly used among studied subjects. In Malaysia Statistics Medicines 2015-2016, it was reported that metoprolol had the highest use, followed by bisoprolol. A study was done by using databases of patients from Norway, England and Germany with stable HF with reduced EF and prescribed with either bisoprolol, metoprolol or carvedilol. As the results, no significance difference was observed in all-cause mortality rate between bisoprolol, carvedilol and metoprolol [16]. β-blockers have been associated with significant reduction in all-cause mortality in patient with HFrEF compared with placebo [17].

Among the HF patients receiving MRAs, majority of them received spironolactone. This data is reflected in Malaysia Statistics Medicines 2015-2016 which showed that spironolactone had higher usage compared to eplerenone. A systematic review on comparison of eplerenone, spironolactone and canrenone had shown significant mortality rate reduction with all MRAs in HF population with left ventricular dysfunction [18]. Eplerenone had reduced risk of CV mortality by 17% as compared to spironolactone with 25% risk reduction of CV mortality. Aside from lower risk reduction in CV mortality, eplerenone manifested significant induced rates of hyperkalemia among HF patients with CKD [19].

Frusemide was the only diuretics being used by HF patients in this study. This is in-line with the Malaysia Statistics Medicines 2015-2016 that showed frusemide had the highest use among the diuretics. An article mentioned that loop diuretics provide more intense and shorter diuresis compared to thiazide diuretics which may result in prolonged diuresis [20]. This may help to avoid adverse effects associated with fluid congestion such as sudden increase in LV filling pressure leading to poor prognosis, correspondingly implementing better fluid overload management in symptomatic HF patients [21].

Studies have shown that there was significant difference in outcomes with utilised doses of HF medications between genders [3]. This study found that females had higher mean ACEI/ARB utilised dose compared to males. A prospective multinational data (ASIAN-HF) from Asia (South Korea, Japan, Taiwan, Hong Kong, China, India, Thailand, Malaysia, Philippines, Indonesia, and Singapore) studied on the prescribing patterns of guideline-recommended medical therapies in HF and its effect on outcomes. In this study, the mean ACEI/ARB utilised doses in male and female groups were 36.32% and 39.69%, and majority of subjects was treated with doses less than 50% of the recommended doses. ASIAN-HF study presented the mean achieved doses in Malaysia was 40% to 50% [22]. This may indicate more underutilisation in dosage of ACEIs/ARBs among study population compared to previous study.

There was no significance difference in β-blockers utilised doses between genders. A meta-analysis of randomised controlled trials was conducted on efficacy and tolerability of β-blockers in females and males with HFrEF. The efficacy of β-blockers presented with equal benefit in both sexes with significant enhanced reduction in all-cause mortality as primary outcome. Secondary outcomes which were cardiovascular hospital readmission and composite clinical outcomes in females and males were similar, hence no association was found in efficacy of β-blockers with gender difference [23]. Median utilised dose of β-blockers was 25% in both genders while majority of subjects was prescribed with less than 50% of the recommended doses. These results were similar in ASIAN-HF study which showed that the median β-blocker prescribed doses were 25% of the guideline-recommended doses and 65% of patients received β-blockers less than 50% of guideline-recommended doses [22]. This may indicate underutilisation of β-blockers as a retrospective cohort study in Italy observed that high dose β-blockers (>50% of recommended target doses) provided better prognosis compared to HFrEF patients in both medium and low dose, hence prognostic role of β-blockers could be considered dose-dependent [24].

MRAs are effective in lowering blood pressure, reducing LV hypertrophy and improving clinical outcome in patients with HFrEF [25]. This study revealed that majority of subjects was more likely treated with MRAs. Comparatively, a similar trend was found in a prospective multinational study across 11 countries in Asia (South Korea, Japan, Taiwan, Hong Kong, China, India, Thailand, Malaysia, Philippines, Indonesia, and Singapore) [22]. However, only around 60% of study population was prescribed with MRAs while all are with reduced ejection fraction. A retrospective study was conducted in Sweden on factors associated with MRA underuse in HFrEF. The potential major reasons were worsening of renal function and hyperkalemia. This could be explained as CKD was a strong predictor of MRA non-use. Relatedly, diuretic use was the strongest independent predictor of MRA use as both MRAs and loop diuretics were used to balance potassium levels [26].

This study found the median diuretic utilised doses were 50% in both sexes and doses above 50% of usual daily doses were most commonly used among study population. This result may be supported by a retrospective study which was conducted in Czech, evaluating whether the relatively higher dose of frusemide can reduce the readmission and mortality rates in HF patients [27]. This study exhibited that the high dose of frusemide (>50% of usual daily dose; >40mg) was correlated with the severity of HF including lower LVEF. With matched samples, this study also found that the higher dose of loop diuretics displayed neutral effect on the readmission and mortality rates in HF patients with LV dysfunction [27].

In ASIAN-HF study, 100% recommended doses of ACEIs/ARBs were less commonly used in older patients [22]. Differently, this study found that age was not correlated with the utilised doses of ACEIs/ARBs and diuretics. As age increases, the utilised doses of ACEIs/ARBs and diuretics increase. This result was expected as arterial stiffness increases with age and is closely associated with the progression of cardiovascular disease [28]. A similar trend was found that significantly more diuretics were given compared to HF patients aged less than 60 years old [29]. This study also found that as age increases, the utilised doses of β-

blockers and MRAs decrease. This trend was supported by a study which demonstrated that elderly patients with HFrEF received significantly fewer β-blockers and MRAs. This may be due to elderly HFrEF patients often received less guideline-recommended medication prescriptions and also in lower dosage [29].

In terms of different ethnicities in this study, there was significant difference found between ethnicities and median MRA utilised doses as Malay and Indian had higher utilised doses of MRAs compared to Chinese and indigenous people. This may be associated with different lifestyle factors and diet habits among different ethnic groups in Malaysia. Lifestyle factors included sedentary lifestyle, physical inactivity, smoking and alcohol consumption while diet habits such as speed of eating, dining out, skipping breakfast and late dinners were found to be associated with increased incidence of metabolic syndrome. This previous study in Cheras Health Centre, Selangor had shown that prevalence of CVD risk factors was highest among Malay and lowest among Chinese, the studied CVD risk factors are obesity, hypercholesterolemia, hypertension, hyperglycaemia and smoking status [30]. Furthermore, an earlier study had demonstrated that Indian ethnicity had the highest diabetes prevalence while low physical activity among Malays and Chinese was associated with increased metabolic syndrome risk [31],[32]. These may prompt the increase in CVD risk and complications, leading to increased incidence and severity of HF.

An interesting result was found in this study, utilised doses of MRAs were weakly and inversely correlated with baseline and current EF. As baseline and current EF increase, MRA utilised doses decrease. MRA treatment significantly improves cardiac structure and function which leads to a decrease in left ventricular filling pressure and reverse cardiac remodelling [33]. In terms of comorbidities in the clinical characteristics, HF patients with hypertension had higher mean ACEI/ARB utilised doses compared to those without hypertension. This result is expected as a study showed that ACEIs/ARBs was associated with 8% risk reduction only in composite endpoint of CV death among patients with hypertension. Meanwhile, ACEI use was associated with 16% reduction in mortality among HF patients with hypertension [34]. This study also showed that patients with IHD had lower mean utilised doses of MRAs compare to those without IHD, however this finding was in contrast with previous study that showed that MRAs reduced morbidity and mortality in HFrEF patients, including those with IHD. These studies demonstrated that MRAs was associated with 15% reduction in all-cause mortality as well as reversal of negative remodelling and decreased ventricular arrhythmias [35]. Furthermore, in this study, patients with CKD had lower mean MRA utilised doses compared to patients without CKD. This trend may be supported by a study which stated that among HF patients with CKD, MRA use was associated with lower risk of all-cause readmission but greater risk of hyperkalaemia and acute renal insufficiency [36]. Despite the risk of hyperkalaemia and acute renal insufficiency, MRAs may be used with careful monitoring in HF patients in the presence of CKD as MRAs showed positive effect on their survival [37]. Higher median utilised doses of MRAs was instead found in patients with AF compared to patients without AF earlier. Studies showed that MRAs may improve atrial conduction and remodelling in HF patients as well as reduce AF recurrence in patients with HFrEF [38],[39]. This may prevent the worsening of HF outcomes.

Result found in this study showed that patients' current EF were significantly higher than their baseline EF with treatment. ACEIs/ARBs, β-blockers and MRAs are disease-modifying drugs in HF as they increase cardiac output by increasing contractility and reducing peripheral resistance [40]. These actions had established their benefits on survival, hospitalisations, quality of life and markers of LV function [41]. ACEIs/ARBs is considered as first-line therapy. A review on efficacy of ACEIs/ARBs in treatment of HF had shown that ACEIs/ARBs were associated with reversal of ventricular remodeling and improved ventricular function [42]. A meta-analysis of randomised clinical trials had demonstrated that β-blockers improved LVEF up to 4.9% from its baseline as well as prognosis for HF patients with reduced EF [43]. Moreover, MRAs had been shown in large randomised clinical trial with significant reductions in CV mortality and morbidity by reducing fibrosis and cardiac remodelling among patients with HFrEF [44],[45]. Based on the previous studies on the benefits of ACEIs/ARBs, β-blockers and MRAs in HF, they may be associated with improve EF among HF patients in this study.

There were few limitations identified in this study. Clinical parameters such as renal profile, blood pressure readings and patients' body weight should be included in this study as these are the factors which may affect the utilisation of HF medications. Secondly, convenience sampling applied in this study may cause inability to generalise the results to the entire HF population as a whole, thus the results may not be representative of the population and prone to sampling bias. Randomisation minimises selection bias and confounding factors which helps the study results to be statistically more reliable. In addition, this research was conducted as retrospective study. The level of evidence of this study may be inferior compared with prospective study as prospective study has fewer potential sources of bias and confounding than retrospective study. While conducting retrospective study, researchers cannot control exposure or outcome assessment which is established at the start of the study. Sample size could be one of the research limitations because the sample size calculation did not include the prevalence of ACEI/ARB, β-blocker, MRA and diuretic usage in Malaysia.

Conclusion

This study concluded that there was no significance difference in utilised doses of ACEIs/ARBs, β-blockers, MRAs and diuretics used in the management of HF between genders among the study population. Instead, there were significant difference in utilised doses of HF medications in relation to the concomitant diseases. This study found a weak and inverse correlation between MRA utilised doses with baseline and current EF among the HF patients and ACEIs/ARBs utilised doses were significantly higher in HF patients with hypertension compared to those without hypertension. This study also found that HF patients with IHD had lower utilised doses of MRAs, however this finding remains controversial. In addition, HF patients with CKD were found to have lower utilised doses of MRAs compared to those without CKD and HF patients with AF had significantly higher MRA utilised doses compared to those without AF. In terms of overall effectiveness, EF was significantly improved among the patients on HF medications. ACEIs/ARBs, β-blockers, MRAs and diuretics were considered as HF first-line medical therapies with established benefits on mortality, hospital

readmissions, quality of life and improved LV functions in HF population. Since there was no difference in utilised doses of HF medications between genders, therefore we recommend the dosage referring to evidence-based current guidelines. Individualised dosing regimens of HF medications and monitoring according to patients' profile is also important to prevent or avoid underutilisation and underdosing of guideline-recommended medications among HF patients as this study observed that dose utilisation of HF medications was not affected by gender differences.

For future research, this retrospective study was unable to provide interventions on the clinician decision-making pharmacotherapy management of HF patients. Hence, future research in HF can be performed as a prospective study on evaluation of factors affecting dose utilisation of HF medications among HF patients. Besides, further research is required to define the factors associated in affecting the dose utilisation of HF medications. Single source study could not represent the HF population in Malaysia. Thus, multi-centre with randomised controlled study can be performed on determining factors affecting dosing of HF medications.

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Conflict of interest

None to declare.

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Table 1 Demographic and clinical characteristics of studied subjects

Variable (N = 131)	Male group (n = 74)		Female group (n = 57)		P-value
	Mean (SD)	Frequency (%)	Mean (SD)	Frequency (%)	
Demographic characteristics					
Age	57.6 (12.51)		59.1 (12.20)		0.478[a]
Gender		74 (56.5)		57 (43.5)	-
Ethnicities					0.143[b]
Malay		32 (43.2)		32 (56.1)	
Chinese		27 (36.5)		11 (19.3)	
Indian		13 (17.6)		10 (17.5)	
Orang Asli		2 (2.7)		4 (7.0)	
Clinical characteristics					
Baseline EF	29.91 (7.40)		29.67 (7.39)		0.851[a]
Current EF	37.19 (14.03)		38.95 (12.59)		0.459[a]
Comorbiditie		73 (98.6)		52 (91.2)	0.085[c]
s		47 (63.5)		30 (52.6)	0.210[b]
		39 (52.7)		33 (57.9)	0.554[b]
Hypertension		37 (50.0)		35 (61.4)	0.193[b]
IHD		12 (16.2)		10 (17.5)	0.840[b]
DM		9 (12.2)		6 (10.5)	0.771[b]
CKD					
AF					

[a] *Independent-T test*
[b] *Fisher Exact*
[c] *Pearson Chi-square*
**P-value < 0.05 shows statistical significance*

Table 2 Utilisation of HF medications among studied subjects

Medication	Frequency (%) (N = 131)		P-value
	Male group (n = 74)	Female group (n = 57)	
Baseline			
ACEIs/ARBs	60 (81.1)	41 (71.9)	0.217[b]
β-blockers	71 (95.9)	53 (93.0)	0.468[c]
MRAs	39 (52.7)	29 (50.9)	0.836[b]
Diuretics	56 (75.7)	43 (75.4)	0.975[b]
Follow-up			
ACEIs /ARBs	60 (81.1)	46 (80.7)	0.956[b]
β-blockers	73 (98.6)	55 (96.5)	0.580[c]
MRAs	45 (60.8)	35 (61.4)	0.945[b]

Diuretics	55 (74.3)	41 (71.9)	0.759[b]
ACEIs/ARBs			
Perindopril	50 (67.6)	40 (70.2)	0.750[b]
Enalapril	1 (1.4)	0 (0.0)	1.000[c]
Captopril	1 (1.4)	0 (0.0)	1.000[c]
Ramipril	0 (0.0)	1 (1.8)	0.435[c]
Valsartan	22 (29.7)	14 (24.6)	0.511[b]
Losartan	4 (5.4)	2 (3.5)	0.697[c]
Irbesartan	0 (0.0)	3 (5.3)	0.080[c]
Telmisartan	6 (8.1)	1 (1.8)	0.137[c]
β-blockers			
Bisoprolol	68 (91.9)	55 (96.5)	0.465[c]
Metoprolol	2 (2.7)	1 (1.8)	1.000[c]
Carvedilol	7 (9.5)	1 (1.8)	0.137[c]
MRAs			
Spironolactone	48 (64.9)	41 (71.9)	0.390[b]
Eplerenone	0 (0.0)	1 (1.8)	0.435[c]
Diuretics			
Frusemide	59 (79.7)	44 (77.2)	0.725[b]

[b] *Fisher Exact*
[c] *Pearson Chi-square*
**P-value < 0.05 shows statistical significance*

Table 3 Comparison of ACEI/ARB utilised doses between genders

Variable (N = 131)	**Male group (n = 74)**	**Female group (n = 57)**	**Mean difference (95% CI)**	**P-value**
Mean (SD) ACEI/ARB utilised doses (%)	36.32 (31.46)	39.69 (33.75)	-3.38 (-14.698, 7.947)	0.556[a]
Recommended ACEI/ARB dose (%)	**Frequency (%)**			
0	14 (18.9)	11 (19.3)		
<50	31 (41.9)	22 (38.6)		
≥50	19 (25.7)	14 (24.6)		
≥100	10 (13.5)	10 (17.5)		

[a] *Independent-T test*
**P-value < 0.05 shows statistical significance*

Table 4 Comparison of β-blockers utilised doses between genders

Variable (N = 131)	**Male group (n = 74)**	**Female group (n = 57)**	**Z Statistics[d]**	**P-value**
Median (IQR) β-blockers utilised doses (%)	25.00 (25.00)	25.00 (25.00)	-0.782	0.434[d]
Recommended β-blockers dose (%)	**Frequency (%)**			

0	1 (1.4)	2 (3.5)
<50	50 (67.6)	32 (56.1)
≥50	17 (23.0)	17 (29.8)
≥100	6 (8.1)	6 (10.5)

[d] *Mann-Whitney test*
**P-value < 0.05 shows statistical significance*

Table 5 Comparison of MRA utilised doses between genders

Variable (N = 131)	**Male group (n = 74)**	**Female group (n = 57)**	**Mean difference (95% CI)**	**P-value**
Mean (SD) MRA utilised doses (%)	26.69 (27.55)	24.56 (22.41)	2.13 (-6.745, 11.000)	0.636[a]
Usual daily MRA dose (%)	**Frequency (%)**			
0	29 (39.2)	22 (38.6)		
<50	20 (27.0)	15 (26.3)		
≥50	21 (28.4)	20 (35.1)		
≥100	4 (5.4)	0 (0.0)		

[a] *Independent-T test*
**P-value < 0.05 shows statistical significance*

Table 6 Comparison of diuretic utilised doses between genders

Variable (N = 131)	**Male group (n = 74)**	**Female group (n = 57)**	**Z Statistics[d]**	**P-value**
Median (IQR) diuretic utilised doses (%)	50.00 (50.00)	50.00 (50.00)	-0.884	0.399[d]
Usual daily diuretic dose (%)	**Frequency (%)**			
0	19 (25.7)	16 (28.1)		
<50	13 (17.6)	11 (19.3)		
≥50	28 (37.8)	24 (42.1)		
≥100	14 (18.9)	6 (10.5)		

[d] *Mann-Whitney test*
**P-value < 0.05 shows statistical significance*

Table 7 Correlation between age and the utilised doses of HF medications

Variable (r, p)	**Age (r, p)**
ACEIs/ARBs	0.025[e] (0.778)
β-blockers	-0.087[e] (0.323)
MRAs	-0.117[e] (0.184)
Diuretics	0.008[e] (0.931)

[e] *Spearman correlation test*
**P-value < 0.05 shows statistical significance*

Table 8 Comparison of utilised doses of HF medications among different ethnicities

Variable	Ethnic	n	Median (IQR) utilised doses (%)	X^2 statistic (df)[g]	P-value
ACEIs/ARBs	Malay	64	25.00 (37.50)	1.06 (3)	0.787[f]
	Chinese	38	25.00 (37.50)		
	Indian	23	50.00 (37.50)		
	Others	6	25.00 (62.50)		
β-blockers	Malay	64	25.00 (25.00)	2.26 (3)	0.520[f]
	Chinese	38	25.00 (28.13)		
	Indian	23	25.00 (12.50)		
	Others	6	25.00 (40.63)		
MRAs	Malay	64	25.00 (50.00)	8.90 (3)	**0.031*[f]**
	Chinese	38	12.50 (50.00)		
	Indian	23	25.00 (25.00)		
	Others	6	12.50 (31.25)		
Diuretics	Malay	64	50.00 (25.00)	3.92 (3)	0.271[f]
	Chinese	38	50.00 (75.00)		
	Indian	23	50.00 (50.00)		
	Others	6	12.50 (62.50)		

[f] *Kruskal Wallis test*
**P-value < 0.05 shows statistical significance*

Table 9 Correlation between baseline and current EF with utilised doses of HF medications

Variable (r, p)	Baseline EF	Current EF
ACEIs/ARBs	0.046[g] (0.598)	0.073[g] (0.407)
β-blockers	0.007[e] (0.934)	-0.070[e] (0.429)
MRAs	-0.386[g] **(<0.001*)**	-0.265[g] **(0.002*)**
Diuretics	-0.104[e] (0.235)	-0.153[e] (0.081)

[e] *Spearman correlation test*
[g] *Pearson correlation test*
**P-value < 0.05 shows statistical significance*

Table 10 Comparison of utilised doses of HF medications between studied subjects with and without hypertension

Variable	n	Utilised doses (%)		Mean difference[a] (95% CI)	Z Statistics[d]	P-value
		Mean (SD)	Median (IqR)			
ACEIs/ARBs						
With hypertension	77	43.83 (34.81)		-14.66 (-25.290, -		**0.007*[a]**

Without hypertension	54	29.17 (26.60)		4.039)		
β-blockers						
With hypertension	77		25.00 (25.00)		-0.086	0.931[d]
Without hypertension	54		37.50 (37.50)			
MRAs						
With hypertension	77	25.65 (25.96)		0.28 (-8.667, 9.221)		0.951[a]
Without hypertension	54	25.93 (24.75)				
Diuretics						
With hypertension	77		50.00 (50.00)		-1.115	0.265[d]
Without hypertension	54		50.00 (25.00)			

[a] *Independent-T test*
[d] *Mann-Whitney test*
**P-value < 0.05 shows statistical significance*

Table 11 Comparison of utilised doses of HF medications between studied subjects with and without IHD

Variable	n	Utilised doses (%)		Mean difference[a] (95% CI)	Z Statistics[d]	P-value
		Mean (SD)	Median (IqR)			
ACEIs/ARBs	72	34.90		6.42 (-5.070,		0.271[a]
With IHD	59	(29.22)		17.906)		
Without IHD		41.31 (35.83)				
β-blockers						
With IHD	72		25.00 (34.38)		-1.202	0.230[d]
Without IHD	59		25.00 (25.00)			
MRAs						
With IH	72	18.75		15.57 (7.149,		**<0.001*[a]**
Without IHD	59	(22.50) 34.32 (26.22)		23.995)		
Diuretics						
With IHD	72		50.00		-1.748	0.081[d]

Without IHD	59	(50.00) 50.00 (25.00)	

[a] *Independent-T test*
[d] *Mann-Whitney test*
**P-value < 0.05 shows statistical significance*

Table 12 Comparison of utilised doses of HF medications between studied subjects with and without DM

Variable	n	Utilised doses (%)		Mean difference[a] (95% CI)	Z Statistics[d]	P-value
		Mean (SD)	Median (IqR)			
ACEIs/ARBs						
With DM	72	37.15		1.41 (-9.89,		0.806[a]
Without DM	59	(32.02) 38.56 (33.10)		12.70)		
β-blockers						
With DM	72		25.00		-1.249	0.212[d]
Without DM	59		(37.50) 25.00 (25.00)			
MRAs						
With DM	72	25.00		1.69 (-7.15,		0.705[a]
Without DM	59	(27.19) 26.69 (23.15)		10.54)		
Diuretics						
With DM	72		50.00		-1.365	0.172[d]
Without DM	59		(25.00) 25.00 (50.00)			

[a] *Independent-T test*
[d] *Mann-Whitney test*
**P-value < 0.05 shows statistical significance*

Table 13 Comparison of utilised doses of HF medications between studied subjects with and without CKD

Variable	n	Utilised doses (%)		Mean difference[a] (95% CI)	Z Statistics[d]	P-value
		Mean (SD)	Median (IqR)			
ACEIs/ARBs						
With CKD	22	34.66		3.76 (-		0.621[a]
Without CKD	109	(34.49) 38.42 (32.08)		11.264, 18.781)		
β-blockers						

With CKD	22		25.00		-0.177	0.860[d]
Without CKD	109		(25.00) 25.00 (25.00)			
MRAs						
With CKD	22	11.36		17.31 (5.921, 28.691)		**0.003*[a]**
Without CKD	109	(18.46) 28.67 (25.65)				
Diuretics						
With CKD	22		50.00		-1.600	0.110[d]
Without CKD	109		(81.25) 50.00 (50.00)			

[a] *Independent-T test*
[d] *Mann-Whitney test*
**P-value < 0.05 shows statistical significance*

Table 14 Comparison of utilised doses of HF medications between studied subjects with and without AF

Variable	Median (IqR) utilised doses (%)		Z Statistics[d]	P-value
	With AF (n = 15)	Without AF (n = 116)		
ACEIs/ARBs	12.50 (50.00)	25.00 (25.00)	-1.656	0.098[d]
β-blockers	37.50 (87.50)	25.00 (25.00)	-1.228	0.219[d]
MRAs	50.00 (25.00)	25.00 (50.00)	-2.692	**0.007*[d]**
Diuretics	50.00 (25.00)	50.00 (50.00)	-0.526	0.599[d]

[d] *Mann-Whitney test*
**P-value < 0.05 shows statistical significance*

Table 15 Comparison between baseline and current EF of studied subjects

Variable	Mean (SD) (N = 131)		Mean difference (95% CI)	P-value
	Baseline	Current		
EF (%)	29.81 (7.37)	37.96 (13.41)	-8.15 (-10.703, -5.593)	**<0.001*[h]**

[h] *Paired-T test*
**P-value < 0.05 shows statistical significance*

Table 16 Correlation between current EF with utilised doses of HF medications

Variable (r, p)	Current EF
ACEIs/ARBs	0.073[g] (0.407)
β-blockers	-0.070[e] (0.429)
MRAs	-0.265[g] **(0.002*)**
Diuretics	-0.153[e] (0.081)

[e] *Spearman correlation test*
[g] *Pearson correlation test*
**P-value < 0.05 shows statistical significance*