Evaluation of demographic, clinical characteristics, and the prescribing practice of guideline-directed medical therapy among chronic heart failure outpatients in multidisciplinary clinics in a large tertiary hospital: a retrospective audit of 1186 patients from 12 years

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Abstract

Background

Adherence to guideline-directed medical therapy (GDMT) remains low particularly in elderly despite several approaches. Previous studies showed that heart failure (HF) patients who receive pharmacist-involved multidisciplinary care may have better clinical outcomes. We evaluated patient characteristics and the practice of receiving individual GDMT in chronic HF patients who attended multidisciplinary clinics.

Methods

A retrospective audit of data of chronic HF patients presenting to two multidisciplinary outpatient clinics at a tertiary hospital between March 2005 and January 2017 was performed. Data were obtained from two clinics, a Multidisciplinary Ambulatory Consulting Service (MACS) clinic which uses a pharmacist-involved model of multidisciplinary care, and a General Cardiology Heart Failure Service (GCHFS) clinic which does not have the active involvement of a pharmacist.

Results

HF with mid-range ejection fraction (HFmrEF) subjects resembled the HF with preserved ejection fraction (HFpEF) patients in terms of age, heart rate (HR), systolic blood pressure (SBP) and having higher prevalence of polypharmacy whereas resembled with the HF with reduced ejection fraction (HFrEF) for the proportion of male distribution and prevalence of ischemic heart disease (IHD). Both the clinics had similar prescribing rates of GDMT and achieved maximal tolerated doses of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARB) in HFrEF, but significantly higher prescription of ACEIs/ARBs (70.5% v. 56.2%) was found in HFpEF patients in the MACS clinic. There was significantly lower rates of β-blockers and mineralocorticoid receptor antagonists (MRAs) prescription in HFrEF and HFpEF patients in both clinics. Use of digoxin in chronic atrial fibrillation (AF) was significantly higher in HFrEF patients (82.5% v. 58.5%), but number of people anticoagulated in presence of AF and prescription of diuretics were significantly lowered in MACS clinic in HFpEF patients. Age, anemia, chronic renal failure, SBP, HR and comorbidities were the significant predictors in a multivariate binary logistic regression for the utilization of GDMT.

Conclusions

Our study concludes that pharmacist is an important member of a multidisciplinary team in the management of chronic heart failure. The other roles of the pharmacist within a multidisciplinary team, including continuity of care, medication compliance and prevention of adverse reactions need further research.

Background

Heart failure HF remains a major public health burden globally. It is a rapidly growing debilitating chronic disease affecting an estimated 38 million people diagnosed worldwide [1]. It has high rates of mortality and morbidity [2], limits functional capacity and is associated with impaired quality of life [3]. Additionally, HF carries a significant financial burden on health care [4] due to HF hospitalizations which are often prolonged, and also subsequent high readmission within 30 days [5]. It is a complex syndrome driven by multiple comorbidities [6] and polypharmacy [7], due to its prevalence in the elderly population [8].

The European Society of Cardiology classification of HF is based on ejection fraction, with HFrEF defined as left ventricular ejection fraction (LVEF) < 40%, LVEF 40-49% for HFmrEF and LVEF > 50% for HFpEF [9]. HFpEF is an emerging area of interest and its prevalence is rapidly growing due to risk factors landscape, and at present is at least 50% [10, 11]. Furthermore, the emergence of HFmrEF presents an interesting development in HF given a meta-analysis demonstrating its shared characteristics with both the HFrEF and HFpEF populations [12]. At present, HFmrEF remains a poorly understood phenotype as no randomized controlled trials have included this particular HF category [13].

While there is significant evidence available in HFrEF management, there is a dearth of evidence-based pharmacotherapies for HFpEF [9]. Guideline-recommended pharmacotherapies for HFrEF such as ACEIs/ARBs [14, 15], β-blockers [16, 17], and MRAs [18] have limited benefits in HFpEF, [19] and HFmrEF [20], likely reflecting a different underlying pathophysiological process of HFpEF. Further research need to be carried out to characterize the pathophysiology, patient's demographics and clinical characteristics to halt the challenges in development of strategies for the management of HFpEF and HFmrEF categories [21].

There is evidence that that higher doses of ACEIs and β-blockers have a more potent effect of reducing mortality and hospitalizations in chronic heart failure (CHF) patients compared to lower doses [22]. Nevertheless, achievement of maximally tolerated HF medical therapy remains low [23]. In a previous study, 29% of CHF outpatients with HFrEF received recommended target dose of ACEIs and 18% received beta-blockers, Furthermore, 33% of patients had no documentation with regards to reasons for a lack of up titration of medical therapy. [24]. Regardless of HF type, there are difficulties in achieving maximal tolerated doses. These gaps have persisted despite HF nurse-led outpatient clinics [25].

Several approaches including pharmacist-assisted multidisciplinary clinics have been explored. In previous studies, pharmacist-assisted multidisciplinary management of CHF resulted in significant increase in prescription of GDMT [26], significant reductions in 30- and 90- day all-cause readmissions and HF hospitalizations [27, 28]. In this study, we aimed to evaluate particularly the influence of a pharmacist on prescribing practices of GDMT in CHF patients from the real-world data from a duration of 12 years.

Methods

This study followed the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) guidelines [29]. Ethics approval was obtained from the Royal Adelaide Hospital Human Ethics Research Committee (R20161105).

Study Design

This was a retrospective observational study of the clinical characteristics of CHF patients with HFrEF, HFmrEF and HFpEF from two multidisciplinary outpatient clinics in a tertiary referral hospital. Data were obtained from CHF patients attending two outpatient clinics, a Multidisciplinary Ambulatory Consulting Service (MACS) clinic which uses a pharmacist-involved model of multidisciplinary care, and a General Cardiology Heart Failure Service (GCHFS) clinic which does not have the active involvement of a pharmacist.

Setting

This study was conducted at a tertiary public hospital in South Australia. Secondary data of CHF patients from March 2005 until January 2017 for the MACS clinic patients, and from March 2006 until January 2017 for the GCHFS clinic patients, were used for this study. There were two systems for the collection and storage of patients' data within the hospital: MATRIX and OACIS, respectively. The MATRIX is a tailored Structured Query Language that allows documentation of comorbidities, medications, patient assessments, and summary of important diagnostic results data management. It allows clinicians to document clinically relevant information, generate evidence-based goals, and to generate letters to patient's primary care physicians. OACIS (Telus Health, Montreal, Canada) was used as the Patient Administration System for administration of inpatient and outpatient visits, as well as for the viewing of radiology and pathology results.

The in-depth model of care of the MACS clinic is in accordance with previous publication [30]. The model briefly constitutes a general nursing assessment including blood pressure and weight measurement, pharmacy medication review, followed by a physician review. Physicians involved in the delivery of MACS clinics included Cardiologists, clinical pharmacologists, General Physicians, and Geriatricians. Patients managed through the GCHFS were seen by a heart failure-trained nurse and a Cardiologist. Both groups of patients had access to a clinical psychologist and an exercise physiologist.

Participants

Patients primarily diagnosed as HF, and those who attended either the MACS clinic or the GCHFS clinic were included. Cardiac imaging confirming clinical HF diagnosis was predominantly echocardiography. Nuclear imaging, cardiac magnetic resonance imaging as well as case notes from external investigations were also utilized. If the left ventricular function was defined as mildly or more impaired at any time, patients were diagnosed as having reduced systolic function. If patients had multiple echocardiography or other forms of imaging, the worst value was considered. Patients were excluded if they did not attend

clinic appointments or had incomplete data sets. Data were collected as part of routine clinical practice. The follow-up of patients varied depending on the date of first presentation in either clinic.

Variables and outcomes

The outcome variables include the demographic, clinical characteristics, comorbidities and use of GDMT in CHF patients between two clinics. These outcome variables were measured between HFrEF, HFmrEF and HFpEF categories (demographics and clinical characteristics) as well as by MACS compared to GCHFS clinics (medication utilization only). The age, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), number of medications used, serum creatinine, hemoglobin, mean cell volume (MCV), and comorbidities were measured per patient. The SBP, DBP and HR are the four consecutive readings at rest, five minutes apart, and average of last three readings. The data utilized were from the last clinic appointment. The hemoglobin, MCV and creatinine are the last values before first presentation to clinic (which would usually represent the last values before hospital discharge) and the weight was measured at first appointment.

Outcome measurements

The LVEF value of <40% for HFrEF, 40-49 % for HFmrEF, and ≥50% for HFpEF was considered for comparison of demographic, clinical characteristics and comorbidities whereas LVEF value <40% for HFrEF and ≥40% for HFpEF was considered for the evaluation of GDMT. It is important to note that the evaluation of GDMT was only considered for HFrEF and HFpEF in our analysis. It is clinically significant because, for the duration of this study, there were no separate guidelines for HFmrEF patients in the hospital where this study was conducted. To perform the evaluation of GDMT, a guideline was developed based on Australian and European guidelines in the management of CHF (*see supplementary data*). Patients data were reviewed for the type of medications prescribed, doses used and contraindications due to patient characteristics.

Classifications for each group of medications was performed by two independent investigators (DRP and JEF) and checked for discrepancies as per the developed guidelines, with disagreements resolved by consensus with a third investigator (SS). It was determined that we were unable to determine the use of evidence-based therapies in CHF patients if they do not visit the MACS clinics at least twice. Therefore, for the comparison of the use of EBT, only patients who had ≥2 visit in MACS clinics were included. Polypharmacy was categorized into three groups: non-polypharmacy (0–4 drugs), polypharmacy (5–9 drugs) and hyperpolypharmacy (≥ 10 drugs) as defined by Onder *et al* 2012 [31].

Study size

During the study period, there was a total of 1186 CHF patients who attended the outpatient clinics and met our eligibility criteria. For the evaluation of EBTs, an individual data of 359 patients from MACS clinic, and 369 patients from the GCHFS clinic were available.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows (Version 25.0.0.1. Armonk, NY: IBM Corp). Results are presented as frequency and percentages for categorical variables and median (IQR) for continuous variables. The normal distribution of the numeric variables was confirmed using Shapiro–Wilk test (P>0.05). Median differences between two clinics was evaluated using Mann–Whitney U test for comparison of demographic and clinical characteristics and use of EBTs between two clinics whereas Kruskal–Wallis test was used for similar comparison among ejection fraction groups. Univariate and multivariate binary logistic regression was performed to determine the predictors of evidence-based practice. Nagelkerke R^2 was used to establish the amount of variance explained by the model. Univariate binary logistic regression was performed to determine the important variables to be included in multivariate analysis. Independent variables which showed a value < 0.25 in univariate analysis were included in the multivariate analysis. Probability values of p <0.05 were chosen to indicate a statistically significant difference.

Results

Participants

A total of 1186 patients were included: 725 patients were in the MACS clinic and 461 patients were in the GCHFS clinic. After excluding 74 patients in the MACS clinic and 54 from the GCHFS clinic who did not have echocardiography, the remaining 651 patients in the MACS clinic and 407 patients in the GCHFS clinic were included to compare their demographics and clinical characteristics by clinics and stratified by ejection fraction (Figure 1). Two patients from the MACS clinic and thirty-eight patients from the GCHFS clinic were excluded due to incomplete data sets). For the evaluation of EBTs, individual data for 489 HFrEF patients and 239 of the HFpEF patients were reviewed for the type of medications prescribed, doses used and contraindications due to patient characteristics. The flow diagram of the study is illustrated in Figure 1.

Descriptive data

Comparison of the differences in demographics, clinical characteristics, and comorbidities by ejection fractions

A comparison of the demographics and clinical characteristics among the CHF patients stratified by ejection fraction is illustrated in Table 1 and Figures 2, Figure 3, and Figure 4. The prevalence of HFrEF, HFmrEF and HFpEF was 56%, 13% and 31%, respectively (p<0.001) (Table 1). The median age of patients in HFpEF and HFmrEF was significantly greater (p < .001) than that of the HFrEF cohort. There was no significant difference in the distribution of weight, DBP and HR, serum creatinine and MCV, among HFpEF, HFmrEF and HFrEF group of patients (Table 1). In contrast, a statistically significant difference (p < .001) was observed for median SBP and number of medications used among HFpEF, HFmrEF and HFrEF group of patients. Hemoglobin level was highest for HFrEF followed by HFmrEF and HFpEF group. The prevalence of hypertension, AF, osteoarthritis, anemia, and asthma for HFmrEF patients lies between

HFrEF and HFpEF whereas there was a highest prevalence of IHD in HFmrEF followed by HFrEF and HFpEF patients ($p < .001$) Table 1. But the prevalence of other comorbidities was similar between HFrEF, HFmrEF and HFpEF patients.

There were significantly greater numbers of females diagnosed with CHF in HFpEF category (Fig 2). It is noteworthy that half number of patients (51.5%) were >80 years of age in HFpEF group followed by HFmrEF (41.2%) and HFrEF (29%) ($p < .001$) (Fig 3). Similarly, the prevalence of hyperpolypharmacy (≥ 10 medications) was highest for HFpEF group patients followed by HFmrEF and HFrEF patients (Fig 4).

Comparison of the differences in demographics, clinical characteristics, and comorbidities by clinics

Demographic and clinical characteristics of CHF patients compared by clinics are illustrated in Table 2. MACS clinic patients were significantly older ($p < .001$), less likely to be male, had a significantly higher SBP ($p < .001$) and DBP ($p < .05$) compared to GCHFS clinic patients. There was also a significant difference in the age group category between the two clinics. For patients with >80 years, the MACS clinic had a much higher prevalence of older patients compared to GCHFS clinic. However, weight and HR were similar between the two clinics. The number of medications used was significantly higher in MACS patients ($p < .001$) compared to GCHFS patients. There also exist significant differences in polypharmacy and hyperpolypharmacy, and their prevalence between the two clinics, respectively.

There was no difference in prevalence of IHD, AF, hyperlipidemia, CRF, solid cancer and gout between the two clinics. The prevalence of major comorbidities was significantly more common in MACS patients compared to GCHFS patients, respectively. The prevalence of patients with multiple comorbidities was statistically significantly higher in the MACS clinic patients compared to the GCHFS clinic patients (Table 2).

Comparison of the use of medications in chronic heart failure patients between clinics with heart failure with reduced and preserved ejection fractions

The MACS clinic had similar rates for the guideline-based prescriptions regarding appropriate use of ACEIs/ARBs (68.4% v. 72%) as well as the rate of appropriate use of the MTD of ACEIs/ARBs (46.3% v. 52%) compared with the GCHFS clinic patients in HFrEF patients. A significantly lower rate of appropriate use of β-blockers (83.1% v. 91.1%), MTDs of β-blockers (31.5% v. 47.3 %), and MRAs (32.1% v. 62.2%) were observed in the MACS clinic patients compared to the GCHFS clinic patients (Table 3). The use of target dose of ACEIs/ARBs was similar, but significantly lower in the MACS clinic compared to those in the GCHFS clinic for the use of β-blockers. Further, the MACS clinic patients had similar rates of prescription for diuretics, but a significantly higher prescription for digoxin in chronic AF (82.5% v. 58.5%) in HFrEF patients.

For patients with HFpEF, a significantly higher prescriptions of ACEIs/ARBs (70.5% v. 56.2%) in MACS clinic, but a significantly lower prescriptions of β-blockers (54% v. 68.5%), MRAs (30.1% v. 48%), furosemide and anticoagulation for AF were observed in the MACS clinic patients compared to those in the GCHFS clinic (Table 4). However, a similar prescription rate for digoxin was seen between two clinics.

Predictors of ACEIs/ARBs, β-blockers, MRAs and maximum tolerated dose of ACEIs/ARBs AND β-blockers use in heart failure with reduced ejection fraction (EF<40) patients.

Age, last clinic SBP, last clinic DBP, AF, anaemia, IHD, CRF, COPD, any cognitive impairment, any solid cancer, any CVA, falls, osteoarthritis, GORD, peripheral vascular disease (PVD), gout, ≥3 comorbidities and any thyroid disease being the significant predictors in the univariate analysis, were included in multivariate analysis of ACEIs/ARBs use (data not shown). Nagelkerke R^2 showed that the above variables used in the multivariate binary logistic analysis model could explain 26.4% in predicting the practice of ACEIs/ARBs use. Age, anaemia, CRF, gout and GORD were the negative predictors whereas, SBP was a positive predictor for the use of ACEIs/ARBs in HFrEF patients in the multivariate analysis (Table 5). Similarly, age, AF, IHD, CRF, COPD, any solid cancer, osteoarthritis, GORD, gout and presence of ≥3 comorbidities being the significant predictors in the univariate analysis, were included in multivariate analysis of the MTD use of ACEIs/ARBs (data not shown). The model explained 13.4% (Nagelkerke R^2) in predicting the practice of MTD of ACEIs/ARBs. Age and CRF were significant negative predictors of the use of MTD of ACEIs/ARBs in the multivariate analysis (Table 5).

Age, gender, HR, COPD, any solid cancer, gout, any anemia, IHD, any cognitive impairment, osteoporosis and any thyroid diseases being the significant predictors in the univariate analysis, were included in multivariate analysis of β-blockers use (data not shown). The model explained 12.9% (Nagelkerke R2) in predicting the use of f β-blockers. HR and gout were the significant negative predictors, but IHD is a significant positive predictor for the use of β-blockers in HFrEF patients in the multivariate analysis (Table 5). Age, gender, HR, COPD, any solid cancer, gout, any anemia, IHD, any cognitive impairment, osteoporosis and any thyroid diseases being the significant predictors in the univariate analysis, were included in multivariate analysis of MTD of β-blockers (data not shown). The model explained 12.9% (Nagelkerke R2) in predicting the use of MTD of β-blockers. HR and gout were the significant negative predictors, but IHD was the significant positive predictor for the use of MTD of β-blockers in HFrEF patients in the multivariate analysis (Table 5).

Age, Gender (male), last clinic SBP, last clinic DBP, last clinic postural BP, AF, anemia, CRF, hypertension, any cognitive impairment, any solid cancer, hyperlipidemia, falls, osteoarthritis, osteoporosis, PVD and ≥3 comorbidities being the significant predictors in the univariate analysis, were included in multivariate analysis of MRA use (data not shown). The model explained 26.4% (Nagelkerke R2) in predicting the use of MRA. Age and SBP were the significant negative predictors for the use of MRAs in HFrEF patients in the multivariate analysis (Table 5).

Predictors of use of ACEIs/ARBs, β-blockers and MRAs in heart failure with preserved ejection fraction (EF>40) patients.

Gender (male), hypertension, CRF, CVA, COPD, cognitive impairment, gout, and falls were significant predictors (p <.25) in the univariate analysis being the significant predictors in the univariate analysis, were included in multivariate analysis of ACEIs/ARBs (data not shown). The model explained 18.5% (Nagelkerke R2) in predicting the use of ACEIs/ARBs. CRF, and cognitive impairment were the significant negative predictors, but hypertension and COPD were the significant positive predictor for the use of ACEIs/ARBs in the multivariate analysis of the HFpEF patients (Table 5).

Hypertension, last clinic HR, last clinic low heart rate (HR<60), anemia, IHD, diabetes, COPD, cognitive impairment, hyperlipidemia, osteoarthritis and GORD being the significant predictors in the univariate analysis, were included in multivariate analysis of β-blockers use (data not shown). The model explained 30.1% (Nagelkerke R2) in predicting the use of β-blockers. HR, COPD and GORD were the significant negative predictors, but IHD was the significant positive predictor for the use of β-blockers in the multivariate analysis of the HFpEF patients (Table 6).

Gender, hypertension, AF, IHD, diabetes, CRF, asthma, hyperlipidemia, osteoporosis, and low standing SBP being the significant predictors in the univariate analysis, were included in multivariate analysis of MRAs use in HFpEF patients (data not shown). The model explained 15.5% (Nagelkerke R2) in predicting the use of MRAs. Only the low standing SBP was a significant positive predictor for the use of MRAs in the multivariate analysis (Table 6).

Discussion

This study is a detailed analysis of demographics, clinical characteristics, comorbidities, and prescribing practice of GDMT in CHF outpatients in a large tertiary referral hospital in South Australia. The HFmrEF subjects resembled the HFpEF patients in terms of age, HR, SBP and having higher prevalence of polypharmacy whereas resembled with the HFrEF for the proportion of male distribution and prevalence of IHD. MACS clinic had similar rates of guideline-based prescribing of ACEIs/ARBs, their MTD and target doses, diuretics, and digoxin use in HFrEF, but significantly higher prescription of ACEIs/ARBs was found in HFpEF patients. There were significantly lower rates of prescription of β-blockers, MTD of β-blockers, target dose of β-blockers, and MRAs prescribed in the both the HFrEF and HFpEF groups in the MACS clinic, as compared to the GCHFS clinic. Additionally, significantly higher prescription for digoxin in chronic AF in HFrEF patients and significantly lower prescription of furosemide and anticoagulation for AF in HFpEF patients were observed in the MACS clinic patients compared to those in the GCHFS clinic.

The HFrEF, HFmrEF and HFpEF patients in this study were much older than the ESC Heart Failure Long-Term (ESC-HF-LT) registry [32]. HFpEF patients in the current study were 2 years older but one year younger for HFrEF group compared with the age of patients in the NSW (Australia) snapshot study [33]. AF prevalence in the current study was in ascending order with the increasing value of LVEF as found in the Swedish Heart Failure Registry [34]. In line with our results, similar findings to the HFmrEF group

resembling HFrEF for male gender, and IHD, were reported in an earlier studies [35, 36]. The current study found a notable difference in demographics and comorbidities with the different cut-offs for EF. Based on above-mentioned results, our study showed intermediate demographic and clinical characteristics for HFmrEF category between HFpEF and HFrEF.

GDMT use was higher in the current study compared to the NSW HF snapshot study for the use of ACEIs/ARBs, β-blockers and MRAs in HFrEF patients [33]. Similar patterns of better use of ACEIs/ARBs, β-blockers and MRAs were evident, but there were slightly lower rates of prescription of diuretics and digoxin observed in current study compared to an another Australian study on chronic HFrEF patients [37]. Importantly, the prescription of ACEIs/ARBs, β-blockers and MRA in current study were similar or even superior than to previous studies conducted in Australia in HFrEF patients [33, 37]. However,, higher prescription rate for ACEIs/ARBs and β-blockers have been reported in studies conducted in the USA [38] and Europe than in our findings [24].

MACS being a multidisciplinary service, combines evidence-based clinical guidelines, patient centred practice, and a shared care approach. The MACS clinic is more likely to be reluctant to prescribe ACEI/s/ARBs due to number of reasons as demonstrated by previous studies such as old age [39], risk of anaemia [40], worsening of renal function [41], contraindications for their use [24], adverse effects associated with higher doses compared to lower doses for ACEIs/ARBs [42], and concomitant use of other mediations due to presence of multiple comorbidities [43]. Although our hypothesis was that the MACS clinic will have better practice of the ACEIs/ARBs, older age, anaemia and CRF being the significant negative predictors, patients received similar pattern of medicines to that of GCHFS clinic. Additionally, a greater number of contraindications for the use of ACEIs/ARBs and presence of polypharmacy were important factors to be considered in the MACS clinic compared to GCHFS clinic. Notably, gout and GORD are negative significant predictors for the utilization of ACEIs/ARBs in HFrEF patients which have not been reported before in the literature. Even though SBP was a significant positive predictor, and MACS clinic patients had higher SBP, impact of negative predictors and other variables as explained above was superior for the utilization of ACEIs/ARBs. Age and presence of CRF were significant negative predictors for the MTD use of ACEIs/ARBs.

Compelling evidence exists regarding underutilization of β-blockers and failure to up-titration in CHF patients including older age (>70 years) and presence of respiratory disease [44], hypotension and polypharmacy [45], concern of side effects, contraindications, and poor experience of GPs [46] low HR and poor adherence to prescriptions [47]. Patients under β-blockers may experience adverse effects-mortality and cardiovascular events associated with high resting HR, as described by Chen *et al* 2019 [48]. Nevertheless, the reluctance of the clinicians to prescribe β-blockers due to potential side effects need further investigation. In line with the previous findings, HR was a significant negative predictor for the use of β-blocker, and HR and older age were the negative significant predictors for the MTD use of β-blockers in our study. Other potential reasons for the lower utilization of β-blockers despite of presence of a pharmacist in the MACS clinic could be higher prevalence of polypharmacy, due to existing comorbidities [45] and presence of contraindication for their use [24, 46] as reported before. Patients were

much older, and the prevalence of gout were significantly higher but IHD and HR were similar in HFrEF patients between two clinics. Notably, gout as a significant negative predictor and GORD as a significant positive predictor for the utilization of β-blocker were found in our study in HFrEF patients which have not been reported before in the literature. In certain instances, the underlying reason for the underutilisation of GDMT may also be unknown.

A critical reason behind the underutilisation of MRAs in HF is due to associated hyperkalaemia and the detrimental effect on renal function as reported earlier [49]. In contrast to previous study, renal function was not a significant predictor in our findings. However, patient age and last clinic SBP were significant negative predictors for the utilisation of MRAs in the current study. There were more patients having contraindications for the use of MRAs in MACS clinic than GCHFS clinic patients, which had certainly some effect on lower prescription. Further research is needed to confirm other relevant reasons for example the occurrence of hyperkalaemia. Presence of digoxin use is more likely if patients have AF [37] as it improves morbidity in HF patients [50]. One key advantage of a pharmacist being on the MACS clinic was that a significantly higher number of patients received digoxin due to higher prevalence of chronic AF in the MACS clinic than in the GCHFS clinic in HFrEF patients.

Our study found that 41.5% of patients were given the recommended target dose for ACEIs/ARBs and 31% of patients received recommended doses of β-blockers. Overall, it is important to note that target dose prescribed in our study were superior than larger studies conducted in Europe [22, 24], and in Asia [51]. The tolerability of specific doses in individual patients with multiple comorbidities and polypharmacy in HF patients should be closely monitored rather than just an approach to reach the target doses [52, 53], therefore, it is crucial that the emphasis for up-titration should be adopted based on an individualised dose approach. According to a systematic review, the widely recognised definition of polypharmacy is a condition that requires the use of five or more medications daily (range = 2 to 11) [54]. The mean number of medications used in the MACS patients was 11 ± 4, much higher than reported indicating that there was substantial polypharmacy in MACS clinic patients. Lower GDMT use in HFrEF patients due to underlying contraindications have been reported previously [55]. The contraindications for use of ACEIs, MTDs of ACEIs, β-blockers and MTD of β-blockers were significantly higher in MACS clinic patients than in GCHFS clinic patients. It can be hypothesized that as many patients have contraindications, clinicians were more reluctant to prescribe GDMT due to lack of more extensive experience of appropriate dosing when patients do not have contraindications. These findings highlighted that contraindications may be one potential reason for lower utilization of GDMT in the MACS clinic in the current study despite the pharmacist's active involvement.

Despite of some dilemma for understanding of the epidemiology, pathophysiology and lack of evidence for the effective management of HFpEF, expert groups have highlighted that the management of HFpEF has been partly addressed due to the possible benefits of currently available medications [56]. In contrast to HFrEF patients, a significantly higher prescription of ACEIs/ARBs but the similar trend of significantly lower prescription of β-blockers and MRAs in the MACS clinic patients compared to GCHFS clinic in HFpEF patients was revealed. The higher prescription of ACEI/ARBs in HFpEF patients in MACS patients

may be due to underlying left atrial hypertension and pulmonary hypertension as explained by Lam *et al* 2018 [57] due to more number of HFpEF patients in the MACS clinic. Hypertension and COPD are the significant positive predictors whereas CRF and cognitive impairment were the significant negative predictors for the utilization of ACEIs/ARBs in our study. In consistent to our study, a previous Australian study demonstrated a significantly lower prescription of ACEIs in HFpEF patients compared to those in HFrEF patients [58]. These findings indicate that patients in the HFpEF category in our study were not over treated. It has also been reported that age is a strong predictor of the lower prescription of β-blockers in the elderly in HFpEF patients [59]. The presence of COPD, gout and last clinic HR were significant positive predictors for the lower use of β-blockers in HFpEF in the current. However, the presence of IHD was a significant positive predictor for the use of β-blockers. Again, the differential prevalence of these comorbidities between the MACS and GCHFS clinics explains why MACS patients have significantly lower prescriptions of β-blockers in our study. The low standing SBP, was associated with a higher prescription of MRAs in HFpEF patients. Indeed, effectiveness of currently available GDMT for HFpEF is still a controversy except a symptomatic management of underlying comorbidities.

A systematic review and meta-analysis revealed that the use of MRAs in HFpEF was associated with ADRs including hyperkalaemia and gynecomastia compared with HFrEF patients [60]. The exact benefits of MRAs in HFpEF patients is still poorly understood [61]; therefore, the generalisation of the role of currently available medications may not be clinically relevant. The MACS clinic, being a holistic model of care, may have considered these ADRs in prescribing MRAs in HFpEF patients, which may be a potential reason for a significantly lower prescription of MRAs in the MACS clinic compared with in the GCHFS clinic. Some cases of inappropriate prescribing were also noticed; for example, two patients were on two β-blockers simultaneously, two patients were on both ACEIs and ARBs and one patient received the wrong dose for apixaban. Similarly, some patients were on contraindicated medications. The benefit of having a pharmacist in the multidisciplinary team is that pharmacists can easily detect cases of inappropriate prescribing and contraindicated medications under usage. The underutilization of β-blockers and MRAs in the MACS clinic in HFrEF and HFpEF patients can not only be generalized just with the presence of a pharmacist compared to GCHFS clinic as the model of practice in MACS clinic is shared decision making by clinicians and a pharmacist for the effective management of CHF outpatients.

Strength and limitations

The major strength of this study is that it includes a large number of real-life data of CHF patients (12 years data) from a large tertiary hospital. In addition, this study compared the similarities and differences of CHF patients for HFrEF, HFmrEF and HFpEF category although the comparison of GDMT use is only between HFrEF and HFpEF category. Only the patients who have echocardiography data to determine the left ventricular function to measure the ejection fraction were included in current analysis. We did have some limitations for this study. While the clinics were set up slightly differently, the main predictor was the presence of a pharmacist in the MACS service and no involvement of a pharmacist in the GCHFS clinic. The most important confounder in this study was the series of different guidelines for the management of CHF across the study duration. The qualifications, experiences, and expertise of the

pharmacists in the MACS group and all the nurses and clinicians in both groups are the effect modifiers in this study. The main bias here was the referral bias, where different types of patients may be referred to the two different clinics. As there were no separate guidelines for HFmrEF patients in the hospital where this study was conducted, evaluation of GDMT was only considered for HFrEF and HFpEF in our analysis. Due to the limitation of funding and study completion timeline, differences in hospitalizations and mortality rates were not evaluated although they are important clinical outcomes.

Conclusions

We concluded that HFmrEF showed an intermediate characteristic falling between HFpEF and HFrEF category. Older age of patients, heart rate, blood pressures, renal dysfunctions, contraindications for use of GDMT, and polypharmacy were the potential reasons for lower prescription of β-blockers and MRAs in the MACS clinic in HFrEF and HFpEF patients. Use of digoxin in chronic AF in HFrEF patients and prescription rate of ACEIs/ARBs in HFpEF patients were significantly higher in the MACS clinic than in GCHFS clinic. The other roles of the pharmacist within a multidisciplinary team, including continuity of care, medication compliance, prevention of adverse reactions and education need further research.

Abbreviations

GDMT
Guideline-directed medical therapy
HF
Heart Failure
CHF
Chronic heart failure
MACS
Multidisciplinary Ambulatory Consulting Service
GCHFS
General Cardiology Heart Failure Service
HFmrEF
Heart failure with mid-range ejection fraction
HFpEF
Heart failure preserved ejection fraction
HFrEF
Heart failure reduced ejection fraction
HR
Heart rate
SBP
systolic blood pressure
DBP

diastolic blood pressure
MCV
mean cell volume
IHD
ischemic heart disease
ACEIs
angiotensin-converting enzyme inhibitors
ARB
angiotensin receptor blockers
MRAs
mineralocorticoid receptor antagonists
AF
atrial fibrillation
LVEF
left ventricular ejection fraction (LVEF)
STROBE
Strengthening of Reporting of Observational Studies in Epidemiology

Declarations

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

No competing interests exist.

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Author's contributions

DRP: study design, development of analysis protocol development, data coding, data analysis, and development of the manuscript draft; SS: analysis protocol development, study design, data custodian, and critically reviewed the manuscript; EFJ: second author on classification of medications as per the

analysis protocol, critically reviewed the manuscript; RM: Supervised the whole work and critical review of the manuscript; CG: consultation for data analysis and critically reviewed the manuscript; DW: Supervised the whole work and critical review of the manuscript. The author(s) read and approved the final manuscript.

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Tables

Table 1. Comparison of demographics and clinical characteristics between ejection fractions.

Comorbidities (%)	Total (n=1056)	Reduced (LVEF<40) (n=594)	Mid-range (LVEF=41-49) (n=136)	Preserved (LVEF>50) (n=326)	P-Value
Age (years), median (IQR)	78 (68-84)	74 (63-82)	80 (70-84)	81 (75-85.2)	<0.001***
Weight (Kg), median (IQR)	77 (65-91.2)	76 (65-91)	76.5 (63-93)	80 (66-94)	0.410
SBP (mmHg), median (IQR)	120 (106-135)	114 (101-130)	122 (110-135)	130 (115-144)	<0.001***
DBP (mmHg), median (IQR)	65 (60-75)	65 (60-76)	65.5 (60-77)	67 (60-75)	0.583
HR (beats/min), median (IQR)	70 (60-80)	71 (61-81)	68 (60-80)	70 (60-81)	0.101
Number of medications used in first appointment, median (IQR)	10 (8-13)	10 (7-13)	10 (8-13)	11 (9-14)	<0.001***
Serum creatinine (mg/dl), median (IQR)	110 (82-152)	112 (86-154.2)	120.5 (86.2-152)	101 (77.2-142.5)	0.058
Hemoglobin (g/L), median (IQR)	102 (108-134)	124 (111-138)	120 (108-129)	119 (105-131)	0.001**
MCV (fL/red cells), median (IQR)	89.5 (86-93.5)	89.2 (86.2-94)	90.2 (85-94)	89.5 (85-93)	0.736

Test of significance between reduced, mid-range and preserved ejection fractions groups was performed by Kruskal-Wallis test for all the variables. P<.05 was considered significant. LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; MCV: mean cell volume; IQR: interquartile range. * p<.05, **p <.01, *** p<.001.

Table 1 contd. Comparison of demographics and clinical characteristics between ejection fractions

Comorbidities (%)	Total (n=1056)	Reduced (LVEF<40) (n=594)	Mid-range (LVEF=41-49) (n=136)	Preserved (LVEF>50) (n=326)	P-Value
Hypertension	690 (65.3)	329 (55.4)	94 (69.1)	267 (82.0)	<0.001***
IHD	592 (56.1)	338 (57.0)	87 (64.0)	167 (51.2)	0.035*
AF	497 (47.1)	261 (44.0)	64 (47.1)	172 (53.0)	0.037*
Hyperlipidemia	529 (50.1)	285 (48.0)	79 (58.1)	165 (51.0)	0.102
Diabetes	450 (43.0)	239 (40.2)	58 (43.0)	153 (47.0)	0.145
Osteoarthritis	211 (20.0)	88 (15.0)	29 (21.3)	94 (29.0)	<0.001***
CRF	328 (3.1)	185 (31.1)	42 (31.0)	101 (31.0)	0.998
COPD	242 (23.0)	127 (21.4)	33 (24.3)	82 (25.2)	0.395
Anemia	204 (19.3)	84 (14.1)	29 (21.3)	91 (28)	<0.001***
Depression/Anxiety	176 (17.0)	95 (16.0)	19 (14.0)	62 (19)	0.332
Any cardiovascular accident	180 (17.0)	96 (16.2)	25 (18.4)	59 (18.1)	0.685
Asthma	94 (9.0)	41 (7.0)	13 (10.0)	40 (12.3)	0.023*
Any solid caner	155 (15.0)	83 (14.0)	22 (16.2)	50 (15.3)	0.744

Test of significance between reduced, mid-range and preserved ejection fractions groups was performed by Kruskal-Wallis test for all the comorbidities. The mean was compared using independent sample t test. was used for categorical variables, comorbidities. P<.05 was considered significant. LVEF: left ventricular ejection fraction; IHD: ischemic heart disease; AF: atrial fibrillation; CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease. p<.05 is considered significant. * p<.05, **p <.01, *** p<.001.

Table 2. Comparison of demographics and clinical characteristics between two clinics.

Demographics and clinical characteristics	Total (n=1184)	MACS (n=723)	GCHFS (n=461)	P-value
Age (years), median (IQR)	78 (68-84)	80 (72-85)	73 (62-81)	<.001***
Age group (years)				
(<40)	26 (2.2)	10 (1.4)	16 (3.5)	
(40-50)	49 (4.1)	13 (2.0)	36 (8.0)	
(50-60)	98 (8.3)	41 (6.0)	57 (12.4)	
(60-70)	180 (15.2)	92 (13.0)	88 (19.1)	<.001***
(70-80)	380 (32.1)	242 (33.5)	138 (28)	
(>80)	451 (38.1)	325 (45.0)	126 (27.3)	
Gender, n (%)				
Male	671 (57.0)	364 (50.3)	307 (67.0)	<.001***
Weight (Kg), median (IQR)	77 (65-91.2)	76.34 (63-90)	78 (66-95)	.072
Systolic blood pressure (mmHg), median (IQR)	120 (106-135)	123 (110-140)	112 (100-130)	<.001***
Diastolic blood pressure (mmHg), median (IQR)	65 (60-75)	67 (59-76)	60 (60-71.5)	.010*
Heart rate (beats/min), median (IQR)	70 (60-80)	70 (60-81)	70 (60-80)	.303
Number of medications used, median (IQR)	10 (8-13)	11 (8-14)	9.0 (7.0-12)	<.001***
Non-polypharmacy (0–4 drugs)	44 (4.2)	21 (4.0)	23 (5.0)	
Polypharmacy (5–9 drugs)	406 (39.2)	184 (32.0)	222 (48.3)	<.001***
Hyper polypharmacy (≥10 drugs)	586 (57.0)	371 (64.4)	215 (47.0)	
Biochemical parameters				
Serum creatinine (mg/dL), median (IQR)	110 (82-152)	110 (82-151)	124 (97-188)	.305
			114.5 (104-136)	.538

Hemoglobin (g/L), median (IQR)	120 (108-134)	120 (109-134)	87.6 (82.4-92.5)	.139
MCV (fL/red), median (IQR)	89.5 (86-93.5)	89.5 (86-94)		

The median difference was compared using Mann-Whitney U test between MACS GCHFS groups for age, weight, systolic blood pressure, diastolic blood pressure, heart rate, number of medications, serum creatine, hemoglobin and MCV. Chi-squared test for other categorical variables; age group, gender, polypharmacy, and risk factors. p<.05 was considered significant. MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service; MCV: mean cell volume. * p<.05, **p <.01, *** p<.001.

Table 2 contd. Comparison of demographics and clinical characteristics between two clinics.

Comorbidities	Total (n=1184)	MACS (n=723)	GCHFS (n=461)	P-value
Hypertension	769 (65.0)	513 (71.0)	256 (55.5)	<.001***
IHD	660 (56.0)	406 (56.2)	254 (55.1)	.764
AF	549 (46.4)	342 (47.3)	207 (45.0)	.437
Hyperlipidemia	578 (49.0)	350 (48.4)	228 (49.5)	.766
Diabetes	489 (41.3)	328 (45.4)	161 (35.0)	<.001***
Gastroesophageal reflux disease	270 (23.0)	187 (26.0)	83 (18.0)	.002**
Osteoarthritis	231 (19.5)	175 (24.2)	56 (12.1)	<.001***
CRF	359 (30.3)	223 (31.0)	136 (29.5)	.650
COPD	270 (23.0)	199 (27.5)	71 (15.4)	<.001***
Anemia	226 (19.1)	163 (22.5)	63 (14.0)	<.001***
Depression/Anxiety	198 (17.0)	139 (19.2)	59 (13.0)	.004**
Osteoporosis	142 (12.0)	117 (16.2)	25 (5.4)	<.001***
Any cardiovascular accident	197 (17.0)	140 (19.4)	57 (12.4)	.002**
All ophthalmological conditions	124 (10.5)	87 (12.0)	37 (8.0)	.032*
Peripheral vascular disease	160 (13.5)	114 (16.0)	46 (10.0)	.005**
Any solid cancer	176 (15.0)	109 (15.1)	67 (14.5)	.867
Gout	188 (16.0)	125 (17.3)	63 (14.0)	.103
Asthma	108 (9.1)	80 (11.1)	28 (6.1)	.004**
Hypo/Hyperthyroidism	144 (12.2)	102 (14.1)	42 (9.1)	.011*
Thromboembolism	87 (7.3)	65 (9.0)	22 (5.0)	.006 **
Cognitive impairment	87 (7.3)	78 (11.0)	9 (2.0)	<.001***
Proportion of patients with				<.001***
≥3 comorbidities	1035 (87.4)	665 (92.0)	370 (80.3)	
≥4 comorbidities	895 (76.0)	593 (82.0)	302 (65.5)	

Chi-squared statistics was used for the comparison of categorical variables between two clinics. p<.05 was considered significant. MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service.; IHD: ischemic heart disease; AF: atrial fibrillation; CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease. * p<.05, **p <.01, *** p<.001.

Table 3. Comparison of the use of medications between clinics with heart failure with reduced ejection fraction (EF < 40) patients.

Use of Medications	Total (n=489)	MACS (n=193)	GCHFS (n=296)	P-value
Contraindications for ACEIs	69 (14.1)	44 (23.0)	25 (8.4)	<.001***
Rate of appropriate use of ACEIs	280 (67.0)	97 (65.1)	183 (67.5)	.617
Contraindications for MTD of ACEIs	69 (14.1)	44 (23.0)	25 (8.4)	<.001***
Rate of appropriate use of MTD of ACEIs	193 (46.0)	64 (43.0)	129 (48.0)	.325
Target dose used for ACEIs	175 (36.0)	60 (31.1)	115 (39.0)	.080
Rate of appropriate use of ACEIs/ARBs	297 (71.0)	102 (68.4)	195 (72.0)	.438
Rate of appropriate use of MTD of ACEIs/ARBs	210 (50.0)	69 (46.3)	141 (52.0)	.264
Target dose of ACEIs/ARBs	203 (41.5)	71 (37.0)	132 (45.0)	.157
Contraindications for β-blockers	11 (2.2)	9 (5.0)	2 (1.0)	.006**
Rate of appropriate use of β-blockers	421 (88.1)	153 (83.1)	268 (91.1)	.008**
Contraindications for MTD of β-blockers	11 (2.2)	9 (5.0)	2 (1.0)	.006**
Rate of appropriate use of MTD of β-blockers	197 (41.2)	58 (31.5)	139 (47.3)	<.001***
Target dose used for β-blockers	151 (31.0)	42 (22.0)	109 (37.0)	<.001***
MRA contraindications	34 (7.0)	31 (16.1)	3 (1.0)	<.001***
MRA used without contraindications	246 (50.3)	62 (32.1)	184 (62.2)	<.001***
Diuretics contraindications	2 (0.41)	2 (1.0)	0 (0)	-
Diuretics used without contraindications	419 (86.0)	162 (84.0)	257 (87.0)	.373
Digoxin contraindications	7 (6.0)	2 (1.0)	5 (1.7)	.552
Digoxin use without contraindications	112 (25.0)	57 (30.0)	65 (22.0)	.059
Use of digoxin in chronic atrial fibrillation	85 (70.0)	47 (82.5)	38 (58.5)	.004**

The group difference was evaluated using Chi-square (χ^2) test. p<.05 is considered significant. EF: ejection fraction; MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service; ACEIs: angiotensin-converting enzyme inhibitors; MTDs: maximum tolerated doses; ARBs: angiotensin receptor blockers; MRAs: mineralocorticoid receptor antagonists. * p<.05, **p <.01, *** p<.001.

Rate of appropriate use of ACEIs was calculated in percentage as the number of patients who received the ACEIs without any contraindications, divided by the number of patients who should have received the ACEIs. The rate of appropriate MTD use of ACEIs was calculated as the number of patients who received the MTD of ACEIs without any contraindications, divided by the number of patients who should have received the MTD of ACEIs. The maximum tolerated dose was calculated as the dose given as a percentage of the target dose. The rate of appropriate use of β-blockers, MTD of β-blockers and target dose of β-blockers were calculated similarly to that of appropriate use of ACEIs and MTD of ACEIs.

Table 4. Comparison of the use of medications between clinics with heart failure with preserved ejection fraction (EF > 40) patients.

Use of Medications	Total (n=239)	MACS (n=166)	GCHFS (n=73)	P-value
ACEIs use	94 (39.3)	71 (43.0)	23 (31.5)	.101
ARB use	64 (27.0)	46 (28.0)	18 (25.0)	.623
ACEIs/ARBs	155 (65.0)	117 (70.5)	41 (56.2)	0.0314*
β-blockers use	139 (58.2)	89 (54.0)	50 (68.5)	.032*
MRA use	85 (35.6)	50 (30.1)	35 (48.0)	.008**
Furosemide	208 (87.0)	139 (84.0)	69 (94.5)	.022*
Digoxin used	60 (25.1)	42 (25.3)	18 (25.0)	.916
Contraindications for anticoagulation in AF	12 (5.0)	10 (6.0)	2 (3.0)	.006**
Anticoagulated in presence of AF without contraindications	80 (33.5)	45 (27.1)	35 (48.0)	.002**

The difference between the clinics was evaluated using Chi-square (χ2) test. Pearson Chi-square <.05 is considered significant. EF: ejection fraction; MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service; ACEIs: angiotensin-converting enzyme inhibitors; MTDs: maximum tolerated doses; ARBs: angiotensin receptor antagonists; MRAs: mineralocorticoid receptor blockers; AF: atrial fibrillation. * p<.05, **p <.01, *** p<.001.

Table 5. Multivariate binary logistic regression for the use of ACEIs/ARBs, β-blockers, and MRAs in heart failure with reduced ejection fraction (EF < 40) patients.

				95% CI for Exp (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
ACEIs/ARBs in heart failure with reduced ejection fraction					
Age	-.033	.010	.968	.944	.992
Last clinic SBP	.020	.020	1.020	1.003	1.037
Anemia	-.707	.024	.493	.267	.910
CRF	-1.228	.000	.293	.174	.492
Gout	-.613	.044	.542	.298	.983
GORD	-.602	.033	.548	.315	.952
MTD of ACEIs/ARBs in heart failure with reduced ejection fraction					
Age	-.032	.000	.968	.952	.984
CRF	-.602	.010	.548	.346	.867
β-blockers in heart failure with reduced ejection fraction					
Last clinic HR	-.028	.007	.973	.953	.992
Gout	-.891	.013	.410	.203	.828
IHD	.583	.048	1.792	1.006	3.191
MTD of β-blockers in heart failure with reduced ejection fraction					
Age	-.040	.000	.961	.943	.979
Last clinic HR	-.026	.003	.974	.958	.991
MRAs use in heart failure with reduced ejection fraction					
Age	-.040	.000	.960	.942	.979
Last clinic SBP	-.034	.000	.966	.955	.978

Variable (s) entered on step 1: last clinic SBP, last clinic DBP, any anemia, CRF, gout, IHD, GORD, any solid cancer, any CVA, PVD, OA, falls, any cognitive impairment, COPD, AF and any thyroid. EF: ejection fraction; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRF: chronic renal failure; IHD: ischemic heart diseases; GORD: gastroesophageal reflux diseases; CVA: cardiovascular accident; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary diseases; AF: atrial fibrillation; ACEIs/ARBs: angiotensin converting enzyme inhibitor/angiotensin receptor antagonists; MTD: maximum tolerated dose; MRAs: mineralocorticoid receptor blockers; HR: heart rate; COPD: chronic obstructive pulmonary diseases; IHD. Only the significant variables in multivariate analysis are shown.

Table 6. Multivariate binary logistic regression for the use of ACEIs/ARBs, β-blockers, and MRAs in heart failure with preserved ejection fraction (EF >40) patients.

				95% C.I. for EXP (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
ACEIs/ARBs in heart failure with preserved ejection fraction					
Hypertension	1.238	.001	3.449	1.677	7.095
CRF	-.686	.036	.504	.266	.955
COPD	.871	.023	2.389	1.129	5.055
Any cognitive impairment	-1.509	.012	.221	.068	.719
β-blockers in heart failure with preserved ejection fraction					
Last clinic HR	-.040	.009	.961	.933	.990
IHD	.740	.023	2.096	1.106	3.971
COPD	-1.262	.001	.283	.137	.584
GORD	-.681	.043	.506	.262	.980
MRAs in heart failure with preserved ejection fraction					
Low standing SBP (BP<115)	.744	.037	2.105	1.044	4.244

Variable (s) entered on step 1: CRF, any CVA, COPD, any cognitive impairment, gout, and falls.
EF: ejection fraction; CRF: chronic renal failure; CVA: cardiovascular accident; COPD: chronic obstructive pulmonary diseases; ACEIs/ARBs: angiotensin converting enzyme inhibitor/angiotensin receptor antagonists. ACEIs/ARBs: angiotensin converting enzyme inhibitor/angiotensin receptor antagonists; MTD: maximum tolerated dose; MRAs: mineralocorticoid receptor blockers. Only the significant variables in multivariate analysis are shown.

Figures

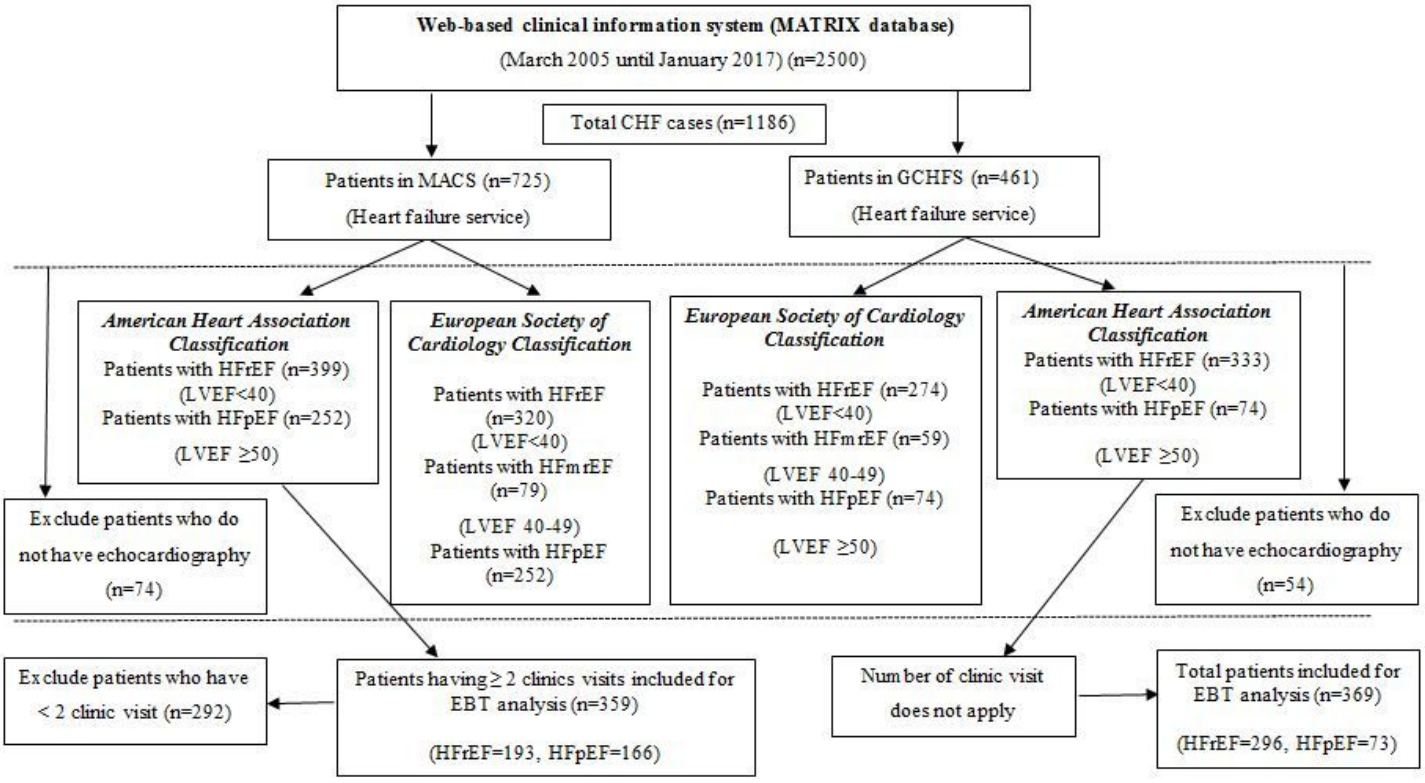

Figure 1

Flow chart of the study. MATRIX: hospital database; HF: Heart Failure; MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service; LVEF: left ventricular ejection fraction; EBT: evidence-based therapies; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction; EBT: evidence-based therapies.

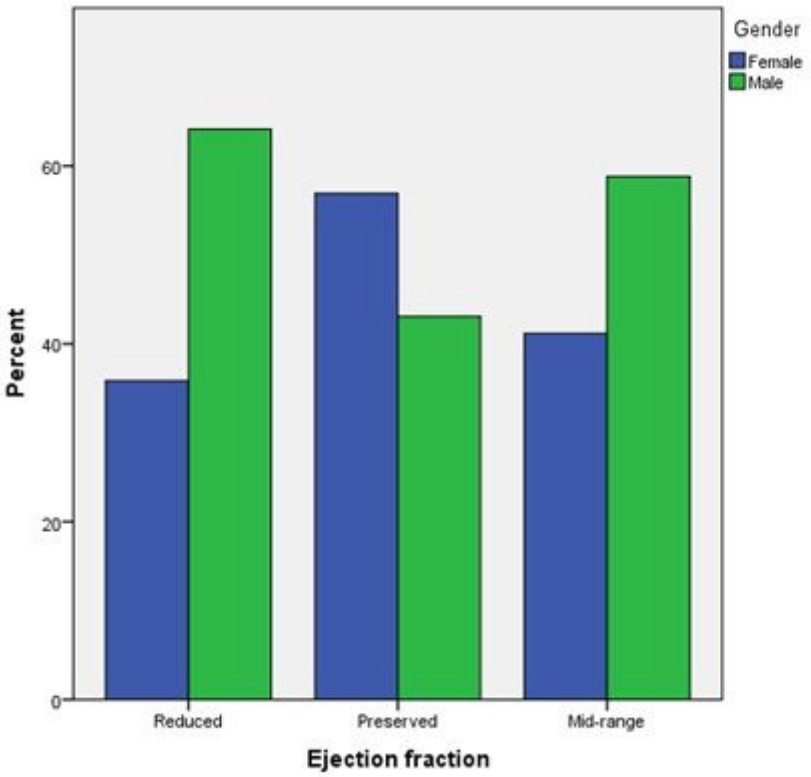

Figure 2

Gender distribution in heart failure with reduced, mid-range and preserved ejection fractions. Kruskal-Wallis test showed a significant difference of gender distribution among three ejection fractions (p<.001). p<.05 was considered significant.

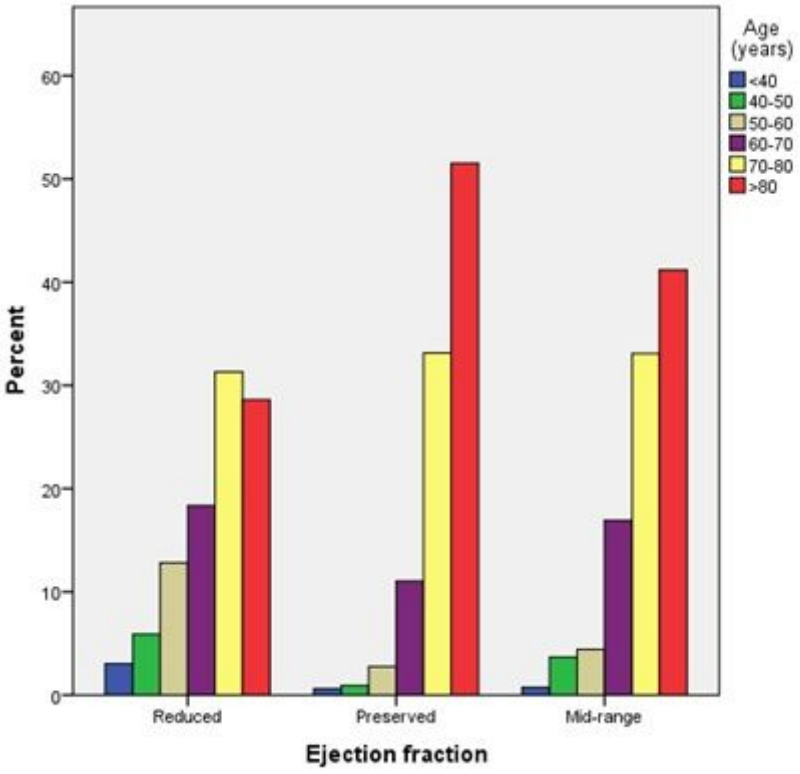

Figure 3

Age distribution in heart failure with reduced, mid-range and preserved ejection fractions. Kruskal-Wallis test showed a significant difference of age distribution among three ejection fractions (p<.001). p<.05 was considered significant.

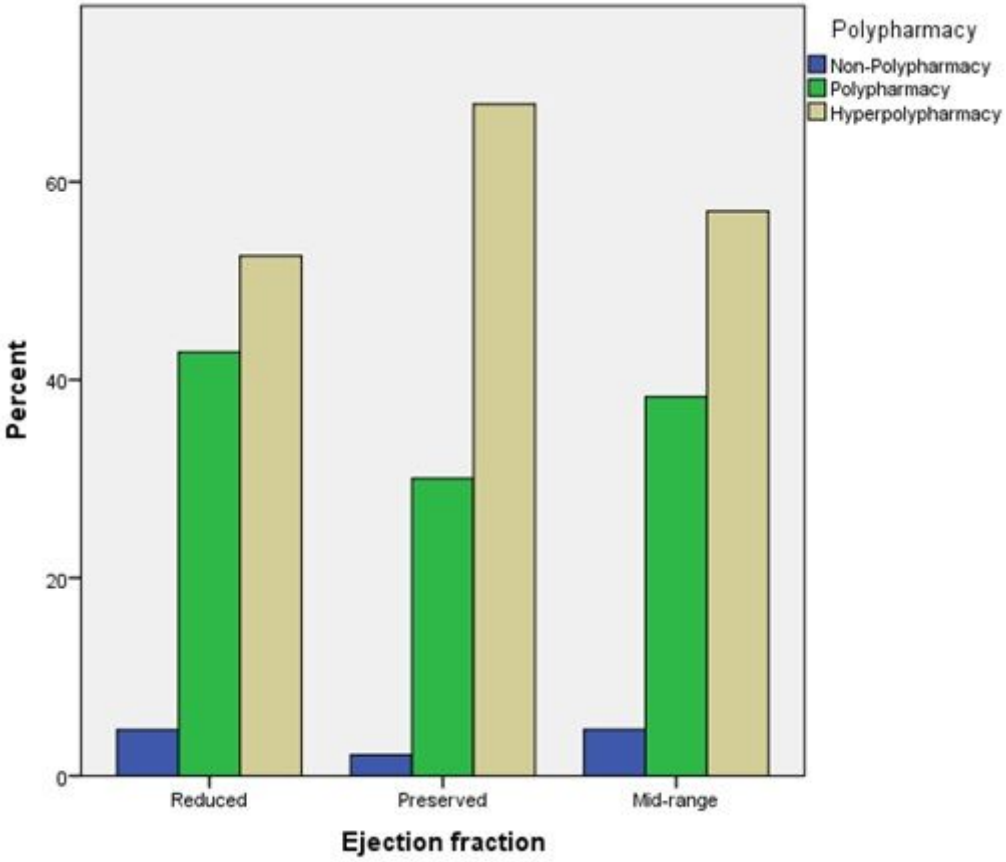

Figure 4

Polypharmacy distribution in heart failure with reduced, mid-range and preserved ejection fractions. Kruskal-Wallis test showed a significant difference of polypharmacy distribution among three ejection fractions (p<.001). p<.05 was considered significant.

Supplementary Files

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- Supplementary.docx