Guideline-Led Prescribing to Ambulatory Heart Failure Patients in a Cardiology Outpatient Service

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Abstract word count: 220 words

Manuscript word count: 2942 words

Abstract

Background: Guidelines recommend heart failure (HF) patients be treated with multiple medications at doses proven to improve clinical outcomes.

Objective: To study guideline-led prescribing in an Irish outpatient HF population.

Setting: Cardiology Outpatient Clinic, Mercy University Hospital, Cork, Ireland.

Methods: Guideline-led prescribing was assessed using the Guideline Adherence Index (GAI-3), that considered the prescribing of ACE inhibitors and angiotensin receptor blockers; beta-blockers and mineralocorticoid receptor antagonists. The GAI-based target dose was calculated based on the prescription of ≥50% of the guideline-recommended target dose of each of the three GAI medications to HF patients with ejection fraction ≤40%. High-GAI was achieved by prescription of ≥2 GAI medicines. Potentially inappropriate prescribing was assessed using a HF-specific tool.

Main outcome measure: Heart failure guideline-led prescribing assessed using the GAI-3.

Results: A total of 127 HF patients, mean age 71.7±13.1 years, were identified in the study. Seventy-one patients had ejection fraction ≤40%. Population mean GAI-3 was 65.8%. When contraindications to therapy are considered, the adjusted GAI-3 increased to 72.9%. The target dose GAI was 18.5%. High-GAI management was prescribed to 54 patients (76.1%). A potentially inappropriate medicine in HF was prescribed to 14 (19.7%) patients.

Conclusion: Most HF patients with ejection fraction ≤40% in this setting received optimal guideline-led prescribing however the proportion of patients achieving the target doses of these agents was suboptimal.

Keywords

Heart failure, Guideline Adherence Index; Guideline-directed Medical Therapies; Guideline-led Prescribing; inappropriate prescribing, renin-angiotensin system, beta-blockers.

Impact of findings on practice

- In heart failure, it is known that prescription of guideline-directed medical therapies at target dose results in improved patient outcomes. This goal is not achieved in all heart failure patients and achievement of target dose is especially challenging.
- Patients with heart failure are at risk of the prescription of potentially inappropriate medicines and in this population one-in-five patients was prescribed such an agent.
- International guidelines recommend the inclusion of a pharmacist in the heart failure multidisciplinary team and the medication problems identified in this work highlight the need for pharmacist interventions in the heart failure outpatient setting in particular.

Introduction

In order to optimise care for heart failure (HF) patients, clinical practice guidelines recommend the prescription of guideline-directed medical therapies (GDMT) at target doses in line with the evidence-base. (1, 2) Adherence to guideline-led prescribing is consistently associated with improved clinical outcomes. In the QUALIFY study, a high rate of guideline-led prescribing was associated with a 50% reduction in all-cause mortality and a 32% reduction of HF-related rehospitalization when compared to moderate or poor rates. (3) In the BIOSTAT-CHF registry, patients with lower doses of ACE inhibitors and angiotensin receptor blockers (ACEI/ARB) and beta-blockers experienced increased mortality risk compared to patients who achieved the target dose of these agents. (4)

Nevertheless, several studies have demonstrated suboptimal adherence to HF guideline-led prescribing in routine clinical practice. (3-5) In the CHAMP-HF study, over one-third of ambulatory HF patients did not receive GDMT despite the absence of contraindications. (5) When patients do receive the recommended medications, they often receive the medications at a dose lower than that recommended in the guidelines. (6) In the CHAMP-HF registry, just 1% of ambulatory HF patients received the target dose of ACEI/ARB, evidence-based beta-blocker (EBBB) and mineralocorticoid receptor antagonist (MRA). (5) Elsewhere, just 50% of HF patients reached the recommended target dose of these agents within three months of discharge. (4)

Guideline-led prescribing in HF may be challenging due to patients' age (7), gender (8), low blood pressure (9), renal dysfunction (9), the presence of pulmonary disorders (10) and the complexity of the medication regimen. (11) A study in the United Kingdom showed that poor

pulmonary function limited beta-blocker prescription in 11% of otherwise eligible HF patients. (10) Elsewhere, 40% of HF patients were not prescribed the indicated ACEI/ARB at discharge due to reduced renal function. (9)

The presence of multimorbidity in HF increases the complexity of medication regimens and the prescription of potentially inappropriate medications. (7,12, 13) There is clear evidence of the harmful effects of medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and non-dihydropyridine calcium channel blockers on HF prognosis and outcomes. (14) Prescription of these medications reduces patient quality of life, contradicts the effects of the GDMT and consequently increases the risk of hospitalization and mortality. (14-16) In an Australian study, NSAIDs were prescribed to 9% of HF patients and non-dihydropyridine calcium channel blockers were prescribed to 2% of HF patients. (12) In an ambulatory HF population, 14.5% were prescribed at least one potentially inappropriate medication despite being cared for in an HF-specific disease-management program. (15)

Aim of study

This study will evaluate guideline-led prescribing to HF patients in an Irish ambulatory setting and determine the prevalence of potentially inappropriate medications in HF in this population.

Ethics approval

Ethics approval for the study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, reference number ECM 4 (c).

Method

The study included all HF patients aged ≥18 years presenting for a scheduled review appointment to the Cardiology Outpatient Clinic in the Mercy University Hospital, Cork, Ireland from March 2016 to February 2017. Where patients attended the clinic on more than one occasion over the study period, only data from their first visit was included in the study.

Data accessed in the patient's medical chart included HF diagnosis, type of HF, ejection fraction, age, gender, comorbidities, blood pressure, heart rate and laboratory investigations. The following information on prescribed medications was also accessed in the medical chart: drug name, dose and frequency.

The European Society of Cardiology (ESC) Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 were used in this study as they are the guidelines that were in place at the initiation of this work. (1) In these guidelines, Heart Failure with reduced Ejection Fraction (HFrEF) is defined as ejection fraction ≤35%. However according to these guidelines, ACEI/ARB and EBBB are indicted for HF patients with EF ≤40% and MRA are indicated for patients with EF ≤35%. Therefore, in calculating guideline adherence, those patients with EF ≤40% were considered.

The primary outcome of the study was to assess HF guideline-led prescribing using the Guideline Adherence Index (GAI-3) (17), the adjusted GAI-3 (18) and the GAI-target dose (19) according to the recommendations of the reference guidelines. The GAI-3 was calculated as the ratio of the medications prescribed to the medications that should theoretically have been prescribed according to the guidelines. These medications are agents within the following classes: ACEI/ARB, EBBB and MRA. (1, 17) The EBBBs in HF are bisoprolol, carvedilol, metoprolol succinate, and nebivolol. (1) The adjusted GAI-3 considered the relative and absolute contraindications to the GAI-3 medications as outlined in the guidelines (Table 1). (1, 18) The GAI-based target dose was calculated as prescription of ≥50% of the guideline-recommended target dose of each of the three GAI medications (Table 1). (1, 19) Where the 2012 guidelines do not state a target dose for the agent, the Irish version of the Summary of Product Characteristics was consulted. (20) The 50–99% and 100% target dose of ACEI/ARB, EBBB and MRA were defined according to the ESC 2012 guidelines (Table 1).

Finally, the GAI population was divided into those with High-GAI based management; that is the prescription of ≥2 GAI-3 medications and those with Low-GAI management; that is the prescription of ≤1 GAI medications. (17-19, 21, 22)

Hyperpolypharmacy was defined as the prescription of ≥10 regular medications per day. (23) Hyperpolypharmacy was used as a measure of medication burden as this population is prescribed a high number of medications, both for HF and for comorbidities.

During the study period the ESC published the Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2016. (2) These updated guidelines introduced a new medication class, angiotensin receptor/neprilysin inhibitors (ARNi). According to the 2016

guidelines, an ARNi is reasonable alternative to an ACEI/ARB for HF patients with EF ≤35% who remain symptomatic despite optimal medical therapy with ACEI/ARB, EBBB and MRA at target or maximally tolerated doses. (2) Therefore, the effect, if any, of this guideline change on GAI-3 achievement in the study population was analysed.

The secondary outcome was to determine the prevalence of potentially inappropriate prescribing using the disease-specific Potentially Inappropriate Medicines in Heart Failure (PIMHF) tool. (15) This tool considers 11 medications to be potentially harmful when used in HF patients. (15) Only medications prescribed regularly were included in the PIMHF analysis. Medications prescribed on an *"as required"* basis were not included as there was no clear indication of how often the patient took these medications.

Statistical analysis

Data are presented as mean ± standard deviation or number (%), as appropriate. Continuous data were compared using the independent Student's t-test. Categorical data were compared using the Chi-square test or Fisher exact test. The Fisher exact test was used where one cell in the test contained a count of five or less and in these cases, the exact point probability was used to identify statistical significance. A *p-value* of <0.05 was regarded as statistically significant. Data were analysed using SPSS® (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Results

Over the study period, 127 HF patients attended the Cardiology Outpatient Clinic. The mean age of patients was 71.7 ± 13.1 years, 83 (65.3%) were male and 44 were female (34.6%). Heart failure type was available for 119 patients and HFrEF was predominant (n=71, 59.7%). An echocardiogram was available for 102 patients and mean ejection fraction was 40.2% ± 14.2%. All patients had ≥1 comorbidity, and the mean number of comorbidities was 7.4 ± 2.7. Hypertension was the most frequently occurring comorbidity (n=79, 66.2%), followed by atrial fibrillation (n=66, 51.9%). Coronary artery disease affected 39 patients (30.7%).

Among the 71 patients with HFrEF, 52 (73.2%) were male and mean age was 68.8 ± 13.7 years. Prescription rates for GAI-3 medicines in this group are given in Table 2. A combination of two GAI-3 medicines was prescribed concomitantly to 36 patients (50.7%), and all three medicines were prescribed concomitantly to 18 patients (25.4%). Prescription of 50%-99% and 100% of the guideline-recommended target doses of ACEI/ARB, EBBB and MRA is displayed in Figure 1. Three patients (4.2%) achieved 50%-99% recommended target doses of all three GAI medicines. No patient achieved 100% target dose of all three GAI medicines.

Among patients with HFrEF no patient experienced a contraindication to ACEI/ARB or MRA therapy. A contraindication to EBBB therapy was present in three HFrEF patients (4.2%). Despite the presence of a contraindication, an EBBB was prescribed to these three patients.

In the HFrEF population, mean GAI-3 was 65.8%. When contraindications to therapy are considered, the adjusted GAI-3 increased to 72.9%. Population GAI-3 based on prescribing ≥50% of the target-dose was 18.5%.

Among the HFrEF population, High-GAI was prescribed to 54 patients (76.1%), (Table 2). Patients with High-GAI were more likely to achieve ≥50% of the target dose of ACEI/ARB and EBBB than those with Low-GAI (Figure 1).

No patient was prescribed an ARNi, therefore, the GAI-3 based on the ESC 2016 guidelines was 65.8%. This means that the GAI-3 was unchanged whether calculated using the ESC 2012 or 2016 guidelines.

Among patients with HFrEF, 14 (19.7%) were prescribed a PIMHF item (Table 2). The most frequently prescribed PIMHF item was non-dihydropyridine calcium channel blockers, prescribed to seven patients (9.9%). Of the patients prescribed a non-dihydropyridine calcium channel blocker, five (7.0%) had a concurrent prescription for an EBBB.

Discussion

The present study used structured prescribing review tools to assess guideline-led prescribing and the prescription of potentially inappropriate medicines in an Irish ambulatory HF population. Over 75% of those with HFrEF achieved High-GAI. The mean GAI-3 for HFrEF patients was 66%; however, when this was adjusted to include target dose achievement, it decreased considerably to 18.5%. One-in-five of the population was prescribed an HF-specific potentially inappropriate medication.

According to a recently published systematic review (25), the GAI-3 reported here for HFrEF patients is comparable to the GAI-3 figures from other Western European countries such as the Austria (76%) (26), Germany (71%) (27) and Switzerland (70%) (28). At 66%, it is moderately higher than the international mean GAI-3 of 63%. (25) Contraindications to therapy had little effect on guideline adherence, in fact 85% of patients with asthma were prescribed an EBBB. The guidelines strongly recommend the use of EBBB in HF (1, 2) and these results indicate that in the specialist cardiology setting, prescribers consider the benefits of EBBB to outweigh its risk of asthma exacerbation in most HF patients.

The prescription rate of MRAs to HFrEF patients was 36% and this is similar to MRA prescription rates in other Europeans reports. (29, 30) Managing MRA therapy is more complicated than managing ACEI/ARB and EBBB therapies due to the incidence of worsening renal function and hyperkalaemia and the need for ongoing monitoring associated with MRA use. (29) The underutilisation of MRA therapy may reflect the low prevalence of coronary artery disease in this population as there is further evidence for MRA use in patients with left ventricular systolic dysfunction post-myocardial infarction. (31)

Not all HF licenced agents were prescribed in the study population. In the EBBB class just two agents, bisoprolol and nebivolol, were prescribed. While metoprolol succinate is evidence-based in HF, this metoprolol salt is not licenced in Ireland. Metoprolol tartrate, the only form of the drug licenced in Ireland, is not licenced for use in HF. (20) Bisoprolol and nebivolol have the advantage over carvedilol of a once daily dosing regimen (20). Furthermore, bisoprolol is the preferred beta-blocker for prescription in Ireland which accounts for the fact that it was prescribed to 67.6% of those patients in the study who were prescribed a beta-blocker. (32)

The achievement of target dose is suboptimal in the current population; indeed, no patient achieved the 100% target dose of all three GDMT. Furthermore, when target dose was considered, guideline adherence decreased considerably. This effect is seen elsewhere in the literature where Hirt and colleagues (22) demonstrated a GAI-3 of 56%, which declined to 3% when target dose was taken into account. The BIOSTAT-CHF registry conducted in 11 European countries and including 2,500 outpatients showed that a minority of patients was prescribed the target dose of ACEI/ARB and EBBB. (4) There is evidence from observational studies demonstrating the benefits of target dose prescribing. (17, 33) In the HF-ACTION study, there was a 21% reduction in all-cause mortality among ambulatory HF patients who achieved EBBB target dose. (33) The benefits of target dose achievement are long known. In the ATLAS trial, HF patients randomised to high dose lisinopril had a 12% lower risk of death or hospitalization for any reason than those randomised to low dose lisinopril. (34) In the HEALL trial, high dose losartan was associated with a 10% reduction in death or HF hospitalisation compared to low dose losartan. (35) Clinical inertia and an overestimation of the risk of intolerance during up-titration, particularly intolerance of EBBB up-titration, are

cited as potential barriers to the achievement of the guideline-recommended target doses of HF medications. (11, 36, 37)

As the reference guidelines were updated during the study period, the GAI-3 analysis was repeated based on the newer guidelines. Applying the ESC 2016 HF guidelines, the population GAI-3 did not change as no patient was prescribed an ARNi. Sacubitril-valsartan was licenced in Ireland during the study period but was not reimbursed by the Irish Primary Care Reimbursement Services until late 2017 and therefore not widely prescribed before that time. (38) Furthermore, given the low rate of target dose achievement in the study population, many patients would not be eligible for prescription of this agent within the guideline recommendations. (2)

The prescription of HF-specific potentially inappropriate medications is higher here than in a previous Irish report that used the PIMHF tool. (15) In that study, prescription of potentially inappropriate medicines to HF patients was associated with an increased risk of death, acute hospitalization and unscheduled outpatient appointment. (15) However, unlike this previous Irish study, the present study population were not enrolled in an HF disease management programme. A disease management programme provides highly structured multidisciplinary HF care, improves prescribing quality, and improves patient outcomes. (39) The ESC guidelines recommend the inclusion of a pharmacist in any such multidisciplinary programme. (2)

As the patients in this study are community-based, it is possible that the general practitioner may make decisions concerning a patient's medications independently from the cardiology service. (40) Given the extent of comorbidities experienced by this cohort, these patients may

also receive prescriptions from other medical specialities. This range of prescribers caring for HF patients may lead to physician encroachment, deprescribing of a GDMT or unwitting prescription of potentially inappropriate medicines. (41, 42) The BIOSTAT-CHF registry found that among 2,516 European outpatients, 76% of discontinued MRAs were not resumed in the outpatient setting. (4) Mockler *et al.* reported that three years post-HF diagnosis, 29% of patients were non-persistent to HF medications and that prescriber decision rather than patient action drove 50% of the non-persistence events. (43)

The drug therapy problems identified in this work point to the need for the inclusion of pharmacists in the HF multidisciplinary team. A number of studies demonstrate a clear benefit of pharmacist delivered post-discharge and outpatient care to HF patients. Lopez Cabezas *et al.* showed that delivery of a post-discharge clinical pharmacy service to HF patients reduced the readmission rate by 35% over 12 months (44) and Lowrie *et al.* have shown that in the outpatient setting, a clinical pharmacy service increased the prescription of GDMTs by 15%. (45) In a study by Bhat *et al.,* the proportion of patients achieving target dose of ACEI/ARB and beta-blocker therapy increased from 4% at baseline to 64% post-pharmacist prescribing intervention. (46)

The GAI was originally developed as a method to quantify prescribing quality for HF patients in Europe and later modified to include target dose, contraindications to therapy, and HF licenced medicines as elements of guideline adherence (17-19). These modifications have increased the complexity of the GAI and enhanced its ability to differentiate from the standard drug utilisation rate approach. However, the GAI and its modified versions has primarily been applied at a population level to examine prescribing patterns. According to a systematic review, no study has "examined the role of the GAI in near-patient assessment; initiatives to improve

guideline adherence or how pharmacists or other members of the health care team may implement the GAI to improve care of complex HF patients". (25)

This study is limited by its small sample size and single centre design that may limit the generalizability of the study results. However, this design contributed to the in-depth analysis of prescribing details in a real-world population. Patient medication data was collected at a single timepoint only, therefore changes over time in medication or dose profile could not be assessed. The reference guidelines for the study were updated during the data collection period. This issue was addressed by applying the updated guidelines and confirming that there was no change in outcome when the analysis was performed using the revised parameters.

Conclusion

The majority of HF patients in this study received guideline-led treatment, however the achievement of target doses was suboptimal. There is considerable opportunity to improve care and outcomes for HF patients by the inclusion of pharmacists in the HF multidisciplinary care team.

Acknowledgements

The research team wishes to acknowledge the nursing and administration staff of the Outpatient Department, Mercy University Hospital for their assistance in this work, in particular Ms Dawn Gosnell and Ms Helen Kelleher.

Funding

This research was funded by an academic collaboration between University College Cork, Ireland and Future University in Egypt.

Conflicts of interest

The authors confirm that they have no conflicts of interest to report.

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Table 1. Heart failure medication class and guideline recommendation, contraindications, agents and daily target dose as outlined in the ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012. (1)

Medication class and guideline recommendation	**Contraindications**	**Agents***	**100% Target Dose (mg/day) †**
An **ACE inhibitor** is recommended for all patients with an EF ≤40%. An **angiotensin receptor blocker** is recommended if an ACE inhibitor is not tolerated.	• History of angioedema • Known bilateral renal artery stenosis • Pregnancy / risk of pregnancy.	Ramipril Lisinopril Perindopril arginine Candesartan Losartan Valsartan	10 20 5 32 150 320
An **evidence-based beta-blocker** is recommended for all patients with an EF ≤40%.	• Second- or third-degree atrioventricular block. • Asthma	Bisoprolol Nebivolol	10 10
A **mineralocorticoid receptor antagonist** is recommended for all patients with persisting symptoms and an EF	• Eplerenone use with strong cytochromes inhibitors	Spironolactone Eplerenone	50 50

≤35%, despite treatment with an ACE inhibitor/ARB and beta-blocker.

* Only those agents within a medication class that were prescribed to one or more patients in the study population are presented in the table.

† The daily target dose of perindopril arginine and is not given in the guidelines however in Ireland, perindopril arginine is licenced for use in heart failure. The daily target dose was identified in the Irish Summary of Product Characteristics for this agent. (22)

Table 2. Characteristics and medication profile of the heart failure patients with ejection fraction ≤40%.

Characteristics	**Heart failure patients with EF ≤ 40% n = 71**	**High-GAI n = 54**	**Low-GAI n = 17**
Age (years)	68.8 ± 13.7	68.7 ± 13.7	68.6 ± 14.2
Male / Female	52 (73.2) / 19 (26.8)	39 (72.2) / 15 (27.8)	13 (76.5) / 4 (23.5)
Systolic blood pressure (mmHg)	127.8 ± 17.8	128.3 ± 17.3	125.9 ± 20.6
Diastolic blood pressure (mmHg)	72.7 ± 12.3	73.6 ± 12.8	69.1 ± 9.4
Heart rate (beats per minute)	79.5 ± 19.9	78.3 ± 19.8	84.5 ± 20.7
Serum potassium	4.8 ± 0.9	4.7 ± 0.9	5.0 ± 1.1
Ejection fraction (%) [a]	27.4 ± 7.8	27.5 ± 7.5	27.1 ± 8.9
Co-morbidities			
Hypertension	41 (59.4)	34 (63.0)	7 (41.2)
Atrial fibrillation	35 (50.7)	24 (44.4)	11 (64.7)
Coronary artery disease	23 (32.4)	18 (33.3)	5 (29.4)
Diabetes	15 (21.1)	13 (24.1)	2 (11.8)
Chronic kidney disease	23 (32.4)	20 (37.0)	3 (17.6)
Asthma	7 (9.8)	5 (9.3)	2 (11.8)
Chronic obstructive pulmonary disease	12 (16.9)	9 (16.7)	3 (17.6)
Number of comorbidities	7.1 ± 2.6	7.2 ± 2.6	6.8 ± 2.9

Heart Failure Medications			
ACE inhibitor / Angiotensin receptor blocker [*]	54 (79.4)	50 (92.6)	4 (28.6)
Evidence-based beta-blocker [*]	60 (88.2)	53 (98.1)	7 (41.2)
Mineralocorticoid receptor antagonist [*]	25 (36.8)	23 (42.6)	2 (14.3)
Digoxin	5 (7.0)	4 (7.4)	1 (5.9)
Ivabradine	2 (2.8)	2 (3.7)	0 (0.0
Loop diuretic	48 (67.6)	39 (72.2)	9 (52.9)
Thiazide diuretic	3 (4.2)	2 (3.7)	1 (5.9)
Device-based therapy [b *]	15 (21.1)	12 (22.2)	3 (20.0)
Number of regular medications	7.5 ± 2.8	8.3 ± 2.8	7.4 ± 2.9
Hyperpolypharmacy	24 (33.8)	21 (38.9)	3 (20.0)
Potentially Inappropriate Medicines in Heart Failure [c]			
Any PIMHF medication	14 (19.7)	9 (16.7)	5 (29.4)
Non-dihydropyridine calcium channel blocker without beta-blocker	2 (2.8)	0	2 (11.8)
Non-dihydropyridine calcium channel blocker with beta-blocker	5 (7.0)	3 (5.6)	2 (11.8)
Oral corticosteroid	4 (5.6)	3 (5.6)	1 (5.9)
Pregabalin	4 (5.6)	3 (5.6)	1 (5.9)
Non-steroidal anti-inflammatory drug	0 (0.0)	0 (0.0)	0 (0.0)
Metformin in poor renal function [d]	1 (1.4)	1 (1.9)	0 (0.0)

Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as mean ± standard deviation. Comparisons were made between heart failure patients with High-GAI and Low-GAI. * indicates $p < 0.05$.

[a] Echocardiogram was available for 62 patients.

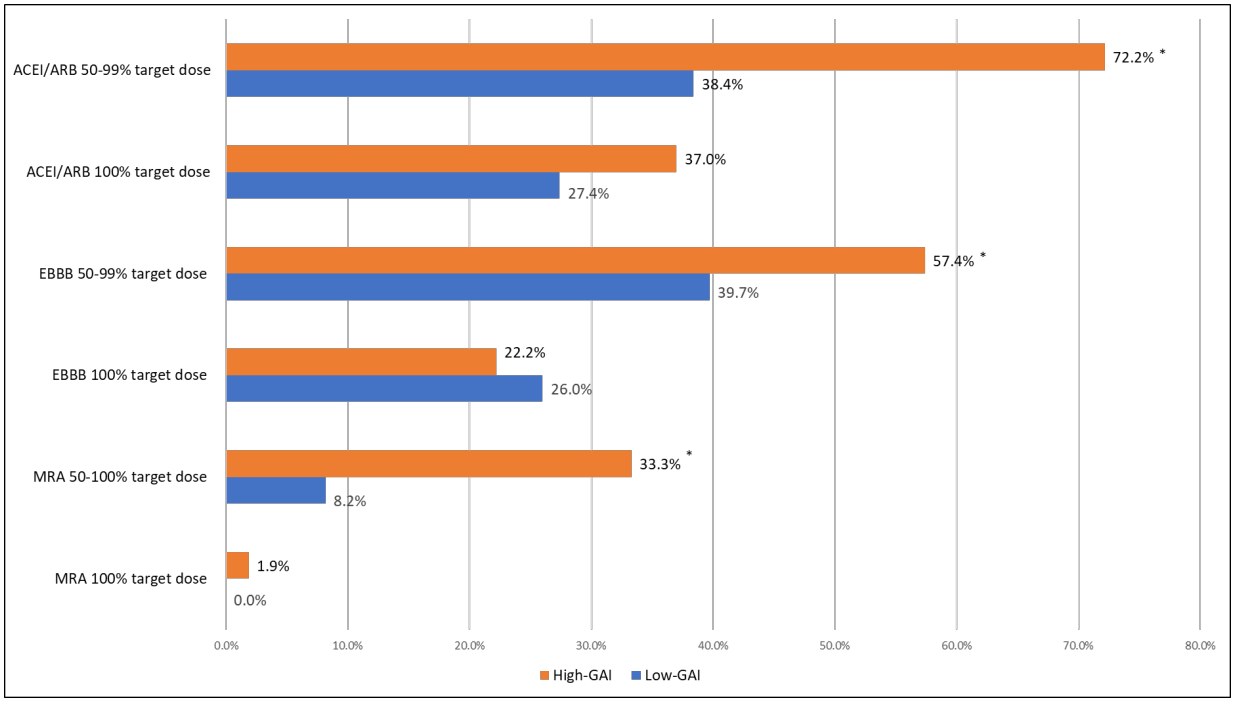
[b] Device-based therapy means implantable cardiac defibrillator or cardiac resynchronisation therapy.

[c] An individual patient may have been prescribed more than one Potentially Inappropriate Medicine in Heart Failure. In total, 16 Potentially Inappropriate Medicines in Heart Failure items were prescribed to 14 patients.

[d] Poor renal function was defined as creatinine clearance < 50 millilitres/minute.

Abbreviation: PIMHF, Potentially Inappropriate Medicines in Heart Failure.

Figure 1. Achievement of 50%-99% and 100% of the recommended target doses of the guideline-directed medical therapies among heart failure patients with ejection fraction ≤40% prescribed High-GAI and Low-GAI management.



The proportion of patients prescribed 50%-99% of the target dose of each medication class was compared between High-GAI and Low-GAI populations. A comparison was made between patients with High-GAI and those with Low-GAI. * There was a statistically significant difference between the High-GAI and Low-GAI patients in achievement of 50%-99% target dose for each of the three GAI medication class ($p < 0.001$ for all three comparisons). There was no significant difference between the High-GAI and Low-GAI patients in the achievement of 100% target dose for each of the three medication classes.

Abbreviations: ACEI/ARB, ACE inhibitor or angiotensin receptor blocker; EBBB, evidence-based beta-blocker; GAI, Guideline Adherence Index; MRA, mineralocorticoid receptor antagonist.