Epidemiology, treatment patterns and in-hospital outcomes of patients with heart failure with reduced ejection fraction: An analysis of the Heart Failure Registry of the Philippine Heart Association

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ABSTRACT

In 2014, the Optimize Heart Failure Care Programme was introduced to 12 cardiology training institutions in the Philippines through partnership with the Philippine Heart Association Council on Heart Failure. The Heart Failure Registry, an ongoing, prospective, multicentre, observational study of patients, is part of this Programme. This study aimed to describe the characteristics, trends in treatment patterns and in-hospital outcomes of heart failure patients with reduced ejection fraction (HFrEF) (ejection fraction of 50% or lower) enrolled in the Heart Failure Registry from 2014 to 2018. The registry included all hospitalised adult patients who fulfill the Framingham criteria for the diagnosis of HF. During the study period, the Heart Failure Registry enrolled 636 patients with HFrEF, with a mean age of 56.7 ± 15.2 years; 60.1% were males. The Heart Failure Registry showed that the use of ACEI/ARBs, beta-blockers, MRAs and ivabradine in patients with HFrEF is suboptimal. Just over half of patients were given angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) (54.9%), while 47.5% received beta-blockers and 26.5% received mineralocorticoid receptor antagonists (MRA). Only 6.6% of patients (6.6%) received ivabradine. The overall in-hospital mortality rate was 3.9%. The utilisation rates of guideline-directed pharmacotherapy, particularly for ACEI/ARBs and beta-blockers, followed the scale of educational activities of the Optimize Heart Failure Care programme. Hence, continuation of the programme, including its educational components, and continuous monitoring of performance measures is recommended.

BACKGROUND

Diseases of the heart are the leading causes of mortality in the Philippines as of 2013.[1] Among the cardiovascular diseases, heart failure (HF) has a reported prevalence of 1.6% (2014) and is a common cause of hospitalisation in the country, with a previously reported in-hospital mortality rate of 8.2%.[2] Poor outcomes of HF could be attributed, in part, to under-utilisation of guideline-directed pharmacotherapy, such as angiotensin receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEI), beta-blockers and mineralocorticoid receptor antagonists (MRA). Registry data from the 2-year Dysfunction Established And Registered symptomatic adult heart failure patients (DEAR Heart) programme (2002-2004) revealed that while 72.0% of hospitalised HF patients in the Philippines received an ARB or ACEI, only 34.0% received a beta blocker and 13.9% received an MRA.[3]

In 2014, the Optimize Heart Failure Care Programme was introduced to 12 cardiology training institutions in the Philippines through partnership with the Philippine Heart Association Council on Heart Failure.[4, 5] The aim of the programme was to improve the outcome of patients through quality care guided by real-world evidence. The major components of the programme include (1) educational activities on the guideline-directed management of heart failure, (2) quality improvement through the use of management checklists in hospitalised heart failure patients, and (3) a Heart Failure Registry with six participating centres. Educational activities were significantly reduced in 2016 due to reductions in funding but were later reactivated in 2017 and 2018. The use of management checklists and implementation of the Heart Failure Registry was uninterrupted.

This paper aims to describe the characteristics, trends in treatment patterns and in-hospital outcomes of HF patients with reduced ejection fraction (HFrEF) (EF of 50% or lower) enrolled in the Heart Failure Registry from 2014 to 2018.

METHODOLOGY

STUDY DESIGN AND INCLUDED PATIENTS

The Heart Failure Registry of the Optimize Heart Failure Care Programme is an ongoing, prospective, multicentre, observational study of patients presenting to participating Philippine cardiology centres. Patients were enrolled at six centres: a national government university hospital and five private hospitals. All centres were tertiary referral hospitals with cardiology training programmes.

The registry included all hospitalised adult patients who fulfill the Framingham criteria[6] for the diagnosis of HF. Lack of consent was the only exclusion criterion. All adult patients (age >18 years) with a primary or secondary diagnosis of HF (International Classification of Disease, 10th revision [ICD-10]) were screened. The diagnosis of HF using the Framingham criteria was validated by two independent reviewers. Those who fulfilled the inclusion criteria were included in the Registry. However, this analysis only included patients with HFrEF (ejection fraction [EF] of 50% or lower). The mother protocol was reviewed and approved by the University of the Philippines-Manila Research Ethics Board and the institutional review boards of the participating centres.

DATA COLLECTION AND ANALYSIS

The charts of all included patients were reviewed, and study-related data were collected using a standardised data collection sheet. Data included age, sex, vital signs on admission, clinical signs and symptoms, documented aetiology of HF, comorbid conditions, prior interventions, alcohol and tobacco

use, echocardiographic findings and functional class. The prescription of guideline-directed pharmacotherapy[7] (i.e., use of beta-blockers, ARBs/ACEIs, MRAs and ivabradine) recommended as maintenance medication was also recorded. Patient follow-up was only until hospital discharge. In-hospital outcomes such as mortality or complications (including cardiogenic shock, arrhythmias, worsening HF, acute coronary syndrome, stroke, need for intensive care, bleeding, renal failure, nosocomial infection, cardiac arrest or adverse drug events) were recorded.

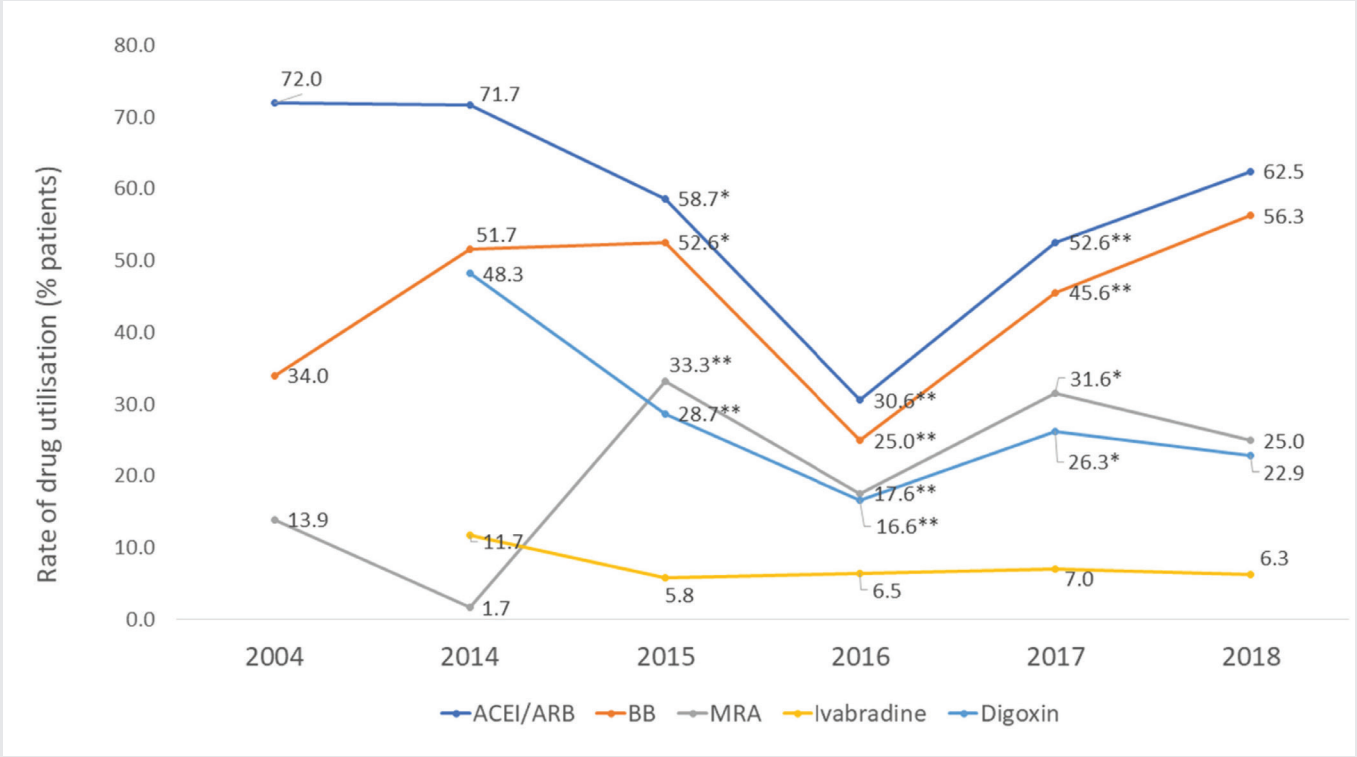
All results were summarised and stratified by year of enrollment. Continuous variables were reported as the mean ± standard deviation (SD) and compared using one-way analysis of variance (ANOVA). Categorical variables were reported as frequencies and percentages and compared using chi-square test.

RESULTS

The Heart Failure Registry enrolled 636 patients with HFrEF from 2014 to 2018, with a mean age of 56.7 ± 15.2 years; 60.1% were males (**Table 1**). Majority had clinical symptoms of congestion (74.1% with crackles, 74.1% with bipedal oedema). The most common aetiology of -HF were ischaemic heart disease (50.0%) and hypertension (35.7%); 7.5% were due to rheumatic heart disease. The mean EF was 34.5 ± 9.7. Majority of patients had New York Heart Association Functional Class III (52.2%), followed by Functional Class II (28.8%). Diastolic dysfunction was present in 31.9% and valvular lesions were present in 49.7%.

Just over half of patients were given ACEI/ARBs (54.9%). Furthermore, only 47.5% received beta-blockers and only a fourth (26.5%) were given MRA. Only 42 patients (6.6%) received ivabradine. **Figure 1** shows the prescription rates of the various pharmacotherapeutic agents by year, including rates from DEAR Heart (2004) as a baseline reference. It showed that majority of patients received an ACEI/ARB (71.7%) and a beta-blocker (51.7%) during the first year of the Optimize Heart Failure Care programme. However, there was significant deterioration of the rate of use of these agents over time, which reached its trough in 2016. The rate of use of MRAs was consistently below 35% throughout the study period, with note of a similar dip in 2016. Ivabradine was prescribed in 5.8% to 11.8% of HFrEF patients in the in-hospital setting throughout the study period. Digoxin was commonly prescribed during hospitalisation (27.3%)—the highest rate of use was observed in 2014 (48.3%) whereas the rates ranged from 16.6% to 28.7% over the following years.

Figure 1: Prescription rate of pharmacotherapeutic agents by year



*P-value versus previous year: *p<0.01; **p<0.001*
DEAR Heart data (2004)3 was used as the 2004 baseline.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; EF, ejection fraction.

Table 1. Baseline characteristics of included patients

	Overall (n = 636)	2014 (n = 60)	2015 (n = 363)	2016 (n = 108)	2017 (n = 57)	2018 (n = 48)
Age (years; mean/SD)	56.7 ± 15.2	56.1 ± 16.7	55.8 ± 14.6	59.3 ± 16.9	57.2 ± 14.6	58.4 ± 14.2
Female gender (n, %)	254 (39.9)	42 (30.0)	155 (42.7)	41 (38.0)	20 (35.1)	20 (41.7)
Systolic BP (mmHg, mean/SD)	124.6 ± 24.8	130.1 ± 32.0	124.5 ± 24.1	125.1 ± 25.6	123.7 ± 22.8	119.3 ± 20.6
Diastolic BP (mmHg, mean/SD)	79.2 ± 13.2	81.1 ± 16.7	79.2 ± 12.4	80.7 ± 13.4	78.2 ± 12.1	74.1 ± 14.5
Heart rate (mmHg, mean/SD)	86.9 ± 19.3	91.1 ± 19.4	85.4 ± 18.4	88.7 ± 20.5	88.4 ± 20.5	87.4 ± 21.9
Edema (n, %)	471 (74.1)	40 (66.7)	281 (77.4)	76 (70.4)	43 (75.4)	31 (64.6)
Crackles (n, %)	471 (74.1)	57 (95.0)	264 (72.7)	74 (68.5)	43 (75.4)	33 (68.8)
Aetiology (n, %)						
Hypertension	227 (35.7)	12 (20.0)	148 (40.8)	32 (29.6)	17 (29.8)	18 (37.5)
Ischaemic heart disease	318 (50.0)	18 (30.0)	208 (57.3)	37 (34.3)	27 (47.4)	28 (58.3)
Valvular non-RHD	57 (9.0)	3 (5.0)	47 (12.9)	1 (0.9)	3 (5.3)	3 (6.3)
Valvular RHD	48 (7.5)	0	32 (8.8)	7 (6.5)	3 (5.3)	6 (12.5)
Cardiomyopathy	51 (8.0)	5 (8.3)	25 (6.9)	10 (9.3)	9 (15.8)	2 (4.2)
Others	159 (25.0)	11 (18.3)	95 (26.2)	19 (17.6)	20 (35.1)	14 (29.2)
Comorbid conditions (n, %)						
Coronary artery disease	155 (24.4)	26 (43.3)	94 (25.9)	11 (10.2)	12 (21.1)	12 (25.0)
Cerebrovascular accident	14 (2.2)	6 (10.0)	2 (0.6)	2 (1.9)	1 (1.8)	3 (6.3)
Hypertension	250 (39.3)	27 (45.0)	160 (44.1)	21 (19.4)	23 (40.4)	19 (39.6)
Chronic kidney disease	53 (8.3)	7 (11.7)	29 (8.0)	9 (8.3)	6 (10.5)	2 (4.2)
Diabetes mellitus	155 (24.4)	17 (28.3)	83 (22.9)	19 (17.6)	26 (45.6)	10 (20.8)
COPD	35 (5.5)	4 (6.7)	21 (5.8)	1 (0.9)	7 (12.5)	2 (4.2)
Prior interventions (n, %)						
Coronary (PCI, CABG)	56 (8.8)	0	30 (8.3)	9 (8.3)	13 (22.8)	4 (8.3)
Valvular	10 (1.6)	0	9 (2.5)	1 (0.9)	0	0
Pacemaker/ICD/CRT	32 (5.0)	1 (1.7)	23 (6.3)	1 (0.9)	4 (7.0)	3 (6.3)
Smoking						
No	303 (47.6)	55 (91.7)	138 (38.0)	66 (61.1)	26 (45.6)	18 (37.5)
Former	190 (29.9)	4 (6.7)	133 (36.6)	18 (16.7)	17 (29.8)	18 (37.5)
Current	143 (22.5)	1 (1.7)	92 (25.3)	24 (22.2)	15 (24.6)	12 (25.0)
Alcohol intake	249 (39.2)	2 (3.3)	173 (47.7)	31 (28.7)	24 (42.1)	19 (39.6)
Ejection fraction (mean/SD)	43.4 ± 15.9	40.5 ± 19.0	34.9 ±9.4	34.8 ± 10.1	33.9 ± 9.6	36.9 ± 9.2
NYHA Functional class						
I	33 (5.2)	0	17 (4.7)	9 (8.3)	5 (8.8)	2 (4.2)
II	183 (28.8)	3 (5.0)	112 (30.9)	35 (32.4)	14 (24.6)	19 (39.6)
III	332 (52.2)	49 (81.7)	185 (51.0)	44 (40.7)	30 (52.6)	24 (50.0)
IV	88 (13.8)	8 (13.3)	49 (13.5)	20 (18.5)	8 (14.0)	3 (6.3)
Atrial fibrillation	17 (2.7)	5 (8.3)	3 (0.8)	3 (2.8)	3 (5.3)	3 (6.3)
Presence of diastolic dysfunction (n, %)	203 (31.9)	42 (70.0)	77 (21.2)	47 (43.5)	28 (49.1)	9 (18.8)
Presence of valvular lesions (n, %)	316 (49.7)	48 (80.0)	141 (38.8)	61 (56.5)	40 (70.2)	26 (54.2)
AS, moderate-severe (n, %)	117 (18.4)	1 (1.7)	19 (5.2)	2 (1.9)	2 (3.5)	1 (2.1)
AR, moderate-severe (n, %)	25 (3.9)	10 (16.7)	11 (3.0)	3 (2.8)	2 (3.5)	6 (12.5)
MR, moderate-severe (n, %)	32 (5.0)	13 (21.7)	63 (17.4)	17 (15.7)	14 (24.6)	10 (20.8)
TR, moderate-severe (n, %)	117 (18.4)	23 (38.3)	80 (22.0)	18 (16.7)	19 (33.3)	8 (16.7)

AR, aortic regurgitation; AS, aortic stenosis; BP, blood pressure; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RHD, rheumatic heart disease; SD, standard deviation; TR, tricuspid regurgitation.

Table 2. Patient outcomes of the Heart Failure Registry (2014-2018)

	Overall (n = 636)	2014 (n = 60)	2015 (n = 363)	2016 (n = 108)	2017 (n = 57)	2018 (n = 48)
Complications (n, %)						
Cardiac	84 (13.2)	8 (13.3)	52 (14.3)	12 (11.1)	7 (12.3)	5 (10.4)
Non-cardiac	51 (8.0)	4 (6.7)	30 (8.3)	9 (8.3)	4 (7.0)	4 (8.3)
Mortality (n, %)	25 (3.9)	2 (3.3)	7 (1.9)	6 (5.6)	7 (12.3)	3 (6.3)
Discharge heart rate (mean, SD)	78.7 ± 12.9	83.5 ± 15.2	79.4 ± 10.5	78.1 ± 10.7	72.8 ± 19.4	78.6 ± 9.09
% with heart rate <70 bpm at discharge	114 (17.9)	8 (13.3)	59 (16.3)	22 (20.4)	16 (28.1)	9 (18.8)

Cardiac complications occurred during hospitalisation in 13.2% of included patients, and 8.0% experienced non-cardiac complications. The overall mortality was 3.9%. **Table 2** shows the outcomes of patients as well as discharge heart rate by year. Heart rate control was generally low, with rates of patients achieving a heart rate of less than 70 bpm ranging from 13.3% (2014) to 28.1% (2017).

DISCUSSION

Angiotensin blockade, in combination with beta-blockers, are recommended for the treatment of symptomatic HF patients with reduced EF (Class I) to reduce the risk of HF hospitalisation and death.[7] However, this study showed that just over half of HF patients enrolled in the Heart Failure Registry were given ACEI/ARBs (56.7%) and only 44.1% received beta-blockers throughout the study period. Closer examination of yearly drug utilisation rates showed that the use of ACEI/ARBs was high during the first few years of the registry but slowly deteriorated up to 2016. A similar trend was associated with the use of beta-blockers, although the rates were generally lower compared to ACEI/ARBs. Furthermore, the improvement in the use of beta-blockers during the implementation of the Optimize Heart Failure Care Programme was more evident compared to ACEI/ARBs due to a lower baseline.

Historically, the use of beta-blockers in HF ran contrary to the conventional belief and was previously contraindicated in HF.[8] It was only during the 1990s and early 2000s that large randomised trials showed the mortality benefit of beta-blockers. The high proportion of NYHA Class IV patients (11% to 18%) may also contribute to the lower rate of beta-blocker use, due to their being contraindicated for decompensated HF. Nonetheless, the effect of inertia in bedside practice cannot be discounted as a possible cause of lower rates of beta-blocker compared with ACEI/ARBs, which were historically never contraindicated for HF. These lower rates could also contribute to the low rates of heart rate control, wherein only 13.3% to 28.1% of patients per year achieved a heart rate of less than 70 bpm upon hospital discharge.

Ivabradine is recommended as a Class IIa recommendation to reduce HF hospitalisation for patients with symptomatic (NYHA class II-III), stable, chronic HFrEF (LVEF ≤35%) who are receiving optimal medical treatment including a beta-blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest. The SHIFT trial (Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial) showed that in these patients, ivabradine use was associated with a reduction in the composite of cardiovascular death or hospitalisation for worsening HF symptoms (HR 0.82; 95% CI 0.75–0.90; $p<0.0001$), primarily driven by hospital admissions for worsening HF (16% in the ivabradine group vs 21% with placebo; HR 0.74, 95% CI 0.66–0.83; $p<0.0001$).[9] Given that patients need to be stable upon initiation, this medication is largely prescribed during outpatient follow-up in the Philippine setting. However, this study showed that 5.8% to 11.8% of patients received ivabradine during hospital admission. There are various reasons for initiating ivabradine in the hospital, including poor tolerance to beta-blockers. However, these reasons are not apparent from the registry data as this information was not collected by the registry. Nonetheless, a recent study showed that initiating ivabradine during the hospitalization period improved treatment persistence with ivabradine and a greater reduction in heart rate through 6 months of follow-up.[10]

The use of digoxin decreased from 48.3% at the start of the registry to a range of 16.6% to 28.7% in later years. However, these rates and the indication for the use of digoxin need to be examined further, given the low rate of atrial fibrillation reported (yearly rate ranging from 0.8% to 8.3%).

The Heart Failure Registry was part of the Optimize Heart Failure Care programme, which also included management checklists and, during the first few years, regular educational meetings of healthcare professionals to raise awareness of the impact of HF interventions on patient outcomes.[4] Registry data suggests that the programme had significant impact in improving the rate of use of beta-blockers (from a 34% baseline to a rate of 51% by 2014. The rate of MRA use had a slightly delayed uptake, from 3.4% in 2014 to 26% the following year. MRA use peaked in 2017 with a rate of 29%.

Similarities and differences can be observed with the implementation of the Optimize Heart Failure Care programme in Ho Chi Minh City Heart Institute in Vietnam against the experiences reported here for the Philippines.[11] Ho Chi Minh City Heart Institute enrolled 257 patients and noted an exceptionally high rate of use of ACEI/ARB (91%) and MRA (77%). The use of beta-blockers and ivabradine were both low, as in the Philippines, although there was note of an increase over the course of 6 months (from 33% to 51% and from 9% to 20%, respectively, $p<0.001$). These prescribing habits were associated with a significant decrease in patients' heart rate, improvement of clinical symptoms and increases in LVEF. There were no reported in-hospital mortality.

The successful implementation in Vietnam highlights that there is room for improvement in the implementation of the Optimize Heart Failure Care programme in the Philippines and the overall management of HF in the country in general. Several factors

affect the adoption of guideline-directed pharmacotherapy for HF, including the knowledge of clinicians, drug access, side effects and patient adherence. The decline of the rate of use of guideline-directed pharmacotherapy coinciding with the discontinuation of educational activities and the subsequent improvement during the following years of reactivation of educational activities cannot be ignored. While a causal relationship cannot be proven by this study, it is good judgement to continue education of clinicians to enhance the knowledge of younger physicians and counter the natural decline in programme implementation performance among all Optimize Heart Failure Care Programme participants. Specialised education in the management of HF and the institutionalisation of monitoring units may also help to uplift the overall care of patients with HF in the country.

Finally, socioeconomic and healthcare system factors significantly affect the quality of care received by a population.[12-14] The Universal Health Care Act was passed into law in the Philippines on February 2019.[15] This law mandates significant healthcare reforms to be implemented over time, including automatic enrollment of all Filipinos to the Philippine Health Insurance Corporation (PHIC), improvement of health facilities especially in underserved areas, addressing gaps in health workers, and other systematic improvements. The Department of Health is in charge of drafting the implementing rules and regulations of the law after public consultations and multi-sectoral dialogues. Given this unique opportunity for systematic change, leaders in healthcare should actively participate in these dialogues to ensure that the needs of patients with HF are addressed.

Certain limitations should be noted in this study. This was a descriptive study, which carries with it a high level of bias. Furthermore, non-random consecutive sampling was used, which indicates that the results reported here may not be generalised to the whole population of patients with HF in the country. Only six of the 12 centres included in the Optimize Heart Failure Care programme participated in the Heart Failure Registry, which significantly limits its scope, sample size, and more importantly, the generalisability of the study results to the overall population. Finally, the study lacked long-term post-discharge follow-up and evaluation of patient adherence to medications. These limitations could be considered as possible future directions for improvement in the implementation of the registry. For example, this study provides an initial glimpse into the HFrEF population in the Philippines, which could form the basis of a larger comprehensive database with longer-term follow-up. Such a larger database would be beneficial to health authorities and clinicians in addressing the burden of heart failure on a national level.

CONCLUSION

The Heart Failure Registry showed that the use of ACEI/ARBs, beta-blockers, MRAs and ivabradine in patients with HF is suboptimal. The utilisation rates of guideline-directed pharmacotherapy, particularly for ACEI/ARBs and beta-blockers, follows the scale of educational activities of the Optimize Heart Failure Care programme. Continuation of the programme, including its educational components, and continuous monitoring of performance measures is recommended.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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