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The treatment gap in patients with chronic systolic heart failure: a systematic review of evidence-based prescribing in practice

Ken Lee Chin[1,2] · Marina Skiba[1,2] · Andrew Tonkin[1] · Christopher M. Reid[1,3] · Danny Liew[1] · Henry Krum[1,2] · Ingrid Hopper[1,2]

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Abstract The extent and impact of under-prescribing of evidence-based pharmacological therapies among heart failure patients with reduced ejection fraction (HFREF) in contemporary practice is unclear. We sought to examine the prescribing patterns of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers (BBs) and mineralocorticoid receptor antagonists (MRAs), and to quantify the estimated 'treatment gap' among HFREF patients in the 'real-world' setting. The MEDLINE, PubMed, EMBASE, CINAHL and CENTRAL databases were searched for registry- or survey-based studies which examined the prescribing rates of ACE inhibitors, ARBs, BBs and MRAs among HFREF patients. Searches were limited to those published in the years 2000–2015. A total of 23 reports, including 83,605 patients, were evaluated. Overall, ACE inhibitors/ARBs, BBs and MRAs were prescribed to 79.8, 81.4 and 36.4 % of patients, respectively. The estimated treatment gaps in the overall population were 13.1 % for ACE inhibitors/ARBs, 3.9 % for BBs and 16.8 % for MRAs. The proportion of patients who received ≥50 % of the guideline-recommended target doses was 72 % for ACE inhibitors, 51 % for ARBs, 49 % for BBs, 53 % for the combination of ACE inhibitors/ARBs and BBs and 83 % for MRAs. Prescribing these drugs according to contemporary guidelines was associated with lower mortality risk. Patients who were elderly, female and with comorbidities were less likely to receive optimal treatment as recommended by the guidelines. ACE inhibitors, ARBs, BBs and MRAs are under-prescribed in eligible HFREF patients. Efforts should be made to improve approaches to closing the treatment gap at both systems of care and individual levels.

Keywords Systolic heart failure · Registry · Survey · Treatment gap

Introduction

Heart failure (HF) remains a major public health burden across the globe. It is increasing in prevalence and associated with poor clinical outcomes and high healthcare costs [1]. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers (BBs) and mineralocorticoid receptor antagonists (MRAs) comprise the cornerstone of contemporary pharmacological treatment for HF patients with reduced ejection fraction (HFREF) [2, 3]. These disease-modifying therapies slow or retard progression of HF by attenuating the deleterious effect of neurohormonal stimulation [2].

Optimal use of ACE inhibitors, ARBs, BBs and MRAs in patients with chronic HF reduces mortality and morbidity in contemporary clinical practice [4, 5]. Despite this, data from large observational studies suggest that these drugs are under-prescribed in chronic HF patients [6]. However, the full extent and impact of under-prescribing of evidence-based pharmacological therapies among patients

In memoriam of Henry Krum.

✉ Ingrid Hopper
ingrid.hopper@monash.edu

[1] Centre of Cardiovascular Research and Education in Therapeutics, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC 3004, Australia

[2] Clinical Pharmacology Department, Alfred Hospital, Melbourne, VIC, Australia

[3] School of Public Health, Curtin University, Perth, WA, Australia

with HFREF in contemporary practice is unclear. It is possible that further improvement in outcomes will be achieved by closing any 'treatment gap' [7].

Few studies have examined the prescribing patterns among HFREF patients in the 'real-world' clinical setting [8, 9]. In addition, the association between prescribing patterns and patient demographics or comorbidities in this population remains unclear. Over the last two decades, concerted efforts to improve patient care through a series of educational and quality improvement programs have been reported [10–12]. The effectiveness of these interventions in improving the optimal use of evidence-based pharmacological therapies deserves further attention. Along these lines, we performed a systematic review to assess the interrelationships between baseline clinical characteristics, prescribing patterns and treatment outcomes among chronic HFREF patients enrolled in contemporary HF registries and population-based surveys. We also aimed to quantify the 'treatment gap' among HFREF patients.

Our review focused on clinical registries and population-based surveys as compared to other study designs (including clinical trials) because they recruit a broader spectrum of HF patients and hence better reflect 'real-world' settings [13]. In addition, registries contain data that are well-defined, usually collected close to the time of commencement of treatment and involve systematic follow-up of patients. For these reasons, registries are considered a reliable source for assessing the quality of patient care and treatment outcomes in clinical practice [14].

Methods

Search methods

We performed this systematic review according to the recommendations in the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analyses) statement [15, 16]. Two reviewers (KLC and IH) systematically searched the PubMed, MEDLINE (Medical Literature Analysis and Retrieval System Online) via Ovid, EMBASE (Excerpta Medical Database), CENTRAL (Cochrane Central Register of Controlled Trials) and CINAHL (Cumulative Index to Nursing and Allied Health Literature) databases for studies published in the years 2000–2015, and which reported prescribing patterns of ACE inhibitors, ARBs, BBs and MRAs among patients with HFREF. We also manually searched the reference lists of relevant review articles, systematic reviews, treatment guidelines, conference proceedings and online trial registries for relevant articles.

Search strategies included both Medical Subject Heading (MeSH) and text word search terms for systolic heart failure; left ventricular dysfunction; registry; survey; systolic heart failu*; chronic heart failu*; myocard* failu*; cardia* failu*; outcom*; registr*; survey*; left ventricular systolic dysfunction; heart failure with reduced ejection fraction; HFREF; reduced ejection fraction; guidelines adherence; guideline-directed; guideline-driven; prescrib* rates; prescrib* pattern; prescription pattern; treatment outcom*; population-based; population based; community-based; community based; evidence based treatment; under-prescrib*; under-utiliz*; optim* treatment. Abstracts were exported into Endnote X7.

Inclusion/exclusion criteria

Studies were eligible for inclusion if they were based on clinical registries or population-based surveys that recruited more than 200 stable patients with HFREF (defined as LVEF $\leq$ 40 % and measured by echocardiogram, nuclear multiple-gated acquisition scan, contrast ventriculogram or magnetic resonance imaging scan) and were not using intravenous (IV) diuretics or inotropes, and reported on prescription of ACE inhibitors, ARBs, BBs and MRAs. Studies which included stable patients with both HFREF and heart failure with preserved ejection fraction (HFPEF) were included if they reported specific data for patients with HFREF. We restricted our search to studies published in the English language.

Selection process

KLC and IH checked all titles and abstracts for studies that potentially met the inclusion criteria. Subsequently, both reviewers independently reviewed and extracted data from eligible full text articles. Discrepancies were resolved by consensus with a third reviewer (AT). We also measured the inter-rater reliability by calculating the level of agreement between the reviewers on the inclusion of the eligible full text articles.

Data extraction

Information was collected on data collection period, number of study participants, baseline clinical characteristics, medical history, prescription of ACE inhibitors, ARBs, BBs, MRAs and treatment outcomes. Selected studies were categorised as registry-based, survey-based, or a composite of the two. Sample size-weighted means and standard deviations (SDs) of all variables of interest were calculated. We compared the clinical characteristics, medical history and prescribing patterns according to age, sex and comorbidities. Where data existed, we examined the association between 'guideline adherence index' (GAI) and treatment outcomes. GAI is the proportion of patients

prescribed the indicated drug and is commonly used to measure quality of care [17].

Definition of comorbidities

Comorbidities were defined as any concomitant disease in HFREF patients based on medical documentation. Data for the following conditions were extracted for our analysis: hypertension, ischemic heart disease, previous myocardial infarction (MI), atrial fibrillation (AF), stroke, diabetes mellitus (DM), chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD)/asthma.

Assessment of risk of bias in included studies

KLC and IH independently assessed the risk of bias of included reports using the Risk of Bias Tool for Non-randomised Studies (RoBANS). Similar to the Cochrane Collaboration's risk of bias tool (for randomised controlled trials), RoBANS is a validated tool which assesses selection, performance, detection, attrition and reporting biases and has been used in other systematic reviews [18–20].

Assessment of treatment gap

A small proportion of patients did not have documented New York Heart Association (NYHA) classification in some of the studies. Hence, the cumulative percentage of the sample size-weighted means of NYHA Class I–IV was less than 100 %. By assuming that those with and without documented NYHA classification were proportionate in terms of disease severity, we estimated the adjusted means of NYHA Class I–IV for the overall population. The adjusted means of NYHA classification were used to estimate the proportion of patients who were eligible for ACE inhibitors/ARBs, BBs and MRAs as recommended by the American College of Cardiology Foundation/American Heart Association and European Society of Cardiology chronic HF guidelines [2, 21–27]. The IMPROVE HF study, which characterised over 15,000 patients recruited from 167 settings of different practice levels, had previously reported that the overall prevalence of contraindication/intolerance to ACE inhibitor/ARBs, BBs and MRAs were 7, 7 and 18 %, respectively [28]. Taken together, we estimated the 'treatment gap' by measuring the proportion of patients who had an indication and no contraindication or limiting side effect but were not prescribed the recommended treatments.

The studies were grouped into US or Europe based. The analysis was repeated when the studies were re-grouped based on study designs; i.e., registry-based, survey-based and composite. We excluded McKee's study [29] as clinicians at the time used Scottish Intercollegiate Guideline Network guidelines on systolic heart failure (number 35) published in 1999. Data from studies which only examined a specific subgroup of HFREF patients were excluded stepwise to evaluate the rigor of the estimated treatment gap.

Assessment of prescribed doses

The beneficial effects of the evidence-based therapies have previously been reported in patients who received $\geq$50 % of the guideline-recommended target doses [30]. Where data existed, an arbitrary cutoff point $\geq$50 % of the target doses of each medication was also used in our analysis to describe the prescribed doses in the individual studies.

Results

Search results

The initial search identified a total of 855 articles, of which 399 were duplicates. Of the remaining 456, 335 did not meet the pre-specified inclusion criteria from review of their titles and/or abstracts. We reviewed the full text of 121 articles and excluded a further 100. Reasons for exclusion are listed in Fig. 1. Two additional articles were identified through references. This resulted in 23 reports [5, 8, 9, 28, 29, 31–48], with data from eight registries and ten surveys being selected for the analysis (Fig. 1). Four of the reports were based on Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF), three from the EuroHeart Failure Survey (EHFS), and two from Impact-Reco Programme I and II. The inter-rater agreement for included articles was 87 %. The risk of bias in individual studies is presented in 'Appendix 1.'

Study characteristics

Data were collected between 1994 and 2012, and the number of patients per study ranged from 252 to 45,392. A total of 83,605 patients with HFREF were included. Characteristics of the individual studies, categorised as registry-based and survey-based, are presented in 'Appendices 2 and 3.' 'Appendices 4 and 5' summarise the characteristics of the US-based and Europe-based studies and the recommendations of the use of ACE inhibitors, ARBs, BBs and MRAs in published chronic HF practice guidelines. Six studies (three registries and three surveys) originated from the US and 12 from Europe (five registries and seven surveys). The study by Hebert et al. [39] did not provide baseline characteristics for the overall study population. Hence, data from this study were only included for the analysis that compared prescribing patterns between patients with and without CKD. Two of the registries

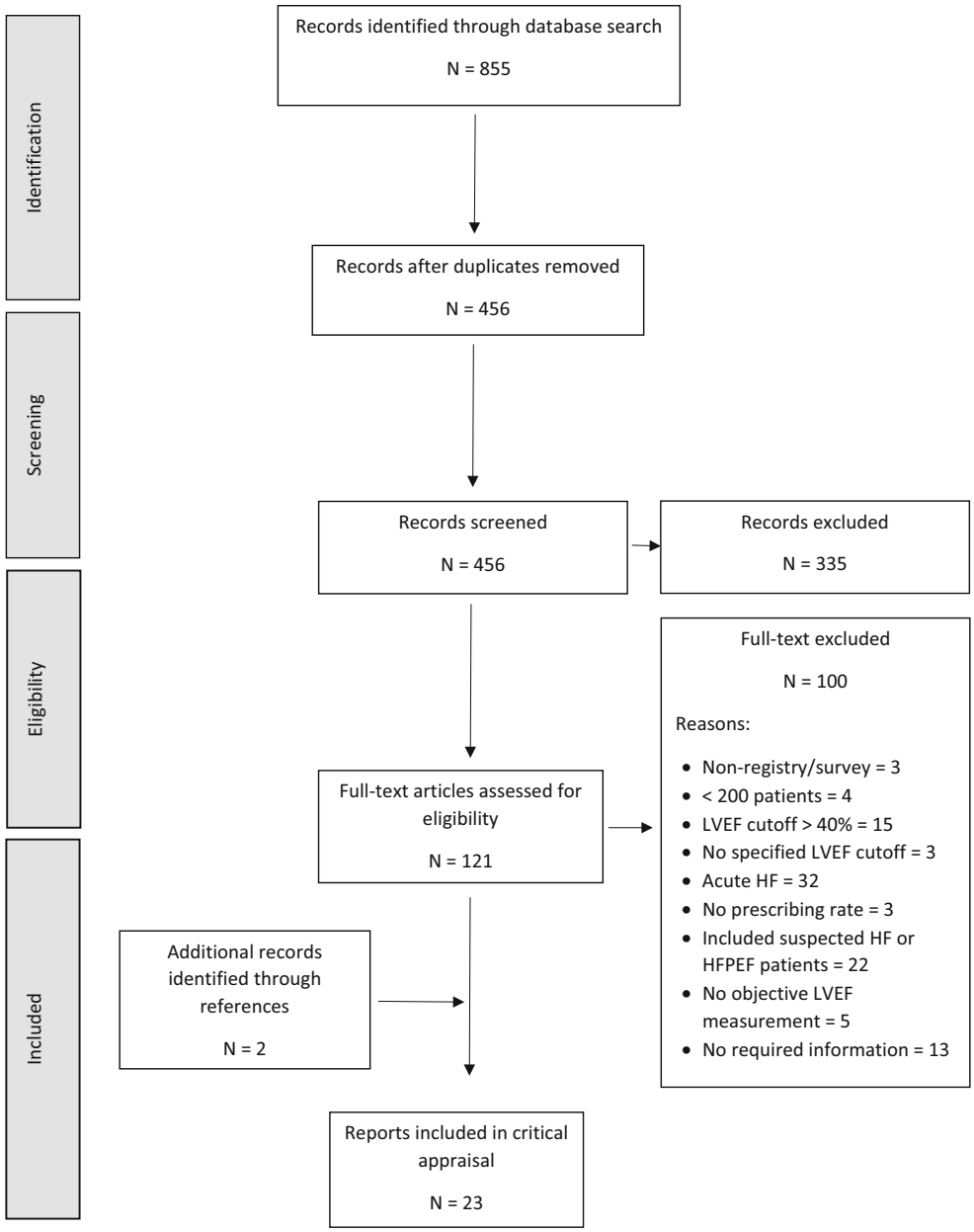

Fig. 1 Study selection process

(IMPROVE HF [9, 28, 35, 40] and National Cardiovascular Data Registry Implantable Cardioverter-Defibrillator Registry (NCDR-ICD) [44]) used LVEF ≤35 % to define systolic dysfunction. The rest used LVEF ≤40 %.

Baseline clinical characteristics and prescribing patterns

Tables 1 summarises clinical characteristics and prescribing rates in the selected studies. Overall, patients had a mean (SD) age of 68.7 (2.4) years, 70.1 % (2.9 %) were male and mean (SD) LVEF was 28.1 % (3.8 %). The mean (SD) prescribing rates were 79.8 % (13.8 %) for ACE inhibitors/ARBs, 81.4 % (12.7 %) for BBs and 36.4 % (10.2 %) for MRAs.

The Cardiovascular Research Network (CVRN) [38] and NCDR-ICD [44] registries only recruited newly diagnosed HFREF patients and patients who had undergone cardiac resynchronisation therapy, respectively. The Shah survey [46] recruited only HFREF patients with diabetes mellitus. When data from these three studies were excluded (n = 49,707), the mean (SD) prescribing rates of ACE

Table 1 Comparison of clinical characteristics in observational studies

Characteristics/study	Registry	Registry (without CVRN [38] + NCDR [44])	Survey	Survey (without Shah [46])	Registry + Survey	Registry + Survey (without CVRN [38] + NCDR [44] + Shah [46])
No. of patients	70,654	21,348	12,951	12,550	83,605	33,898
No. of studies contributing	8	6	9	8	17	14
Age (year)	68.9 ± 1.5	68.1 ± 2.7	66.8 ± 5.2	67.2 ± 4.8	68.7 ± 2.4	67.8 ± 3.4
Male sex (%)	69.5 ± 2.1	71.9 ± 2.2	73.7 ± 4.0	73.7 ± 4.1	70.1 ± 2.9	72.6 ± 3.1
NYHA class (%)						
I	6.9 ± 9.9	19.4 ± 2.2	11.2 ± 3.5	11.2 ± 3.5	7.1 ± 9.1	18.8 ± 4.2
II	16.5 ± 10.2	28.9 ± 9.3	47.4 ± 11.3	47.4 ± 11.3	19.8 ± 13.9	34.3 ± 12.8
III	62.3 ± 31.1	20.0 ± 7.3	37.4 ± 7.9	36.9 ± 8.6	60.8 ± 28.7	22.8 ± 9.6
IV	6.1 ± 2.7	2.4 ± 0.4	11.9 ± 17.6	8.3 ± 13.6	6.4 ± 4.9	3.3 ± 5.5
Previous HF hospitalisation (%)	71.2 ± 12.5	71.2 ± 12.5	100.0[a]	100.0[a]	77.4 ± 17.4	77.4 ± 17.4
LVEF (%)	26.4 ± 2.7	26.4 ± 2.7	31.2 ± 3.9	31.5 ± 3.6	28.1 ± 3.8	28.2 ± 3.8
SBP (mmHg)	123.1 ± 5.9	120.9 ± 3.0	122.1 ± 10.3	122.1 ± 10.3	122.9 ± 6.3	121.1 ± 4.9
Heart rate (/min)	72.4 ± 1.1	72.4 ± 1.1	74.6 ± 4.2	74.6 ± 4.2	72.9 ± 2.1	72.9 ± 2.1
Serum creatinine (mg/dL)	1.4 ± 0.1	1.4 ± 0.1	1.3 ± 0.2	1.3 ± 0.2	1.4 ± 0.1	1.4 ± 0.1
eGFR (mL/min/1.73 m^2)	71.5 ± 7.8	78.5 ± 4.7	69.1[a]	69.1[a]	71.2 ± 6.9	76.1 ± 6.1
Medical history (%)						
Hypertension	71.3 ± 7.3	63.3 ± 6.8	48.4 ± 6.3	48.0 ± 6.1	67.7 ± 11.0	57.7 ± 9.9
Ischemic heart disease	57.4 ± 14.1	59.2 ± 12.2	55.1 ± 10.6	54.9 ± 10.8	57.0 ± 13.2	57.6 ± 11.4
Previous myocardial infarction	45.0 ± 4.3	39.3 ± 2.4	44.2 ± 10.4	44.2 ± 10.4	44.9 ± 4.9	40.7 ± 5.7
Atrial fibrillation	30.7 ± 3.2	32.7 ± 4.5	24.3 ± 5.5	24.3 ± 5.5	29.7 ± 4.2	29.4 ± 6.3
Stroke	13.0 ± 2.8	10.5 ± 3.0	11.9 ± 3.7	11.9 ± 3.7	12.9 ± 2.8	11.4 ± 3.3
Diabetes mellitus	37.2 ± 6.6	33.6 ± 4.9	27.7 ± 14.1	25.4 ± 3.3	35.7 ± 8.7	30.5 ± 5.8
Renal insufficiency	29.3 ± 8.3	29.3 ± 8.3	12.9 ± 12.4	11.2 ± 8.5	17.3 ± 13.4	16.3 ± 11.8
COPD/Asthma	22.8 ± 4.3	17.2 ± 2.9	19.1 ± 2.3	19.1 ± 2.3	22.5 ± 4.2	17.6 ± 2.8
Use of therapies (%)						
ACEI	64.1 ± 1.8	60.2 ± 11.5	74.7 ± 6.0	74.7 ± 6.0	65.7 ± 4.9	72.8 ± 8.2
ARB	19.0 ± 3.2	34.1 ± 5.8	16.1 ± 11.2	16.1 ± 11.2	18.6 ± 5.0	18.5 ± 12.0
ACEI/ARB	76.2 ± 15.5	82.1 ± 4.2	87.4 ± 7.0	87.4 ± 7.2	79.8 ± 13.8	84.0 ± 5.8
BB	85.0 ± 8.3	85.7 ± 2.3	61.5 ± 14.1	61.3 ± 14.4	81.4 ± 12.7	76.7 ± 15.0
MRA	37.1 ± 10.6	40.0 ± 8.4	34.9 ± 10.6	34.7 ± 10.7	36.4 ± 10.2	38.0 ± 9.3

All values are sample size-weighted mean ± SD

CVRN Cardiovascular Research Network registry, *NCDR-ICD* National Cardiovascular Data Registry, *NYHA* New York Heart Association, *HF* heart failure, *LVEF* left ventricular ejection fraction, *SBP* systolic blood pressure, *eGFR* estimated glomerular filtration rate, *COPD* chronic obstructive pulmonary disease, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BB* beta blockers, *MRA* mineralocorticoid receptor antagonists

[a] Data from a single study

inhibitors/ARBs, BBs and MRAs were 84.0 % (5.8 %), 76.7 % (15.0 %) and 38.0 % (9.3 %), respectively.

Treatment gap

The registries were predominantly US-based (92 %), while the surveys were mostly European (90 %) (Table 2). The estimated treatment gaps in the overall population were 13.1 % for ACE inhibitors/ARBs, 3.9 % for BBs and 16.8 %s for MRAs. In addition, the estimated treatment gaps in the registries (16.8 % for ACE inhibitors/ARBs, 0.5 % for BBs and 19.4 % for MRAs) were different to the surveys (5.2 % for ACE inhibitors/ARBs, 20.1 % for BBs and −7.9 % for MRAs). When each of the included studies was compared with the relevant practice guidelines, MRAs may have been prescribed for indications other than HF in some of the patients in the EHFS [42], FUTURE [32] and Scrutinio's [45] surveys. Assuming that all NYHA Class III/IV patients were indicated for MRAs as recommended by the European guidelines 2001 and 2005, the prescribing rates of MRAs in these three studies exceeded the proportion of patients who were eligible for the treatment by 4, 4, and 9.5 %, respectively.

Prescribed doses

There were only four studies (all from Europe) which evaluated the prescribed doses compared with guideline-recommended target doses (Table 3). More than 70 % of patients were prescribed with ≥50 % of the guideline-recommended target doses of ACE inhibitors. In addition, only half of patients were prescribed with ≥50 % of the guideline-recommended target doses of BBs. When ACE inhibitors/ARBs were prescribed together with a BB, 53 % of the patients were treated with ≥50 % of the guideline-recommended target doses [32]. Prescribed doses of MRAs were not assessed in a standardised manner. All patients who were treated with spironolactone were prescribed with at least 12.5 mg/day in the IMPACT-RECO I studies [33]. A total of 83 % of patients prescribed with MRAs were treated with ≥50 % of guideline-recommended target doses in the EHFS survey [8]. In the IMPROVE HF registry, 73 % of the patients who were eligible for MRAs were treated at or above target doses [28].

Prescribing patterns according to demographics and comorbidities

Prescribing rates according to age, gender and comorbidities are presented in Tables 4 and 5. Table 6 summarises the independent predictors derived from multivariable analysis explaining the prescription of drugs. Patients who were elderly, female or had renal failure were less likely to be prescribed ACE inhibitors/ARBs and MRAs. In addition, increasing age, being female and the presence of asthma/COPD were strong predictors for the under-prescribing of BBs.

Treatment outcomes

From the selected studies, only two registries evaluated the impact of optimal prescribing of ACE inhibitors/ARBs, BBs and MRAs on outcomes. Prescribing these drugs according to guidelines was associated with lower mortality risk in multivariable analyses. In the University Hospital HEidelberg, the Klinikum LUdwigshafen and the TKH MAnnheim (HELUMA) registry, where surviving patients were followed for an average of 38 months (from 23 to 56 months), mortality risk was reduced by 27 % (adjusted HR 0.73, 95 % CI 0.57–0.92) when ACE inhibitors/ARBs, BBs and MRAs were prescribed according to 2005 European guidelines [36]. Similarly, in the Austrian Heart Failure Registry, in which patients were followed for an average of 2.8 years (1.6–4.4 years), mortality risk was reduced by 45 % (adjusted HR 0.55, 95 % CI 0.34–0.90) when ACE inhibitors/ARBs and BBs were prescribed at ≥50 % of the recommended target doses recommended in 2008 European guidelines [5].

Discussion

Our results highlight several pressing issues regarding the medical management of HFREF patients. Prescribing rates of evidence-based drugs appear to vary according to age, sex and comorbidities, and the treatment gap lies between 4 and 17 %. Nearly half of the HFREF patients were treated with ≤50 % of the target doses of BBs. Information about the true impact of following evidence-based strategy in treating HFREF patients were limited as we only found two studies reporting such data. Nevertheless, the importance of closing the treatment gap is highlighted by the finding that optimisation of treatment according to guidelines was associated with reduced mortality.

Prescribing rates reported in other studies which included patients with LVEF > 40 % [4, 49, 50] were lower compared with those included in our review. In a large international survey conducted in 15 European countries, the Improvement Programme in Evaluation and Management of Heart Failure initiative (IMPROVEMENT-HF) reported that the prescribing rates of ACE inhibitors, BBs and combination of ACE inhibitors and BBs were 60, 34 and 20 %, respectively. The doses prescribed were about 50 % of those recommended in European guidelines [49]. Several years later, the Medical Management of Chronic Heart Failure in Europe and its related costs (MAHLER)

Table 2 Estimated treatment gap

Drug class	Proportion of patients eligible for therapy (A) (%)	Prevalence of contraindication/ intolerance[a] (B) (%)	Proportion of patients remained indicated for treatment (A–B) (%)	Proportion of eligible patients prescribed with treatment (C) (%)	Treatment gap (A–B) − (C) (%)	No. of patients from US-based studies (%)	No. of patients from Europe-based studies (%)	Total population (%)
A. Registries and surveys						65,923 (79)	17,282 (21)	83,205 (100)
ACEI/ARB	100.0	7.0	93.0	79.9	13.1			
BB	92.5	7.0	85.5	81.6	3.9			
MRA	71.4	18.0	53.4	36.6	16.8			
B. Registry + Survey (excluding CVRN [38] + Shah [46])						61,608 (78)	17,282 (22)	78,890 (100)
ACEI/ARB	100.0	7.0	93.0	84.1	8.9			
BB	92.4	7.0	85.4	83.1	2.3			
MRA	71.4	18.0	53.4	38.3	15.1			
C. Registry + Survey (excluding CVRN [38] + NCDR [44] + Shah [46])						16,216 (48)	17,282 (52)	33,498 (100)
ACEI/ARB	100.0	7.0	93.0	84.1	8.9			
BB	76.3	7.0	69.3	77.2	−7.9			
MRA	33.0	18.0	15.0	38.3	−23.3			
D. Registry						64,687 (92)	5967 (8)	70,654 (100)
ACEI/ARB	100.0	7.0	93.0	76.2	16.8			
BB	92.5	7.0	85.5	85.0	0.5			
MRA	74.5	18.0	56.5	37.1	19.4			
E. Registry (excluding CVRN [38])						60,773 (91)	5967 (9)	66,740 (100)
ACEI/ARB	100.0	7.0	93.0	82.1	10.9			
BB	92.5	7.0	85.5	86.9	−1.4			
MRA	74.5	18.0	56.5	40.0	16.5			
F. Registry (excluding CVRN [38] + NCDR [44])						15,381 (72)	5967 (28)	21,348 (100)
ACEI/ARB	100.0	7.0	93.0	82.1	10.9			
BB	72.6	7.0	65.6	85.7	−20.1			
MRA	31.7	18.0	13.7	40.0	26.3			
G. Survey						1236 (10)	11,315 (90)	12,551 (100)
ACEI/ARB	100.0	7.0	93.0	87.8	5.2			
BB	89.6	7.0	82.6	62.5	20.1			
MRA	45.7	18.0	27.7	35.6	−7.9			
H. Survey (excluding Shah [46])						835 (7)	11,315 (93)	12,150 (100)
ACEI/ARB	100.0	7.0	93.0	87.9	5.1			
BB	89.2	7.0	82.2	62.4	19.8			
MRA	43.5	18.0	25.5	35.4	−9.9			

McKee study was excluded from analysis

CVRN Cardiovascular Research Network registry, *NCDR-ICD* National Cardiovascular Data Registry, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BB* beta blockers, *MRA* mineralocorticoid receptor antagonists

[a] Heywood et al. [28]

study were conducted as a multicenter observational study in six European countries. In that study, the prescribing rates of ACE inhibitors, ARBs, BBs and spironolactone were 69, 17.6, 53 and 28 %, respectively. GAI was high for ACE inhibitors (85.4 %) but lower for BBs (58 %) and spironolactone (36 %) [4]. Both studies did not have any pre-specified ejection fraction. In Japan, the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) registry demonstrated that the prescribing rates of ACE inhibitors/ARBs and BBs were 72.3 and 49 %, respectively [50]. In that study, LVEF < 50 % was used as the cutoff point to define HFREF.

We found older age, female gender and presence of comorbidities to be independent predictors of under-prescribing, which is accord with the results of previous studies [11, 51, 52]. The IMPROVEMENT-HF survey also

Table 3 Prescribed doses

Study	No. of patients studied (*n*)	ACEI			ARB			BB			ACEI/ARB and BB		
		Patients prescribed [*n* (%)]	Meet target dose [*n* (%)]		Patients prescribed [*n* (%)]	Meet target dose [*n* (%)]		Patients prescribed [*n* (%)]	Meet target dose [*n* (%)]		Patients prescribed [*n* (%)]	Meet target dose [*n* (%)]	
			<50 %	≥50 %		<50 %	≥50 %		<50 %	≥50 %		<50 %	≥50 %
Impact-Reco I [33]	1917	1361 (71)	259 (19)	1102 (81)	403 (21)	189 (47)	214 (53)	1246 (65)	660 (53)	586 (47)	1150 (60)[a]	–	–
Impact-Reco II [34]	1974	1342 (68)	215 (16)	1127 (84)	592 (30)	302 (51)	290 (49)	1382 (70)	636 (46)	746 (54)	1303 (66)[a]	–	–
EHFS [8]	3658	2848 (77.9)	1176 (41.3)	1672 (58.7)	219 (6)[a]	–	–	1679 (45.9)	948 (56.5)	731 (43.5)	–	–	–
FUTURE [32]	661	473 (72)	66 (14)	407 (86)	107 (16)	47 (44)	60 (56)	512 (77)	214 (42)	298 (58)	443 (67)	208 (47)	235 (53)
Total population	8210	6029 (73)	1717 (28)	4312 (72)	1101 (13)	538 (49)	563 (51)	4816 (59)	2459 (51)	2357 (49)	443 (67)	208 (47)	235 (53)

EHFS EuroHeart Failure Survey, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BB* beta blockers

[a] Numbers were excluded from the total population

found that prescribing of guideline-recommended treatment varied significantly between countries [52].

The American College of Cardiology Foundation/American Heart Association and European Society of Cardiology have made concerted efforts in implementing performance measures, quality improvement and educational programs, public reporting of hospital-level performance data and provision of easy-to-access brief summary of updated practise guidelines to clinicians [2, 3]. However, the number of patients dying or being readmitted in the year after hospital discharge remains high [53]. Our results raise important questions concerning the effectiveness of various improvement programs that have been implemented in the US and Europe over the last decade. There is an urgent need to consolidate efforts and possibly re-examine the effectiveness of current approaches in closing the treatment gap at all levels. Current approaches to overcome barriers to optimal utilisation of evidence-based pharmacological treatments are usually segregated (either prescriber-focused or patient-focused) [54–57] and lack cohesion. It is noteworthy that barriers such as health literacy, polypharmacy, adherence to medication, perceived susceptibility to adverse events, clinical inertia and treatment costs are closely intertwined and not exclusive. Hence, there must be synergy between various improvement programs and a focus should be on transitions of care between hospitals and the community. Another issue worth considering is the potential mismatch between what medications clinicians think their patients are taking and what their patients are actually taking.

Greater efforts to optimise the use of ACE inhibitors, ARBs, BBs and MRAs are warranted. Clinicians' concerns about adverse effects and the often lengthy time needed for up-titration are recognised as major obstacles in reaching target doses in stable HF patients, rather than real intolerance to a drug [58].

One-way forward is greater use of registries for pharmacovigilance. The proposed INTERnational Congestive Heart Failure (INTER-CHF) registry may be an ideal platform to benchmark the quality of care provided by institutions or countries [59]. Secondly, there could be more collaborative initiatives among authoritative bodies; such as those between the American Heart Association and American Diabetes Association [60, 61], to promote practice improvement. Thirdly, organised programs which incorporate an integrated multidisciplinary approach to patient care should be implemented. For example, the involvement of nurses and pharmacists in HF management programs resulted in improved prescribing at target doses, medication adherence and quality of life, while reducing rates of readmissions, medication errors, mortality and costs [62, 63]. Fourthly, incorporation of electronic triggers in established electronic prescribing systems may further

Table 4 Prescribing rates according to demographics and non-cardiovascular comorbidities

Study	Background therapies (%)	Age				Gender				Comorbidities (%)											
										Diabetes mellitus				Chronic kidney disease				COPD/asthma			
		n	≤76 years	*n*	≥76 years	*n*	Male (%)	*n*	Female (%)	*n*	Yes (%)	*n*	No (%)	*n*	Yes (%)	*n*	No (%)	*n*	Yes (%)	*n*	No (%)
IMPROVE HF [9, 35, 40]	ACEI/ARB	10,483	82.3	4791	73.3	10,925	79.8	4446	78.9	5229	77.8	10,152	80.6	6877	75.6	6287	84.5	2530	75.8	12,851	80.0
	BB		87.7		81.3		85.5		86.1		87.5		87.1		85.6		88.2		81.4		88.9
	MRA		39.9		26.6		35.4		37.9		33.3		33.3		37.3		39.7		33.3		32.5
		n	<75 years	*n*	≥75 years																
Impact-Reco I [33, 34]	ACEI/ARB	–	93.0	–	84.0	1421	90.0	496	87.0	468	92.0	1449	89.0	249	79.0	1668	91.0	378	91.0	1539	89.0
	BB		71.0		57.0		66.0		63.0		66.0		65.0		58.0		66.0		43.0		71.0
	MRA		–		–		–		–		–		–		–		–		–		–
		n	<75 years	*n*	≥75 years																
Impact-Reco II [33, 34]	ACEI/ARB	–	95.0	–	89.0	–	–	–	–	461	95.0	1513	92.0	214	85.0	1760	93.0	413	92.0	1561	93.0
	BB		76.0		60.0		–		–		72.0		70.0		62.0		71.0		46.0		76.0
	MRA		–		–		–		–		–		–		–		–		–		–
Hebert et al. [39]	ACEI/ARB	–	–	–	–	–	–	–	–	–	–	–	–	338	91.0	963	95.0	–	–	–	–
	BB		–		–		–		–		–		–		96.0		97.0		–		–
	MRA		–		–		–		–		–		–		17.0		21.0		–		–
Scrutinio et al. [45]	ACEI	–	–	–	–	–	–	–	–	–	–	–	–	423	77.5	528	87.3	–	–	–	–
	ARB		–		–		–		–		–		–		22.5		12.5		–		–
	ACEI/ARB		–		–		–		–		–		–		–		–		–		–
	BB		–		–		–		–		–		–		59.8		78.4		–		–
	MRA		–		–		–		–		–		–		62.9		51.1		–		–
EHFS [41]	ACEI	–	–	–	–	2490	80.0	1094	74.0	–	–	–	–	–	–	–	–	–	–	–	–
	BB		–		–		49.0		39.0		–		–		–		–		–		–
	MRA		–		–		32.0		25.0		–		–		–		–		–		–
Total population[a]	ACEI/ARB	10,483[b]	82.3[b]	4791[b]	73.3[b]	14,836	81.0	6036	79.7	6158	80.2	13,114	82.8	8101	76.7	11,206	87.9	3321	79.5	15,951	82.1
	BB		87.7[b]		81.3[b]		77.5		75.7		84.7		82.7		83.2		82.5		72.6		85.9
	MRA		39.9[b]		26.6[b]		34.8		35.4		33.3[b]		33.3[b]		37.8		38.2		33.3[b]		32.5[b]

EHFS EuroHeart Failure Survey, *COPD* chronic obstructive pulmonary disease, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BB* beta blockers, *MRA* mineralocorticoid receptor antagonists

[a] Sample size-weighted mean

[b] Data from a single study

Table 5 Baseline characteristics and prescribing patterns according to presence of chronic kidney disease

Characteristics/study	IMPROVE HF [40]		Scrutinio et al. [45]		Hebert et al. [39]		Total population[a]	
Chronic kidney disease	Yes	No	Yes	No	Yes	No	Yes	No
No. of patients	6877	6287	423	528	338	963	7638	7778
Age (year)	73.4	61.6	70.9	58.6	62.0	54.0	72.8 ± 2.9	60.5 ± 3.1
Male sex (%)	66.1	76.9	78.5	79.2	68.0	64.0	66.9 ± 3.5	75.5 ± 5.3
Ischemic HF etiology (%)	71.2	60.3	57.4	42.4	82.0	80.0	70.9 ± 4.8	61.5 ± 10.1
NYHA class (%)								
I	17.8	22.4	–	–	20.0	28.0	17.9 ± 0.7	23.1 ± 2.7
II	26.1	27.9	–	–	35.0	34.0	26.5 ± 2.7	28.7 ± 2.9
I/II	43.9	50.3	–	–	55.0	62.0	44.4 ± 3.3	51.9 ± 5.6
III	20.4	16.3	58.9	36.9	35.0	29.0	23.2 ± 11.2	19.3 ± 7.7
IV	2.9	2.2	–	–	10.0	10.0	3.2 ± 2.1	3.2 ± 3.7
III/IV	23.3	18.5	58.9	36.9	45.0	39.0	26.2 ± 11.1	22.3 ± 9.5
LVEF [% (mean)]	25.3	25.6	27.4	28.2	28.0	29.0	25.5 ± 0.9	26.2 ± 1.5
SBP (mmHg)	120.0	120.6	–	–	135.0	130.0	120.7 ± 4.5	121.8 ± 4.5
Heart rate (/min)	72.1	73.0	–	–	–	–	72.1[b]	73.0[b]
Serum creatinine (mg/dL)	2.4	1.0	1.6	1.0	–	–	2.4 ± 0.3	1.0 ± 0.0
eGFR, mL/min/1.73 m^2 (mean)	–	–	–	–	42.0	94.0	42.0[b]	94.0[b]
Medical history (%)								
Hypertension	65.4	59.3	46.8	36.2	–	–	64.3 ± 6.1	57.5 ± 8.7
Previous myocardial infarction	40.6	38.8	–	–	–	–	40.6[b]	38.8[b]
Atrial fibrillation	36.4	26.0	24.6	20.6	–	–	35.7 ± 3.9	25.6 ± 2.0
Stroke	–	–	7.6	4.9	–	–	7.6[b]	4.9[b]
Diabetes mellitus	37.9	30.7	33.3	17.6	42.0	30.0	37.8 ± 1.7	29.7 ± 4.0
COPD/asthma	17.9	15.5	20.6	13.3	–	–	18.1 ± 0.9	15.3 ± 0.8
Background therapies (%)								
ACEI	–	–	77.5	87.3	–	–	77.5[b]	87.3[b]
ARB	–	–	22.5	12.5	–	–	22.5[b]	12.5[b]
ACEI/ARB	75.6	84.4	–	–	91.0	95.0	76.3 ± 4.6	85.8 ± 5.1
BB	85.6	88.2	59.8	78.4	96.0	97.0	84.6 ± 7.8	88.6 ± 4.9
MRA	37.3	39.7	62.9	51.1	17.0	21.0	37.8 ± 9.0	38.2 ± 8.6

Yes: eGFR < 60 ml/min/1.73 m^2/No: eGFR ≥ 60 ml/min/1.73 m^2

HF heart failure, *NYHA* New York Heart Association, *LVEF* left ventricular ejection fraction, *SBP* systolic blood pressure, *eGFR* estimated glomerular filtration rate, *COPD* chronic obstructive pulmonary disease, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BB* beta blockers, *MRA* mineralocorticoid receptor antagonists

[a] Sample size-weighted mean ± SD

[b] Data from a single study

improve the adherence to contemporary practice guidelines. Finally, individually tailored measures to improve self-care strategies may be useful in improving medication adherence. When appropriate, innovative patient support measures via telemonitoring, reminders and educational letters circulated through handheld communicating devices and social media may be useful.

Study limitations

There are limitations to our study that warrant discussion. Our data were gathered only from the US and Europe. We did not find any relevant publication from other parts of the world. Other discrepancies in the study designs and data collection methods of the studies included in our analysis

Table 6 Independent predictors of prescription of pharmacological treatments for HFREF

Study	Drug class	Predictors	Adjusted OR (95 % CI)	*P* value
IMPROVE HF [9, 28]	ACEI/ARB	Increasing age	0.869 (0.835–0.903)	<0.0001
		Male	1.136 (1.020–1.264)	0.0199
		Prior PCI	0.82 (0.72–0.95)	0.0059
		Atrial fibrillation/flutter	0.81 (0.70–0.94)	0.0044
		Diabetes	1.37 (1.21–1.55)	<0.0001
		Hypertension	1.43 (1.25–1.64)	<0.0001
		eGFR	0.94 (0.88–0.99)	0.018
	BB	Increasing age	0.846 (0.808–0.886)	<0.0001
		Prior CABG	0.78 (0.67–0.90)	0.0007
		COPD	0.72 (0.59–0.89)	0.002
		Diabetes	1.22 (1.06–1.40)	0.0065
		HF etiology of IHD	3.31 (2.33–4.71)	<0.0001
	MRA	Increasing age	0.811 (0.753–0.874)	<0.0001
		Male	0.793 (0.693–0.985)	0.0358
EHFS [41]	ACEI	Gender	0.72 (0.61–0.86)	OR > 1; higher prevalence in women
	BB	Gender	0.76 (0.65–0.89)	
	Spironolactone	Gender	0.75 (0.64–0.89)	
Impact-Reco [34]	ACEI/ARB	Age ≥ 75 years old	0.50 (0.39–0.65)	<0.0001
		Renal failure	0.40 (0.30–0.54)	<0.0001
	BB	Age ≥ 75 years old	0.48 (0.41–0.57)	<0.0001
		NYHA III/IV	0.65 (0.56–0.77)	<0.0001
		COPD/asthma	0.29 (0.24–0.35)	<0.0001
		Coronary disease	1.52 (1.3–1.78)	<0.0001
	Spironolactone	Age ≥ 75 years old	0.68 (0.58–0.79)	<0.0001
		LVEF (%)	0.97 (0.96–0.98)	<0.0001
		Coronary disease	0.75 (0.65–0.87)	<0.0001
		Renal failure	0.59 (0.46–0.76)	<0.0001

IMPROVE HF Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting Registry, *EHFS* EuroHeart Failure Survey, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BB* beta blockers, *MRA* mineralocorticoid receptor antagonists, *PCI* percutaneous coronary intervention, *eGFR* estimated glomerular filtration rate, *CABG* coronary artery bypass grafting, *COPD* chronic obstructive pulmonary disease, *HF* heart failure, *IHD* ischemic heart disease, *NYHA* New York Heart Association, *LVEF* left ventricular ejection fraction

may have also affected our results. The definition of comorbidities may differ between studies and could have changed with time. In addition, temporal changes in the uptake of ACE inhibitors, ARBs, BBs and MRAs, in tandem with changes made to the site-specific formularies and practice guidelines from the year 2000–2015 may have confounded our findings. Our findings on prescribed doses and impact of guideline-directed treatment on outcomes should be read with care as the data are limited and selection bias may be present in a registry data.

Contraindication/intolerance rates reported by Heywood et al. [28] were used because individual patient data were not available, and we acknowledge that these may not have been representative. However, the study population was at least large and included patients with various mortality risk levels.

Finally, we also acknowledge that in clinical practice, withholding or withdrawing treatment or using low doses may be necessary in patients who develop hypotension, hyperkalaemia, decreased renal function or other side effects. Such instances do not represent suboptimal treatment.

Conclusion

Our results suggest that the use of evidence-based medications, namely ACE inhibitors, ARBs, BBs and MRAs, remains suboptimal among HFREF patients. In view of the complexity in managing HFREF patients, it is crucial for clinicians, policy makers and other healthcare stakeholders to consolidate efforts and re-examine the effectiveness of

current strategies in closing the treatment gap at the systems as well as individual levels.

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Compliance with ethical standards

Conflict of interest All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Appendix 1

See Table 7.

Appendix 2

See Table 8.

Appendix 3

See Table 9.

Appendix 4

See Table 10.

Appendix 5

See Table 11.

Table 7 Risk of bias assessment

Report	Study	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome	Incomplete outcome data	Selective reporting
Registry							
Fonarow et al. [35]	IMPROVE HF	Low	Low	Low	Low	Unclear	Low
Heywood et al. [28]		Low	Low	Low	Low	Unclear	Low
Heywood et al. [40]		Low	Low	Low	Low	Unclear	Low
Yancy et al. [9]		Low	Low	Low	Low	Unclear	Low
Frankenstein et al. [37]	HELUMA	Unclear	Low	Unclear	Unclear	Unclear	Low
Stålhammar et al. [47]	Swedish registry	Low	High	Low	Low	High	Unclear
Goldberg et al. [38]	CVRN	High	Low	High	Unclear	Unclear	Unclear
Schneider et al. [44]	NCDR-ICD	High	High	Low	Unclear	High	Unclear
Poelzl et al. [5]	HIR Austria	High	Low	High	Unclear	Unclear	Unclear
von Scheidt et al. [48]	EVITA-HF	Unclear	High	High	High	Unclear	Unclear
Anguita et al. [31]	VIDA-IC	High	High	High	High	Unclear	Unclear
Survey							
Lainščak et al. [8]	EHFS	High	Low	High	Low	High	Low
Lenzen et al. [41]		High	Low	High	Low	High	Low
Lenzen et al. [42]		High	Low	High	Low	High	Low
de Groote et al. [33]	Impact-Reco I and II	High	Low	High	High	Unclear	Unclear
de Groote et al. [34]		High	Low	High	High	Unclear	Unclear
Shah et al. [46]		High	Low	Low	Unclear	Unclear	Unclear
Franke et al. [36]		High	Low	Low	Unclear	Unclear	Unclear
McKee et al. [29]		High	High	High	Unclear	Unclear	Unclear
Scrutinio et al. [45]		High	Low	High	Unclear	Unclear	Low
Loh et al. [43]		High	Unclear	Low	Low	Unclear	Unclear
Cohen Solal et al. [32]	Future	High	High	High	High	Unclear	Unclear
Hebert et al. [39]		High	Low	Unclear	Unclear	Unclear	Unclear

IMPROVE HF Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting Registry, *HELUMA* University Hospital HEidelberg, the Klinikum LUdwigshafen and the TKH MAnnheim Registry, *CVRN* Cardiovascular Research Network registry, *NCDR-ICD* National Cardiovascular Data Registry, *HIR Austria* Austrian Heart Failure Registry, *EVITA-HF* The EVIdence-based TreAtment in Heart Failure Registry, *EHFS* EuroHeart Failure Survey

Table 8 Baseline characteristics in the selected registries

Characteristics/study	HELUMA [37]	IMPROVE HF [9, 28, 35, 40]	Swedish registry [47]	CVRN [38]	NCDR-ICD [44]	HIR Austria [5]	EVITA-HF [48]	VIDA-IC [31]
Country	Germany	United States	Sweden	United States	United States	Austria	Germany	Spain
Setting	2 outpatient cardiology clinics	167 outpatient cardiology practices	31 primary care centers	4 study sites	1300 facilities	Multicenter outpatient clinics nationwide	16 heart centers	115 outpatient specialists (cardiologists or internal medicine) clinics
Data collection method	Prospective	Prospective	Retrospective	Retrospective	Retrospective	Prospective	Prospective	Prospective
Data collection period	2001–2007	2005–2007	2005–2007	2005–2008	2006–2008	2006–2010	2009–2013	2011–2012
Inclusion criteria for EF (%)	≤40	≤35	≤40	≤40	≤35	≤40	≤40	≤40
N (No.)	1811	15,381	252	3914	45,392	1014	1853	1037
Age (year)	61.1	68.7	74.1	69.1	69.3	65.0	70.0	70.6
Male sex (%)	76.8	71.0	69	67.4	68.5	72.6	75.7	69.9
NYHA class (%)								
I	24.5	20.1	–	–	1.5	17.0	–	–
II	36.2	26.1	–	–	11.6	57.7	–	–
I/II	60.7	46.2	–	–	13.1	74.7	70.3	54.9
III	37.4	17.7	–	–	79.2	24.0	–	–
IV	1.8	2.5	–	–	7.6	1.3	–	–
III/IV	39.2	20.2	–	–	86.8	25.3	29.7	45.1
Previous HF hospitalisation (%)	–	–	–	–	–	–	64.6	83.0
LVEF (%)	30.0	25.5	–	–	–	–	–	33.7
SBP (mmHg)	–	120.0	–	132.8	–	128.0	–	127.0
Heart rate (/min)	75	72	–	–	–	73	–	73.9
Serum creatinine (mg/dL)	1.1	1.4	–	–	–	–	–	1.3
eGFR (mL/min/1.73 m^2)	81.0	–	–	66.4	–	74.0	–	–
Medical history (%)								
Hypertension	59.9	61.7	34.9	63.3	75.7	62.4	75.8	79.2
Ischemic heart disease	36.3	65.2	16.6	9.2	60.7	35.5	55.6	50.3
Previous myocardial infarction	–	39.4	44.0	–	47.4	31.3	40.0	43.5

Table 8 continued

Characteristics/ study	HELUMA [37]	IMPROVE HF [9, 28, 35, 40]	Swedish registry [47]	CVRN [38]	NCDR-ICD [44]	HIR Austria [5]	EVITA-HF [48]	VIDA-IC [31]
Atrial fibrillation	–	30.8	39.6	23.5	30.5	34.2	39.2	45.5
Stroke	–	–	5.9	4.8	13.9	–	9.3	13.7
Diabetes mellitus	23.1	34.0	23.0	17.9	40.5	28.1	38.7	44.0
Renal insufficiency	–	–	4.7	–	–	32.6	33.4	24.9
COPD/asthma	23.0	16.5	7.1	29.4	24.8	23.3	14.6	19.0
Background therapies (%)								
ACEI	–	–	76.7	–	64.2	–	–	56.2
ARB	–	–	25.7	–	18.6	–	–	36.1
ACEI/ARB	86.9	80.0	–	44.3	–	90.5	84.5	92.3
BB	86.8	86.0	86.3	53.4	87.4	87.8	85.9	76.6
MRA	48.6	36.0	53	21.2	–	42.7	47.0	66.4

HELUMA University Hospital HEidelberg, the Klinikum LUdwigshafen and the TKH MAnnheim Registry, *IMPROVE HF* Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting Registry, *CVRN* Cardiovascular Research Network registry, *NCDR-ICD* National Cardiovascular Data Registry, *HIR Austria* Austrian Heart Failure Registry, *EVITA-HF* The EVIdence-based TreAtment in Heart Failure Registry, *NYHA* New York Heart Association, *HF* heart failure, *LVEF* left ventricular ejection fraction, *SBP* systolic blood pressure, *eGFR* estimated glomerular filtration rate, *COPD* chronic obstructive pulmonary disease, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BB* beta blockers, *MRA* mineralocorticoid receptor antagonists

Table 9 Baseline characteristics in the selected surveys

Characteristics/ study	Shah et al. [46]	Franke et al. [36]	McKee et al. [29]	EHFS [8, 30, 41]	Scrutinio et al. [45]	Impact-Reco I [33, 34]	Impact-Reco II [33, 34]	Loh et al. [43]	FUTURE [32]
Country	United States	Germany	Scotland	24 European countries	Italy	France	France	United States	France
Setting	Single center	2 centers	Single center	115 hospitals	Single center	Private cardiologist clinics	Private cardiologist clinics	Single center	Private cardiologist clinics
Data collection period	1994–2008	1995–2005	1999–2001	2000–2001	2001–2009	2004–2005	2005–2006	2005–2010	2007–2008
Inclusion criteria for EF (%)	≤40	≤40	<40	<40	≤40	≤40	≤40	≤40	≤40
N (No.)	401	2023	400	3658	951	1917	1974	835	792
Age (year)	56.0	–	71.0	67.0	63.9	70.0	70.0	53.9	71.0
Male sex (%)	75.0	80.2	65.0	71.0	78.9	74.0	71.0	73.1	74.0
NYHA class (%)									
I	–	12.7	–	–	–	–	–	5.9	13.0
II	–	46.4	–	–	–	54.0	48.0	21.4	60.0
I/II	–	59.1	61.0	75.0	–	54.0	48.0	27.3	73.0
III	42.0	39.0	–	–	–	–	–	43.9	24.0
IV	45.0	1.9	–	–	–	–	–	28.7	3.0
III/IV	87.0	40.9	39.0	25.0	46.7	46.0	52.0	72.6	27.0
Previous HF hospitalisation (%)	–	–	–	–	–	–	–	–	100
LVEF (%) (mean)	24.0	–	–	33.0	28.1	33.0	33.0	22.3	–
SBP (mmHg)	–	–	–	–	–	126.0	126.0	104.0	–
Heart rate (/min)	–	–	–	–	–	73.0	73.0	82.0	–
Serum creatinine (mg/dL)	1.5	–	–	–	1.2	–	–	1.5	1.2
eGFR (mL/min/1.73 m^2)	–	–	–	–	69.1	–	–	–	–
Medical history (%)									
Hypertension	60.0	42.0	33.0	50.0	41.1	51.0	54.0	40.9	56.0
Ischemic heart disease	60.0	46.4	70.0	69.0	49.1	49.0	50.0	40.5	53.0
Previous myocardial infarction	–	–	–	53.0	–	36.0	36.0	–	–
Atrial fibrillation	–	18.5	38.0	23.0	21.4	24.0	24.0	37.9	29.0
Stroke	–	–	13.5	14.0	6.1	–	–	–	8.0
Diabetes mellitus	100.0	21.2	22.0	28.0	24.6	24.0	23.0	30.5	30.0
Renal insufficiency	57.2	10.5	4.0	6.0	–	13.0	11.0	–	37.0
COPD/asthma	–	–	14.3	–	16.5	20.0	21.0	–	18.0
Background therapies (%)									
ACEI	–	–	–	78.0	83.4	71.0	68.0	–	–
ARB	–	–	–	6.0	16.6	21.0	30.0	–	–
ACEI/ARB	87.0	96.2	73.0	82.0	–	91.0	93.0	78.8	83.0
BB	66.0	62.7	28.0	46.0	72.6	65.0	70.0	87.1	74.0
MRA	44.0	30.2	13.0	29.0	56.2	35.0	35.0	57.9	31.0

EHFS EuroHeart Failure Survey, *NYHA* New York Heart Association, *HF* heart failure, *LVEF* left ventricular ejection fraction, *SBP* systolic blood pressure, *eGFR* estimated glomerular filtration rate, *COPD* chronic obstructive pulmonary disease, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BB* beta blockers, *MRA* mineralocorticoid receptor antagonists

Table 10 US-based studies and ACC/AHA guideline recommendations for the treatment of patients with heart failure

Characteristics/study	Shah et al. [46]	IMPROVE HF [9, 28, 35, 40]	CVRN [38]	NCDR-ICD [44]	Loh et al. [43]	Total population	ACC/AHA 1995 [21]	ACC/AHA 2001 [22]	ACC/AHA 2005 [23]	ACC/AHA 2009 [24]
Data collection period	1994–2008	2005–2007	2005–2008	2006–2008	2005–2010		1. ACE inhibitors for all patients with significantly reduced LVEF unless contraindicated 2. BB for high risk patients after AMI; patients with dilated cardiomyopathy, unless contraindicated	1. ACE inhibitor for patients with stage A to C HF, unless contraindicated 2. BB in all patients with stage B to C HF, unless contraindicated 3. Spironolactone in patients with stage C HF and recent or current NYHA class IV symptoms, preserved renal function, and a normal potassium concentration, unless contraindicated 4. ARB in patients with stage C HF who are intolerant of ACE inhibitors; in addition or alternative to ACE inhibitors, unless contraindicated	1. ACE inhibitor for patients with stage A to C HF, unless contraindicated 2. BB in all patients with stage B to C HF, unless contraindicated 3. Addition of aldosterone antagonist in selected patients with stage C HF and NYHA class III-IV who can be carefully monitored for preserved renal function and normal potassium concentration. Cr: $\leq$ 2.5 mg/dL (men) or $\leq$ 2.0 mg/dL (women) and potassium $<$ 5.0 mEq/L 4. ARB in patients with stage A to C HF who are intolerant of ACE inhibitors; post-MI; in addition or alternative to ACE inhibitors as 1st line therapy, unless contraindicated	1. ACE inhibitor for patients with stage A to C HF, unless contraindicated 2. BB in all patients with stage B to C HF, unless contraindicated 3. Addition of aldosterone antagonist in selected patients with stage C HF and NYHA class III-IV who can be carefully monitored for preserved renal function and normal potassium concentration. Cr: $\leq$ 2.5 mg/dL (men) or $\leq$ 2.0 mg/dL (women) and potassium $<$ 5.0 mEq/L 4. ARB in patients with stage A to C HF who are intolerant of ACE inhibitors; post-MI; in addition or alternative to ACE inhibitors as 1st line therapy, unless contraindicated
Inclusion criteria for EF (%)	$\leq$40	$\leq$35	$\leq$40	$\leq$35	$\leq$40					
N (No.)	401	15,381	3914	45,392	835	65,923				
Age (year)	56.0	68.7	69.1	69.3	53.9	68.9 ± 2.2				
Male sex (%)	75.0	71.0	67.4	68.5	73.1	69.1 ± 1.4				
NYHA class (%)										
I	–	20.1	–	1.5	5.9	6.2 ± 9.8				
II	–	26.1	–	11.6	21.4	15.4 ± 7.7				
I/II	–	46.2	–	13.1	27.3	21.6 ± 17.5				
III	42.0	17.7	–	79.2	43.9	63.2 ± 30.7				
IV	45.0	2.5	–	7.6	28.7	6.9 ± 5.3				
III/IV	87.0	20.2	–	86.8	72.6	70.1 ± 33.1				
LVEF (%)	24.0	25.5	–	–	22.3	25.3 ± 0.9				
SBP (mmHg)	–	120.0	132.8	–	104.0	121.8 ± 7.7				
Heart rate (/min)	–	72.0	–	–	82.0	72.5 ± 3.1				
Serum creatinine (mg/dL)	1.5	1.4	–	–	1.5	1.4 ± 0.0				
eGFR (mL/min/1.73 m^2)	–	–	66.4	–	–	66.4				
Medical history (%)										
Hypertension	60.0	61.7	63.3	75.7	40.9	71.2 ± 8.0				
Ischemic heart disease	60.0	65.2	9.2	60.7	40.5	58.4 ± 14.2				
Previous myocardial infarction	–	39.4	–	47.4	–	45.4 ± 4.9				
Atrial fibrillation	–	30.8	23.5	30.5	37.9	30.2 ± 2.2				
Stroke	–	–	4.8	13.9	–	13.2 ± 3.5				
Diabetes mellitus	100.0	34.0	17.9	40.5	30.5	37.9 ± 8.4				
Renal insufficiency	57.2	–	–	–	–	57.2				
COPD/asthma	–	16.5	29.4	24.8	–	23.1 ± 4.7				
Background therapies (%)										
ACEI	–	–	–	64.2	–	64.2				

Table 10 continued

Characteristics/study	Shah et al. [46]	IMPROVE HF [9, 28, 35, 40]	CVRN [38]	NCDR-ICD [44]	Loh et al. [43]	Total population	ACC/AHA 1995 [21]	ACC/AHA 2001 [22]	ACC/AHA 2005 [23]	ACC/AHA 2009 [24]
ARB	–	–	–	18.6	–	18.6				
ACEI/ARB	87.0	80.0	44.3	–	78.8	73.3 ± 16.3				
BB	66.0	86.0	53.4	87.4	87.1	84.9 ± 9.1				
MRA	44.0	36.0	21.2	–	57.9	34.2 ± 8.9				

IMPROVE HF Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting Registry, *CVRN* Cardiovascular Research Network registry, *NCDR-ICD* National Cardiovascular Data Registry, *ACC/AHA* American College of Cardiology Foundation/American Heart Association, *NYHA* New York Heart Association, *HF* heart failure, *LVEF* left ventricular ejection fraction, *SBP* systolic blood pressure, *eGFR* estimated glomerular filtration rate, *COPD* chronic obstructive pulmonary disease, *ACE inhibitors* angiotensin-converting enzyme inhibitors, *BB* beta blockers, *ARB* angiotensin receptor blockers, *MRA* mineralocorticoid receptor antagonists, *MI* myocardial infarction, *Cr* serum creatinine

Table 11 Europe-based studies and ESC guideline recommendations for the treatment of patients with heart failure

Characteristics/study	Franke et al. [36]	EHFS [8, 41, 42]	HELUMA [37]	Scrutinio et al. [45]	Impact-Reco I [33, 34]	Impact-Reco II [33, 34]	Swedish registry [47]	HIR Austria [5]
Data collection period	1995–2005	2000–2001	2001–2007	2001–2009	2004–2005	2005–2006	2005–2007	2006–2010
Inclusion criteria for EF (%)	≤40	<40	≤40	≤40	≤40	≤40	≤40	≤40
N (No.)	2023	3658	1811	951	1917	1974	252	1014
Age (year)	–	67.0	61.1	63.9	70.0	70.0	74.1	65.0
Male sex (%)	80.2	71.0	76.8	78.9	74.0	71.0	69.0	72.6
NYHA class (%)								
I	12.7	–	24.5	–	–	–	–	17.0
II	46.4	–	36.2	–	54.0	48.0	–	57.7
I/II	59.1	75.0	60.7	–	54.0	48.0	–	74.7
III	39.0	–	37.4	–	–	–	–	24.0
IV	1.9	–	1.8	–	–	–	–	1.3
III/IV	40.9	25.0	39.2	46.7	46.0	52.0	–	25.3
Previous HF hospitalisation (%)	–	–	–	–	–	–	–	–
LVEF (%)	–	33.0	30.0	28.1	33.0	33.0	–	–

Table 11 continued

Characteristics/study	Franke et al. [36]	EHFS [8, 41, 42]	HELUMA [37]	Scrutinio et al. [45]	Impact-Reco I [33, 34]	Impact-Reco II [33, 34]	Swedish registry [47]	HIR Austria [5]
SBP (mmHg)	–	–	–	–	126.0	126.0	–	128.0
Heart rate (/min)	–	–	75.0	–	73.0	73.0	–	73.0
Serum creatinine (mg/dL)	–	–	1.1	1.2	–	–	–	–
eGFR (mL/min/1.73 m^2)	–	–	81.0	69.1	–	–	–	74.0
Medical history (%)								
Hypertension	42.0	50.0	59.9	41.1	51.0	54.0	34.9	62.4
Ischemic heart disease	46.4	69.0	36.3	49.1	49.0	50.0	16.6	35.5
Previous myocardial infarction	–	53.0	–	–	36.0	36.0	44.0	31.3
Atrial fibrillation	18.5	23.0	–	21.4	24.0	24.0	39.6	34.2
Stroke	–	14.0	–	6.1	–	–	5.9	–
Diabetes mellitus	21.2	28.0	23.1	24.6	24.0	23.0	23.0	28.1
Renal insufficiency	10.5	6.0	–	–	13.0	11.0	4.7	32.6
COPD/asthma	–	–	23.0	16.5	20.0	21.0	7.1	23.3
Background therapies (%)								
ACEI	–	78.0	–	83.4	71.0	68.0	76.7	–
ARB	–	6.0	–	16.6	21.0	30.0	25.7	–
ACEI/ARB	96.2	82.0	86.9	–	91.0	93.0	–	90.5
BB	62.7	46.0	86.8	72.6	65.0	70.0	86.3	87.8
MRA	30.2	29.0	48.6	56.2	35.0	35.0	53.0	42.7

Table 11 continued

Characteristics/ study	FUTURE [32]	EVITA-HF [48]	VIDA-IC [31]	Total population	ESC 2001 [25]	ESC 2005 [26]	ESC 2008 [27]	ESC 2012 [2]
Data collection period	2007–2008	2009–2013	2011–2012		1. ACE inhibitors in asymptomatic and symptomatic patients with reduced LVEF, i.e., <40–45 % (1st line treatment), unless contraindicated 2. BB in all patients in NYHA class II to IV, on standard treatment, including diuretics and ACE inhibitors, unless contraindicated. In patients with LVSD, with or without symptomatic HF, following an AMI long-term BB is recommended in addition to ACE inhibition 3. Spironolactone in advanced HF (NYHA III-IV), in addition to ACE inhibition and diuretics, unless contraindicated 4. ARB could be considered in patients who do not tolerate ACE inhibitors; in combination with ACE inhibitors	1. ACE inhibitors are recommended as 1st line in patients with a reduced LVEF < 40–45 % with or without symptoms, unless contraindicated 2. BB in all patients in NYHA class II to IV, on standard treatment, including diuretics and ACE inhibitors, unless contraindicated. In patients with LVSD, with or without symptomatic HF, following an AMI long-term BB is recommended in addition to ACE inhibition 3. Aldosterone antagonists are recommended in addition to ACE inhibitors, BB and diuretics in advanced HF (NYHA III–IV) with systolic dysfunction; in addition to ACE inhibitors and BB in HF after MI with LVSD and signs of HF or diabetes 4. ARB could be considered in patients who do not tolerate ACE inhibitors; in combination with ACE inhibitors	1. Unless contraindicated or not tolerated, an ACEI should be used in all patients with symptomatic HF and a LVEF ≤ 40 % 2. Unless contraindicated or not tolerated, a BB should be used in all patients with symptomatic HF and an LVEF ≤ 40 % 3. Unless contraindicated or not tolerated, the addition of a low-dose of an aldosterone antagonist should be considered in all patients with an LVEF ≤ 35 % and severe symptomatic HF, i.e., currently NYHA functional class III or IV, in the absence of hyperkalemia and significant renal dysfunction 4. Unless contraindicated or not tolerated, an ARB is recommended in patients with HF and an LVEF ≤ 40 % who remain symptomatic despite optimal treatment with an ACEI and BB, unless also taking an aldosterone antagonist	1. ACE inhibitor is recommended, in addition to a BB, for all patients with an EF ≤ 40 % 2. BB is recommended, in addition to an ACE inhibitor (or ARB if ACE inhibitor not tolerated), for all patients with an EF ≤ 40 % 3. MRA is recommended for all patients with persisting symptoms (NYHA class II-IV) and an EF ≤ 35 %, despite treatment with an ACE inhibitor (or an ARB if ACE inhibitor is not tolerated) and a BB 4. ARB is recommended in patients with an EF ≤ 40 % and (1) unable to tolerate an ACE inhibitor because of cough (patient should also receive a BB and an MRA); or (2) persisting symptoms (NYHA class II-IV) despite treatment with an ACE inhibitor and a BB who are unable to tolerate an MRA
N (No.)	792	1853	1037	17,282				
Age (year)	71.0	70.0	70.6	67.7 ± 3.4				
Male sex (%)	74.0	75.7	69.9	74.1 ± 3.5				
NYHA class (%)								
I	13.0	–	–	17.3 ± 6.0				
II	60.0	–	–	48.7 ± 8.2				
I/II	73.0	70.3	54.9	58.9 ± 19.8				
III	24.0	–	–	60.8 ± 9.4				
IV	3.0	–	–	1.9 ± 0.6				
III/IV	27.0	29.7	45.1	35.6 ± 7.6				
Previous HF hospitalisation (%)	100.0	64.6	83	77.4 ± 17.4				
LVEF (%)	–	–	33.7	32.2 ± 1.8				
SBP (mmHg)	–	–	127.0	126.5 ± 0.9				
Heart rate (/min)	–	–	73.9	73.6 ± 0.9				
Serum creatinine (mg/dL)	1.2	–	1.3	1.2 ± 0.1				
eGFR (mL/min/ 1.73 m^2)	–	–	–	76.1 ± 6.1				
Medical history (%)								
Hypertension	56.0	75.8	79.2	55.5 ± 12.0				
Ischemic heart disease	53.0	55.6	50.3	51.4 ± 11.9				
Previous myocardial infarction	–	40.0	43.5	42.4 ± 8.4				
Atrial fibrillation	29.0	39.2	45.5	27.3 ± 8.5				
Stroke	8.0	9.3	13.7	11.3 ± 3.4				

Table 11 continued

Characteristics/study	FUTURE [32]	EVITA-HF [48]	VIDA-IC [31]	Total population	ESC 2001 [25]	ESC 2005 [26]	ESC 2008 [27]	ESC 2012 [2]
Diabetes mellitus	30.0	38.7	44.0	27.6 ± 6.7				
Renal insufficiency	37.0	33.4	24.9	16.6 ± 11.8				
COPD/asthma	18.0	14.6	19.0	19.3 ± 3.6				
Background therapies (%)								
ACEI	–	–	56.2	72.8 ± 8.2				
ARB	–	–	36.1	18.5 ± 12.0				
ACEI/ARB	83.0	84.5	92.3	88.3 ± 5.3				
BB	74.0	85.9	76.6	69.0 ± 15.3				
MRA	31.0	47.0	66.4	39.5 ± 11.4				

EHFS EuroHeart Failure Survey, *HELUMA* University Hospital HEidelberg, the Klinikum LUdwigshafen and the TKH MAnnheim Registry, *HIR Austria* Austrian Heart Failure Registry, *EVITA-HF* The EVIdence-based TreAtment in Heart Failure Registry, *ESC* European Society of Cardiology, *NYHA* New York Heart Association, *HF* heart failure, *LVEF* left ventricular ejection fraction, *SBP* systolic blood pressure, *eGFR* estimated glomerular filtration rate, *COPD* chronic obstructive pulmonary disease, *ACE inhibitors* angiotensin-converting enzyme inhibitors, *BB* beta blockers, *ARB* angiotensin receptor blockers, *MRA* mineralocorticoid receptor antagonists, *MI* myocardial infarction, *LVSD* left ventricular systolic dysfunction

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