Effects of European Society of Cardiology guidelines on medication profiles after hospitalization for heart failure in 22,476 Dutch patients: from 2001 until 2015

Willemien J. Kruik-Kollöffel [1,2] · Gerard C.M. Linssen [3] · H. Joost Kruik [3] · Kris L.L. Movig [4] · Edith M. Heintjes [5] · Job van der Palen [6,7]

Abstract

Prescriber adherence to guideline-recommended medication in patients with heart failure (HF) in clinical practice is suboptimal. We analyzed how evolving guideline recommendations influenced medication profiles after a first HF hospitalization. We extracted medication profiles from the Dutch PHARMO Database Network for 22,476 patients with a diagnosis of HF at hospital discharge between 2001 and 2015. The percentage of patients prescribed the combination of a beta-blocker (BB) and an angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB) increased from 24 to approximately 45% within this 15-year period. The percentage of patients who also used a mineralocorticoid-receptor antagonist (MRA) reached approximately 20%. The probability of being prescribed these combinations decreased with increasing age. As a consequence of the policy change in the ESC guideline 2001, the use of BB increased from less than 40% in 2001 to about 70% by 2015. The percentage of patients prescribed an ACEI and/or an ARB, an MRA, or a diuretic was about stable, at respectively 63%, 37%, and 82%. Although the 2012 ESC guideline also advised MRA in the New York Heart Association (NYHA) class II, there was no increase in MRA prescriptions. Compliance with the ESC guidelines varied for the individual recommendations. Remarkably, there was no significant increase in MRA prescriptions. At the same time, developments were demonstrated, which were not instigated by the guidelines, like the shift from ACEI to ARB. Although the exact HF classification of our patients was unknown, given a relatively stable case mix, our data provide insight into "real-world" pharmacological management.

Keywords Heart failure · Drug therapy · Pharmacoepidemiology · Guideline adherence · Practice guideline · Health plan implementation

✉ Willemien J. Kruik-Kollöffel
w.kruik@sxb.nl

1   Department of Clinical Pharmacy, Saxenburgh Group, P.O. Box 1, 7770 AA Hardenberg, the Netherlands

2   Department of Clinical Pharmacy, Hospital Group Twente, Almelo and Hengelo, the Netherlands

3   Department of Cardiology, Hospital Group Twente, Almelo and Hengelo, the Netherlands

4   Department of Clinical Pharmacy, Medisch Spectrum Twente, Enschede, the Netherlands

5   PHARMO Institute, Utrecht, the Netherlands

6   Medical School Twente, Medisch Spectrum Twente, Enschede, the Netherlands

7   Department of Research Methodology, Measurement and Data Analysis, University of Twente, Enschede, the Netherlands

Introduction

Despite substantial advances of medical therapy in the past two decades, morbidity and mortality of patients with heart failure (HF) remain high [1]. Specific disease-modifying HF drugs have been incorporated into the European (ESC) practice guidelines. However, use of advocated medication in real-world clinical practice is still suboptimal [2–6]. Jefferies et al. [7] talk about the concept of the "therapeutic inertia". Identifying facilitators and barriers to implementation are important to improve the penetration of guidelines and are a priority for the heart failure field to make a significant step forward. Analyses of real-world data of HF therapies may enhance our understanding of optimal medical therapy.

Angiotensin-converting-enzyme inhibitors (ACEI) are important in the treatment of HF. The key evidence for the use of ACEI is outlined in the 2016 ESC guidelines [1], a firm

position they had acquired already in the ESC guideline 1997 [8]. The angiotensin-receptor blockers (ARB) were first mentioned in the ESC guideline 2001 [9] and were recommended since then for patients unable to tolerate an ACEI. Beta-blockers (BB) are recommended since the ESC guidelines 2001 and reduce mortality and morbidity in symptomatic patients with HF with reduced ejection fraction (HFrEF), even on top of treatment with an ACEI [1, 9]. Spironolactone, a mineralocorticoid-receptor antagonist (MRA), was only mentioned in the section of diuretics in the 1997 guideline [8]. In the guidelines of 2001, 2005, and 2008, it obtained an independent position in the treatment of patients with HF NYHA III and IV [9–11]. In the 2012 guidelines [12], due to the EMPHASIS-HF trial [13], MRA was also advised in symptomatic HF patients NYHA class II [1]. These historic developments have led to ACEI/ARB, BB, and MRA nowadays forming the cornerstone of pharmacological treatment in patients with HFrEF [1]. According to the 2016 ESC guideline, only slightly fewer patients with HF with preserved ejection fraction (HFpEF) and HF with mid-range ejection fraction (HFmrEF) appear to receive ACEI/ARB, BB, and MRA [1]. In HFpEF, according to the US guideline for HF [14], BB, ACEI/ARB, and MRA could be prescribed to a considerable proportion of these patients. Diuretics are the cornerstone of management of congestion, despite the emergence of ACEI, BB, and MRA, although evidence of large, well-controlled clinical trials is lacking.

We reviewed the penetration of guidelines on the basis of the prescription of evidence-based medication in a large cohort of patients at discharge after a first hospital admission for HF in the Netherlands between 2001 and 2015, a period in which major progress is made in the treatment of HF. We analyzed the relationship between guideline-directed recommendations over a 15-year period and actual trends or changes in medication after a first HF hospitalization. The focus was on ACEI/ARB, BB, MRA, and diuretics. Although the exact HF classification of our patients was unknown, our large database still provides a valid insight in how the guidelines with respect to HF medical therapy were adhered to from 2001 until 2015. After all, according to the 2016 ESC guideline, only slightly fewer patients with HFpEF and HFmrEF appear to receive ACEI/ARB, BB, MRA, and diuretics [1]. Our specific questions are presented in Table 1.

Methods

We extracted from the PHARMO Database Network 22,476 patients in the Hospitalization Database with a diagnosis of HF or hypertensive heart disease with (congestive) HF at hospital discharge with their medication from the linked Out-Patient Pharmacy Database, in the Netherlands, between 2001 and 2015. The PHARMO Database Network is a population-based, medical record linkage system covering more than four million Dutch inhabitants. Its linkage algorithms have been validated and the Database Network forms a representative sample of the Dutch population [15, 16].

The linked Hospitalization Database of PHARMO comprises hospital admissions for more than 24 h and admissions for less than 24 h for which a bed is required. PHARMO has access to data of over 80% of the hospitals in the Netherlands from the national Dutch Hospital Data Foundation. The records include information on hospital admission and discharge dates, discharge diagnoses, and procedures. Primary diagnoses are coded in a standardized way after discharge by trained employees according to the WHO International Classification of Diseases.

Patient population

We included patients with a first discharge diagnosis of HF (ICD-9428; ICD-10 I50) or hypertensive heart disease with (congestive) HF (ICD-9402; ICD-10 I11.0) between 2001 and 2015. Patients in both diagnosis groups were clustered for analyses. Patients with rheumatic heart disease with HF (ICD-9398.91; ICD-10 I09.81) or hypertensive heart and renal disease with HF (some subgroups of ICD-10 I13) represented less than 0.05% within this group and were therefore excluded. For a planned admission for HF, i.e., pacemaker implantation, different ICD codes are applicable. It was considered to be the first admission for HF if there was no known previous admission in at least 3 years, assuming one expects a patient in the Dutch health care system to be admitted to the same hospital with a rehospitalization for HF. Only patients 18 years and older were included. Information on HF etiology, comorbidities, left ventricular function, e.g., HFrEF or HFpEF or functional class (NYHA) was not available.

Prescription data were retrieved from the linked Out-Patient Pharmacy Database of PHARMO, which comprises drug dispenses from primary and secondary care prescriptions, dispensed by outpatient pharmacies, representing 3.8 million residents throughout the Netherlands. Drug dispenses are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System. Healthcare coverage regarding the reimbursement of concerned drugs was similar for all Dutch citizens. Dispenses from 4 months before HF hospital admission until 4 months after discharge were collected.

Hospital data were available up to and including 2015. For each patient, periods of uninterrupted use around the time of the hospitalization were formed prior to analysis, based on periods of uninterrupted data availability for both pharmacy and hospitalization data. Completeness of available data was influenced by changes in data governance per hospital and pharmacy. It is relevant to know that in the Netherlands, healthcare coverage regarding the reimbursement of

Table 1 Heart failure treatment guidelines of the European Society of Cardiology over the years 1997–2016

	1997 [8]	2001 [9]	2005 [10]	2008 [11]	2012 [12]	2016 [1]
Prescribe ACEI?	ACEIs should be considered as first-line therapy in patients with a reduced LVEF who present with complaints of fatigue or mild dyspnea on exertion without signs and symptoms of volume overload.	ACEIs are recommended as first-line therapy in patients with a reduced left ventricular systolic function expressed as a subnormal ejection fraction, i.e., < 40–45%.	ACEIs are recommended as first-line therapy in patients with a reduced left ventricular systolic function expressed as a subnormal ejection fraction, i.e., < 40–45% with or without symptoms.	Unless contraindicated or not tolerated, an ACEI should be used in all patients with symptomatic HF and a LVEF ≤ 40%.	A beta-blocker and an ACEI should both be started as soon as possible after diagnosis of HFrEF.	ACEIs have been shown to reduce mortality and morbidity in patients with HFrEF and are recommended unless contraindicated or not tolerated in all symptomatic patients.
ARB instead of ACEI?	Not mentioned	ARBs could be considered in patients who do not tolerate ACEIs for symptomatic treatment. However, it is unclear whether ARBs are as effective as ACEIs for mortality reduction.	ARB can be used as an alternative to ACEI in symptomatic patients intolerant to ACEIs to improve morbidity and mortality.	An ARB is recommended as an alternative in patients intolerant of an ACEI. In these patients, an ARB reduces the risk of death from a cardiovascular cause or hospital admission for worsening HF.	Recommended to reduce the risk of HF hospitalization and the risk of premature death in patients with an LVEF ≤ 40% and unable to tolerate an ACEI because of cough.	An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACEI.
ACEI as well as ARB?	Not mentioned	In combination with ACEI, ARBs may improve HF symptoms and reduce hospitalizations for worsening HF.	ARBs can be considered in combination with ACEIs in patients who remain symptomatic, to reduce mortality.	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 beta-blocker, unless also taking an aldosterone antagonist.	Recommended to reduce the risk of HF hospitalization in patients with an LVEF ≤ 40% and persisting symptoms (NYHA class II–IV) despite treatment with an ACEI and a beta-blocker who are unable to tolerate an MRA.	The combination of ACEI/ARB should be restricted to symptomatic HFrEF patients receiving a beta-blocker who are unable to tolerate an MRA, and must be used under strict supervision.
Prescribe beta-blocker?	The effect of beta-blockade in HF has been studied predominantly in idiopathic dilated cardiomyopathy and therefore the recommendations for the use of beta-blockers in HF are currently limited to these patients.	Beta-blocking agents are recommended for the treatment of all patients with stable, mild, moderate, and severe HF from ischemic or non-ischemic cardiomyopathies and reduced LVEF, in NYHA class II to IV, on standard treatment, including diuretics and ACEIs, unless	Beta-blockers should be considered for the treatment of all patients (in NYHA class II–IV) with stable, mild, moderate, and severe HF from ischemic or non-ischemic cardiomyopathies and reduced LVEF on standard treatment, including diuretics, and ACEIs, unless there is a contraindication.	Unless contraindicated or not tolerated, a beta-blocker should be used in all patients with symptomatic HF and an LVEF ≤ 40%.	A beta-blocker and an ACEI should both be started as soon as possible after diagnosis of HFrEF.	Beta-blockers have been shown to improve survival in patients with HFrEF and are recommended for the treatment of every patient with HFrEF, unless contraindicated or not tolerated.

Table 1 (continued)

	1997 [8]	2001 [9]	2005 [10]	2008 [11]	2012 [12]	2016 [1]
Which beta-blocker?	Beta-blocking agents studied in placebo-controlled large trials and therefore recommended: metoprolol, carvedilol, bisoprolol.	there is a contraindication. Although a reduction in mortality and hospitalization has been demonstrated with several beta-blockers in chronic HF, a class-effect has not been established.	Differences in clinical effects may be present between different beta-blockers in patients with HF. Accordingly, only bisoprolol, carvedilol, metoprolol succinate, and nebivolol can be recommended.	Indications, based upon patients enrolled in the RCTs. Commonly used: metoprolol, carvedilol, bisoprolol, nebivolol.	Evidence-based doses of disease-modifying drugs used in key randomized trials in HF: metoprolol, carvedilol, bisoprolol, nebivolol.	Which beta-blocker and what dose: metoprolol, carvedilol, bisoprolol, nebivolol.
Prescribe MRA?	Section diuretics: In severe HF the addition of low-dose spironolactone to ACEI and diuretics may be useful in the absence of hypokalemia.	Aldosterone antagonism is recommended in advanced HF (NYHA III-IV), in addition to ACEI and diuretics to improve survival and morbidity	Aldosterone antagonists are recommended in addition to ACEIs, beta-blockers, and diuretics in advanced HF (NYHA III–IV) with systolic dysfunction to improve survival and morbidity.	Unless contraindicated or not tolerated, the addition of a low-dose of an aldosterone antagonist should be considered in all patients with an LVEF $\leq 35\%$ and severe symptomatic HF, i.e., currently NYHA functional class III or IV, in the absence of hyperkalemia and significant renal dysfunction.	Potentially all patients with persisting symptoms (NYHA class II-IV) and an LVEF $\leq 35\%$ despite treatment with an ACEI (or ARB) and beta-blocker.	Potentially all patients with persisting symptoms (NYHA class II–IV) and an LVEF $\leq 35\%$ despite treatment with an ACEI (or ARB) and a beta-blocker.
Eplerenone instead of spironolactone?	Not mentioned	The new selective aldosterone receptor antagonist eplerenone, with a lower affinity for androgen and progesterone receptors than spironolactone, may reduce the risk of gynecomastia, but needs further evaluation. Ongoing trials will assess the effect of eplerenone on morbidity and mortality.	Not mentioned	Outside the post-infarction indication, the main indication for eplerenone is in men with breast discomfort and/or enlargement caused by spironolactone.	Male patients treated with spironolactone may uncommonly develop breast discomfort or gynecomastia (switching to eplerenone should be considered).	Male patients treated with spironolactone may uncommonly develop breast discomfort or gynecomastia (switching to eplerenone should be considered).
Which type of diuretic?	Mild HF can be treated with a thiazide diuretic, but as HF worsens, a loop diuretic is usually	Mild HF can be treated with a thiazide diuretic, but as HF worsens, a loop diuretic is usually	Initial diuretic treatment: loop diuretics or thiazides. Insufficient response:	In general, a loop diuretic will be required in moderate or severe HF. A thiazide may be	Loop diuretics are usually preferred to thiazides in HFrEF although they act synergistically	Thiazide diuretics can be used in patients with preserved renal function and mild symptoms of

Table 1 (continued)

	1997 [8]	2001 [9]	2005 [10]	2008 [11]	2012 [12]	2016 [1]
	necessary. In severe HF, thiazides have a synergistic effect with loop diuretics and may be used in combination. It is probable that this combination is superior in terms of efficacy or adverse effects, to increasing the dose of a loop diuretic.	necessary. In severe HF, thiazides have a synergistic effect with loop diuretics and may be used in combination. Patients with severe HF often require increasing doses of loop diuretics.	combine loop diuretics and thiazides.	used in combination with loop diuretics for resistant edema, but with caution. Most patients are prescribed loop diuretics rather than thiazides due to the higher efficiency of induced diuresis and natriuresis. Insufficient response or diuretic resistance: combine loop diuretic and thiazide/metolazone.	and the combination may be used (usually on a temporary basis) to treat resistant edema.	congestion. However, the majority patients require loop diuretics (or combined with a thiazide diuretic and an MRA) due to the severity of HF symptoms and steadily deteriorating kidney function.
Furosemide or bumetanide?	Not mentioned	At equivalent doses, all loop diuretics produce a comparable increase in urine output.	Not mentioned	Insufficient response or diuretic resistance: consider switching from furosemide to bumetanide or torasemide.	Insufficient diuretic response/diuretic resistance: consider switching from furosemide to bumetanide or torasemide.	Insufficient diuretic response/diuretic resistance: consider switching from furosemide to bumetanide or torasemide.

HF heart failure, *ACEI* angiotensin-converting-enzyme inhibitor, *MRA* mineralocorticoid-receptor antagonist

HFrEF heart failure with reduces ejection fraction, *ARB* angiotensin-receptor blocker, *LVEF* left ventricular ejection fraction

concerned drugs or hospitalizations is similar for all Dutch citizens.

Data processing and statistical analysis

The major developments in the ESC guidelines with regard to HF medical treatment during the study period are presented in Table 1. The recommendations of each class of disease-modifying HF drug and diuretics have been specified from 1997 until 2016.

Dispensing data were used as a proxy variable for prescribing and usage of drugs. Analyses of drug use were performed on the lowest available level of the ATC classification 2017, preferably the 5th level (chemical substance). Alterations in ATC classifications during our study period were accounted for. Based on the last dispensing of a drug before hospital admission and the first dispensing after discharge, the medication profile on discharge was established, accepting a 30-day gap between consecutive dispensings as uninterrupted use of a specific class of drugs [17]. A new drug started at discharge should be dispensed between 1 day before and 7 days after discharge to be assigned to the medication profile on discharge. Dispensings with ATC group V ("Various") were deleted, with the exception of V03 (i.e., "all other therapeutic products", like iron-chelating agents and drugs for treatment of hypercalcemia). Only patients with drug dispenses before as well as after admission were included, including at least one cardiovascular drug (ATC group C, cardiovascular system) at discharge.

Characteristics of the study cohort are presented as means (SD) or medians (interquartile range) for continuous variables and frequencies (%) for categorical variables.

The observational research file was created using SAS programs organized within SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC) and conducted under Windows using SAS version 9.4. Statistical analysis was performed using SPSS software version 24 (IBM SPSS Statistics, Armonk, NY, USA). Descriptive statistics were used to summarize the characteristics of the study cohort. To assess the relation between age and the probability to follow the guidelines, logistic regression was used.

Results

Baseline characteristics of our cohort, comprising 22,476 Dutch HF patients over a 15-year period are presented in Table 2. The mean age was 76.8 years, 50.9% were females. The percentage of females was lowest in 2008 (48.5%) and highest in 2015 (54.2%), and there seems to be a slight increase in the percentage of females over time. The mean number of drugs prescribed on discharge was 7.6, and was lowest in 2001 (mean 6.9) and highest in 2011 (mean 8.0). The most prescribed drugs (2nd level ATC group) were diuretics in

Table 2 Characteristics of the study cohort

Patient characteristics	
Total number of patients	22,476
Number of patients/study year (SD)	1498 (455)
Age: mean (SD)	76.8 (10.9)
Gender: female %	50.9%
Characteristics of the hospital admission	
Discharge diagnosis:	
Heart failure (HF)	22,241
Hypertensive heart disease with (congestive) HF	235
Length of stay in days: median (interquartile range)	6 (3.0–11.0)
Medication profile on discharge	
Number of drugs (SD)	7.57 (3.56)
ACEI/ARB	62.7%
Beta-blocker	59.6%
HF beta-blocker	51.2%
MRA	37.0%
Diuretics excluding MRA	81.8%
Diuretics including MRA	83.8%
Beta-blocker + ACEI/ARB	40.4%
Beta-blocker + ACEI/ARB + MRA	17.1%
Top 10 prescribed therapeutic subgroups	
ATC group	
Diuretics (C03)	82.1%
Antithrombotic agents (B01)	66.3%
Agents acting on the renin-angiotensin system (C09)	62.8%
Beta-blocking agents (C07)	59.6%
Cardiac therapy (C01)	46.8%
Drugs for acid-related disorders (A02)	39.1%
Lipid modifying agents (C10)	38.9%
Psycholeptics (N05)	26.9%
Drugs used in diabetes (A10)	25.5%
Drugs for obstructive airway diseases (R03)	20.1%

HF beta-blockers: bisoprolol, carvedilol, metoprolol, or nebivolol

ACEI/ARB angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB)

MRA mineralocorticoid-receptor antagonist

SD standard deviation

82.1% of the patients (C03), antithrombotic agents in 66.3% (B01), and agents acting on the renin-angiotensin system in 62.8% (C09). Drugs for acid-related disorders (A02) were the most prescribed non-cardiovascular drugs. The median length of hospital stay decreased from 8 to 5 days, while the mean age on admission increased from 75.3 to 78.6 years (SD 10.9 years). The prescription rates for all four classes of drugs are shown in Fig. 1.

Figure 2 shows that 63% of the patients were prescribed an ACEI, an ARB, or both. The contribution of ARB increased, while the percentage of the patients using ACEI as well as ARB increased until 2008 and decreased thereafter, not reaching 3% of the patients.

The use of BB increased from less than 40% in 2001 to about 70% at the end of our study period, as shown in Fig. 3. The BB with a market authorization for HF and mentioned in the ESC guidelines dominated, in particular metoprolol. Sotalol accounted for 4.6% and other BB for only 4.1%.

During 2001–2015, a stable 37% of the patients used MRA, which did not change during that 15-year period. In 2001, the percentage was 34.6%, in 2015 36.5%, range over the 15-year period 33.5–41.8%. Eplerenone, introduced in the Netherlands in 2004, was prescribed to 2–4% of the patients.
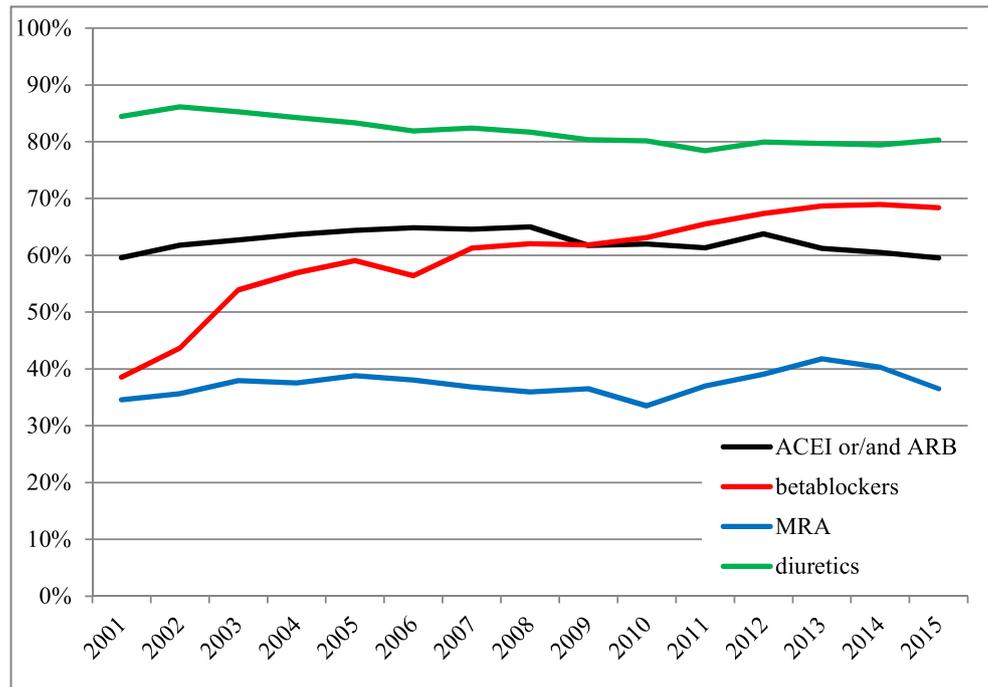
More than 80% of the patients were prescribed a diuretic drug. The loop diuretic was prescribed most frequently in 71.8% of the patients as monotherapy and to 4.9% of the patients combined with thiazides (low-ceiling diuretics) and/or a potassium-sparing agent. Other diuretics or combinations of diuretics were prescribed considerably less. The use of furosemide versus bumetanide, the only two loop diuretics available in the Netherlands during the study period, was stable, about 65% and 35%, respectively.

The percentage of patients prescribed a BB and an ACEI or ARB, the first step in the treatment of symptomatic HFrEF according to the guideline 2016 [1], increased from 24% to approximately 45%, see Fig. 4. The percentage of patients who also used an MRA reached approximately 20%. Data for men and women were very similar. With each additional year of age, the chance of being prescribed ACEI/ARB and BB decreased by 2%, while being prescribed an MRA as well decreased by 1.5% with each year that patients are older, see Fig. 5.

Discussion

Our study showed the evolving pattern over 15 years in the medication profile at discharge after a first hospitalization for HF in the Netherlands. This reflects the developments in evidence-based HF medication and the ESC guidelines, respectively. Other studies covered a (much) shorter time frame (3–12 years) and were (much) smaller (N = 1825–16,052) [2–6, 18]. The mean age, gender distribution and co-

Fig. 1 Prescription of groups of heart failure medication. ACEI angiotensin-converting-enzyme inhibitor, ARB angiotensin-receptor blocker, MRA mineralocorticoid-receptor antagonist

Angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers

In our cohort, the percentage of patients prescribed an ACEI and/or an ARB did not rise considerably above 60% during the 15-year study period. However, the ratio of ACEI and ARB did change: more patients were prescribed an ARB instead of an ACEI in the course of the years, whereas the position of ARB in the guidelines from 2001 until 2016 remained unchanged "in patients unable to tolerate ACEI". In 2001, 13% of ACEI and/or ARB were for an ARB, while this percentage has risen to 35% in 2015. A similar trend was seen in the Dutch population in general, as these numbers rose from 28 to 45% [19]. The combination of ACEI and ARB for HFrEF had been recommended in a selected group of patients up to and including the 2012 guidelines [12]. This combination was reviewed by the European Medicines Agency in 2014 [20], which suggested that benefits are thought to outweigh risks only in selected patients with HFrEF in whom other treatments are unsuitable. The 2016 ESC guidelines were adapted accordingly. The combination of ACEI and ARB did not rise above 3% of the patients in our study in 2008 and thereafter dropped. Bouvy et al. [2] concluded that ACEI was still not initiated in many subjects who might benefit from them. In their study of an earlier cohort of the same

medication in our study were comparable to those studies, which may imply that our results are representative for a typical HF population.

PHARMO Database in the 1990s, the percentage of patients being prescribed ACEIs 6 months after discharge after a first hospital admission for HF rose from 49.8 to 54.8%, which matches our numbers. In other studies (Eschalier [3], Koudstaal [5], Maggioni [6] and Tavazzi [18]), observed percentages were between 61.4 and 78.0%. Gilstrap et al. [4] found in their "Get with the Guidelines Heart Failure", a North-American quality improvement initiative, percentages reaching up to 90.5%.

Beta-blockers

Only four BB have been tested in key randomized clinical trials in HFrEF and received market approval of regulatory authorities. Bisoprolol [21], metoprolol [22], and nebivolol [23] are selective β1-blocking agents, whereas carvedilol [24] is both an alpha- and beta-blocking agent, although the β-blocking effect is 10 times greater. There is no clinical evidence that other BB reduce mortality. Sotalol, a BB without market authorization for HF, was probably prescribed to patients with cardiac arrhythmias together with HF. The prescription percentages of the four BB with market authorization rose in our study from 38.5% in 2001 to 68.4% in 2015. In the aforementioned study by Bouvy et al. [2], the percentage of patients prescribed BB rose from 11.3 to 28.7% in 1998. From other studies (Eschalier [3], Koudstaal [5], Maggioni [6] and Tavazzi [18]), percentages between 50.7 and 71.8% were published. Only Koudstaal and coworkers [5] reported on

Fig. 2 Prescription of ACEI and/or ARB. ACEI angiotensin-converting-enzyme inhibitor, ARB angiotensin-receptor blocker
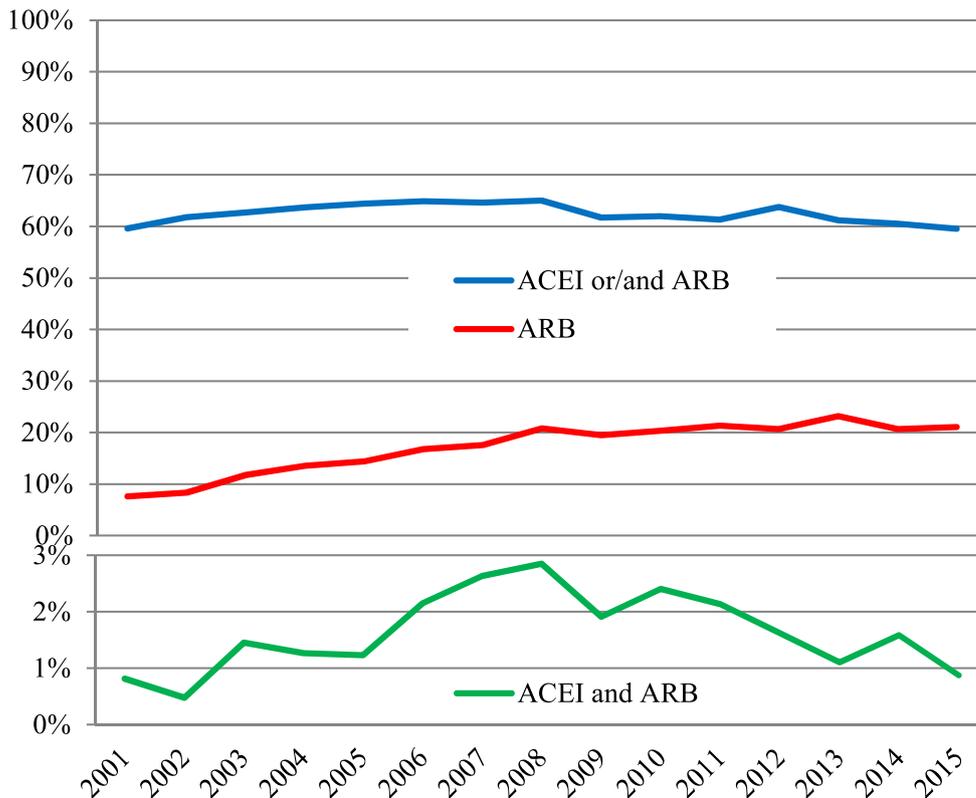
separate percentages for all BB (34.6%) and BB with a market authorization for HF (22.2%). Our figures resemble those found in other studies, although we do not know the type of HF of our patients.

Mineralocorticoid-receptor antagonists

The percentage of patients prescribed an MRA in our study remained on average 37% during the 15-year period, although

the position of MRA in the guidelines evolved from the use as an additional diuretic to prevent or treat diuretic-induced hypokalemia [8] into the prominent one it achieved in the 2012 guideline [12]. At the introduction of the ESC guidelines, the importance of thorough implementation of guidelines was emphasized, so it was therefore remarkable that we could not find an effect on prescription behavior of this considerable change in the guidelines for MRA, based on the results of the EMPHASIS-HF trial [13]. Others (Eschalier [3], Koudstaal [5], Maggioni [6], Tavazzi

Fig. 3 Prescription of beta-blockers. ■ All beta-blockers
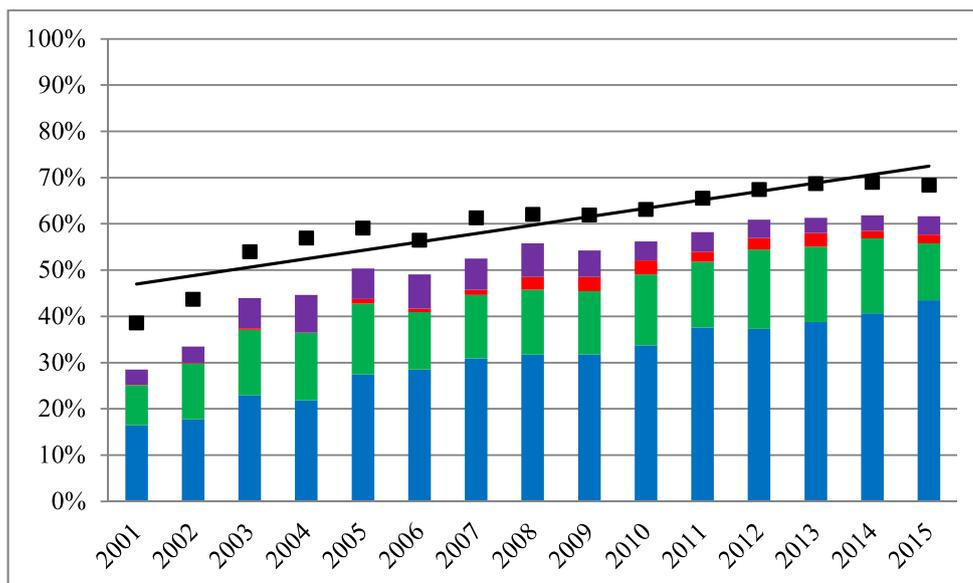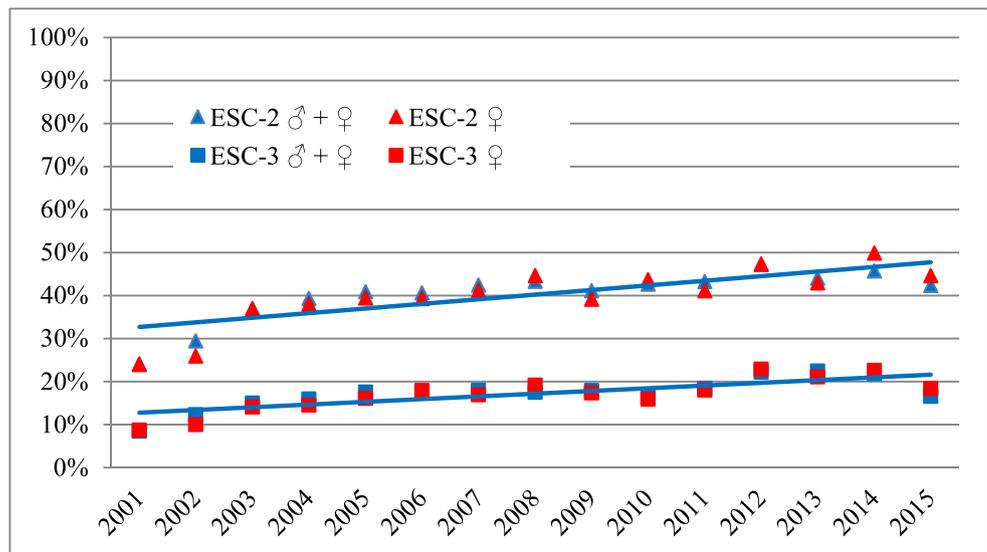■ Carvedilol ■ Nebivolol
■ Bisoprolol ■ Metoprolol

Fig. 4 Patients prescribed optimal medical therapy. ESC-2: Beta-blocker + (angiotensin-converting-enzyme inhibitor and/or angiotensin-receptor blocker). ESC-3: Beta-blocker + (angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker + mineralocorticoid-receptor antagonist

[18] and Ferreira [25]) observed percentages between 14.2 and 56%. Once again, our 37% is in the middle of this range, although we do not know the type of HF of our patients. Ferreira et al. studied the determinants and pattern of use of MRA in HFrEF [25]. Patients who were prescribed an MRA at baseline were younger, more often male, had higher body mass index, lower sodium, higher proportion of hypertension history, and ACE/ARB prescription. They concluded that MRA was largely under-prescribed and frequently discontinued. Therefore, although the percentage we found does not differ from other studies, we can only speculate about the explanation for the absence

of a rise in prescriptions for MRA during the course of years. A possible explanation may be the conservative strategy to prescribe an MRA to a vulnerable group of HF patients already treated with an ACE/ARB, BB, and in most cases also a diuretic. Savarese et al. recently speculated about this same phenomenon [26]. The increasing age of the patients (i.e., mean age on admission increased from 75 years to almost 79 years) can only explain this finding to a limited extent. Eplerenone did not reach meaningful percentages of patients and its use is therefore probably limited to patients with specific side effects on spironolactone, as described in Table 1.

Fig. 5 Probability of being prescribed HF medical treatment. ESC-2: Beta-blocker + (angiotensin-converting-enzyme inhibitor and/or angiotensin-receptor blocker). ESC-3: Beta-blocker + (angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker + mineralocorticoid-receptor antagonist
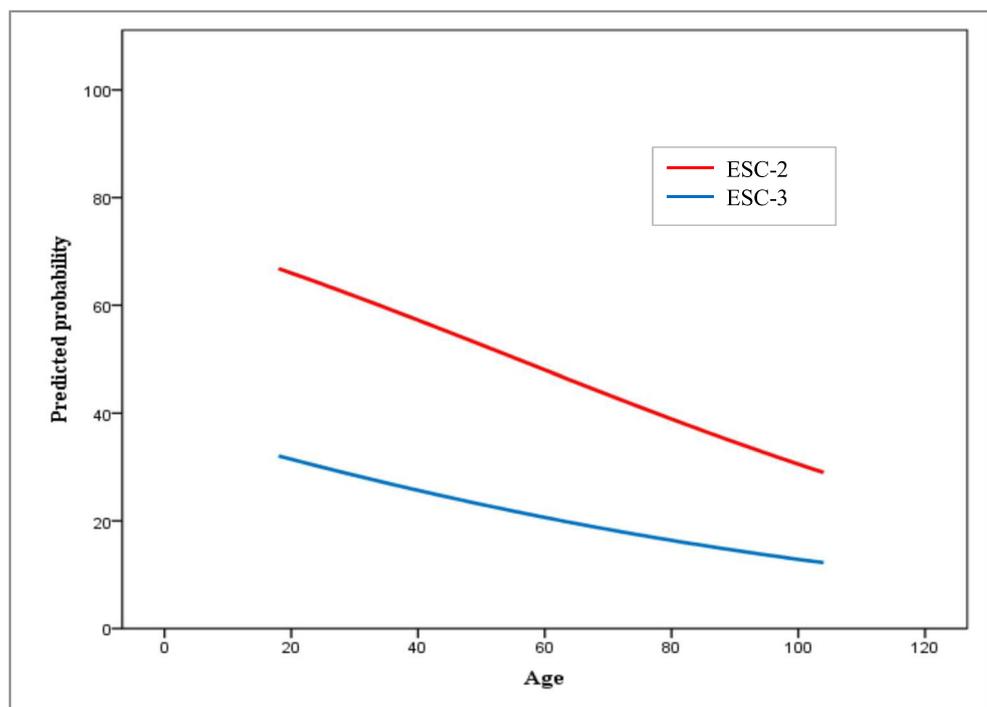
Diuretics

In a recent review of diuretic treatment in HF [27], the primary focus is on loop diuretics, of which only furosemide and bumetanide are available in the Netherlands during the study period. Diuretics are prescribed in more than 80% of our patients. Most of the patients require loop diuretics, as recommended in the ESC guidelines [1]. Thiazides as monotherapy could be prescribed for hypertension. Other investigators reported the same percentages for the prescription of diuretics (Bouvy [2], Koudstaal [5], Maggioni [6] and Tavazzi [18]). There was no shift from furosemide to bumetanide or vice versa during the course of the study period.

HF medical treatment

ACEI, BB, and—in patients with NYHA class II HF—MRA have shown to improve survival in patients with HFrEF and are recommended nowadays for the treatment of every patient with HFrEF, unless contraindicated or not tolerated [1]. In our study, however, the percentage of patients prescribed an ACEI (or ARB) and a BB rose only to a percentage of about 45%. The percentage of patients who also used an MRA reached approximately 20%. Importantly, data for men and women were very similar in our study, which is remarkable considering the conflicting data in other reported studies [5, 28]. Also, strikingly, with increasing age, disease-modifying drugs like ACEI/ARB, BB, and MRA are less prescribed. This might be due to the increased incidence of comorbidities and co-medication in elderly patients or to the greater prevalence of HFpEF among older patients [29]. This trend has also been demonstrated in a recently published cross-sectional registry in HF outpatient clinics in the Netherlands (CHECK-HF) [30].

Furthermore, real-world patients tend to be older and have more contraindications than patients in clinical trials. Over the years, in our cohort, patients were older and the length of hospital stay decreased. Other investigators found percentages of 37.2% for the combination of BB and MRA and 8.4% or 42% for the combination ACEI/ARB, BB, and MRA 8.4% or 42% [3, 31]. In the ESC Heart Failure Long-Term Registry [6], the reasons for non-adherence to the guidelines were investigated. A considerable part of the non-use in their study could be explained by contraindications or intolerance. Only in 3.2%, 2.3%, and 5.4% of the cases for respectively ACEI/ARB, BB, and MRA, the undertreatment was unexplained.

Strengths and limitations

Although the exact HF classification of our patients was unknown, our large database provided insights in real-world HF medical therapy from 2001 until 2015. The mean age, gender distribution, and co-medication of our study cohort are comparable to other studies. The proportion of HFpEF in the total population of HF patients has increased from 43.0 (period 1995–2004) to 56.2% (period 2005–2014) [32] that probably did not influence the trends we observed. However, those trends should be interpreted with caution due to the change in case mix. Also, there is relatively little difference in the medical treatment of HFrEF versus HFpEF which makes it likely that the change in case mix was not the driver for little changes in medical treatment over time [1]. The lack of more detailed information on the patient or the type of HF is a significant issue. The databases in the PHARMO Database Network do not contain this information. Due to privacy legislation, there was no option to retrieve this information afterwards. This information would have made our conclusions much more robust. Also, we have no data on the doses of the prescribed HF drugs. Some studies seem to prove the importance of the right (i.e., maximally tolerated) dose, while others are not able to support this, or even refute it [33].

The probabilistic linkage by PHARMO between the Hospitalization Database and the Outpatient Pharmacy Database has been validated previously [15] and has an accuracy of about 95%. As it is highly unlikely that HF patients did not receive at least one drug in anatomical main group C in the medication profile, we only included patients with dispenses before as well as after a hospitalization and at least one drug in anatomical main group C in the medication profile on discharge to eliminate likely mislinked patients.

A part of the patients will still be in the start-up phase of disease-modifying therapy, because it is their first hospital admission for HF. We chose to investigate the medication profile at discharge and not to include new prescriptions once a patient had been discharged, because of the potential for rapid deterioration of the disease. The Italian Network on Heart Failure study reported data not only at discharge, but also 1 year later [18]. The prescription for ACEI/ARB increased in that year by 1%, BB increased by 3%, MRA decreased by 4%, and diuretics decreased by 2%. These figures suggest the aspect of uptitration is marginal. However, the CHECK-HF registry reported considerably higher prescription percentages for ACEI/ARB (84% as compared to 72.7% in our cohort), BB (86% versus 59.6%), and MRA (56% versus 37.0%) [30]. The vast majority of patients in that registry (77%) had HFrEF.

Conclusions

Our study showed to what extent the ESC guidelines influenced prescription behavior at discharge after a first hospitalization for heart failure, during 2001–2015. However, the compliance with the guidelines varied for the individual recommendations. Remarkably, there was no significant increase in MRA prescription. At the same time, some developments were demonstrated, which were not instigated by the

guidelines, like the shift from ACEI to ARB. Our data provide insight into "real-world" pharmacological management in an unselected HF population during a 15-year period. As far as we know, this study is unique given the number of patients it pertains and the duration of the study period. Further research is needed to elucidate the reasons for non-adherence and to develop strategies for improvement. Especially the elderly HF patient might benefit from more widespread prescription of disease-modifying drugs.

Compliance with ethical standards

Conflict of interests E.M. Heintjes is an employee of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. This study, however, was not supported by a pharmaceutical company. W.J. Kruik-Kollöffel, G.C.M. Linssen, H.J. Kruik, K.L.L. Movig, and J. van der Palen have no conflicts of interest or financial ties to disclose.

Ethical improvement For this kind of study, formal consent is not required.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, Van der Meer P (2016) 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 18(8):891–975

2. Bouvy ML, Heerdink ER, Leufkens HG, Hoes AW (2003) Patterns of pharmacotherapy in patients hospitalised for congestive heart failure. Eur J Heart Fail 5(2):195–200

3. Eschalier R, Chenaf C, Mulliez A, Yalioua A, Clerfond G, Authier N, Vorilhon C, Citron B, Pereira B, Jean F, Souteyrand G, Motreff P, Eschalier A, Lusson JR (2015) Impact of clinical characteristics and management on the prognosis of unselected heart failure patients. Cardiovasc Drugs Ther 29(1):89–98. https://doi.org/10.1007/s10557-015-6572-y

4. Gilstrap LG, Fonarow GC, Desai AS, Liang L, Matsouaka R, DeVore AD, Smith EE, Heidenreich P, Hernandez AF, Yancy CW, Bhatt DL (2017) Initiation, continuation, or withdrawal of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and outcomes in patients hospitalized with heart failure with reduced ejection fraction. J Am Heart Assoc 6(2):e004675

5. Koudstaal S, Pujades-Rodriguez M, Denaxas S, Gho JMIH, Shah AD, Yu N, Patel RS, Gale CP, Hoes AW, Cleland JG, Asselbergs FW, Hemingway H (2017) Prognostic burden of heart failure recorded in primary care, acute hospital admissions, or both: a population-based linked electronic health record cohort study in 2.1 million people. Eur J Heart Fail 19(9):1119–1127

6. Maggioni AP, Anker SD, Dahlstrom U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Crespo-Leiro M, Drozdz J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavoliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L (2013) Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 15(10):1173–1184

7. Jefferies JL, Ibrahim NE (2018) Are guidelines merely suggestions? J Am Coll Cardiol 72(4):367–369. https://doi.org/10.1016/j.jacc.2018.05.023

8. Task Force of the Working Group on Heart Failure of the European Society of Cardiology (1997) The treatment of heart failure. Eur Heart J 18(5):736–753. https://doi.org/10.1093/oxfordjournals.eurheartj.a015339

9. Remme WJ, Swedberg K (2001) Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 22(17):1527–1560. https://doi.org/10.1053/euhj.2001.2783

10. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Lévy S, Linde C, Lopez-Sendon JL, Nieminen MS, Piérard L, Remme WJ (2005) Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology. Eur Heart J 26(11):1115–1140. https://doi.org/10.1093/eurheartj/ehi204

11. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K (2008) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 29(19):2388–2442. https://doi.org/10.1093/eurheartj/ehn309

12. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GYH, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PTT, Voors AA, Zannad F, Zeiher A (2012) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 33(14):1787–1847. https://doi.org/10.1093/eurheartj/ehs104

13. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B (2011) Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 364(1):11–21

14. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld JA (2017) 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Failure Society of America. J Am Coll Cardiol 70(6):776–803. https://doi.org/10.1016/j.jacc.2017.04.025

15. Herings RMC, Pedersen L (2012) Pharmacy-based medical record linkage systems. In: Strom BL, Kimmel SE, Hennessy S (eds) Pharmacoepidemiology, 5th edn. Wiley-Blackwell, Oxford, pp 270–286

16. Pharmo. PHARMO Database Network. https://www.pharmo.nl/what-we-have/pharmo-database-network/. Accessed 4 November 2018

17. Catalan VS, LeLorier J (2000) Predictors of long-term persistence on statins in a subsidized clinical population. Value Health 3(6): 417–426. https://doi.org/10.1046/j.1524-4733.2000.36006.x

18. Tavazzi L, Senni M, Metra M, Gorini M, Cacciatore G, Chinaglia A, Di Lenarda A, Mortara A, Oliva F, Maggioni AP (2013) Multicenter prospective observational study on acute and chronic heart failure: one-year follow-up results of IN-HF (Italian Network on Heart Failure) outcome registry. Circ Heart Fail 6(3):473–481

19. The Drug Information System of National Health Care Institute. https://www.gipdatabank.nl/ Accessed 4 November 2018

20. European Medicines Agency (EMA). PRAC recommends against combined use of medicines affecting the renin-angiotensin (RAS) system, 11 April 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/04/news_detail_002066.jsp&mid=WC0b01ac058004d5c1. Accessed 4 November 2018

21. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL (2002) Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 106(17):2194–2199

22. CIBIS-II Investigators and Committees (1999) The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. Lancet 353(9146):9–13. https://doi.org/10.1016/S0140-6736(98)11181-9

23. Flather MD, Shibata MC, Coats AJ, van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Böhm M, Anker SD, Thompson SG, Poole-Wilson PA (2005) Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 26(3):215–225. https://doi.org/10.1093/eurheartj/ehi115

24. MERIT-HF Study Group (1999) Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet 353(9169): 2001–2007. https://doi.org/10.1016/S0140-6736(99)04440-2

25. Ferreira JP, Rossignol P, Machu JL, Sharma A, Girerd N, Anker SD, Cleland JG, Dickstein K, Filippatos G, Hillege HL, Lang CC, ter Maaten JM, Metra M, Ng L, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zwinderman AH, Voors A, Zannad F (2017) Mineralocorticoid receptor antagonist pattern of use in heart failure with reduced ejection fraction: findings from BIOSTAT-CHF. Eur J Heart Fail 19(10):1284–1293

26. Savarese G, Carrero JJ, Pitt B, Anker SD, Rosano GMC, Dahlstrom U, Lund LH (2018) Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. Eur J Heart Fail 20(9):1326–1334

27. Ellison DH, Felker GM (2017) Diuretic treatment in heart failure. N Engl J Med 377(20):1964–1975

28. Hoes AW (2016) Beta blockers for heart failure. BMJ 353(8054): i2074

29. Komajda M, Hanon O, Hochadel M, Lopez-Sendon JL, Follath F, Ponikowski P, Harjola VP, Drexler H, Dickstein K, Tavazzi L, Nieminen M (2009) Contemporary management of octogenarians hospitalized for heart failure in Europe: euro heart failure survey II. Eur Heart J 30(4):478–486. https://doi.org/10.1093/eurheartj/ehn539

30. Brunner-La Rocca HP, Linssen GC, Smeele FJ, van Drimmelen AA, Schaafsma HJ, Westendorp PH, Rademaker PC, van de Kamp HJ, Hoes AW, Brugts JJ (2019) Contemporary drug treatment of chronic heart failure with reduced ejection fraction: the CHECK-HF registry. JACC Heart Fail 7(1):13–21

31. British Society for Heart Failure. National Heart Failure Audit, April 2014–March 2015. https://www.ucl.ac.uk/nicor/audits/heartfailure/documents/annualreports/heartfailurepublication14_15. Accessed 4 November 2018

32. Vasan RS, Xanthakis V, Lyass A, Andersson C, Tsao C, Cheng S, Aragam J, Benjamin EJ, Larson MG (2018) Epidemiology of left ventricular systolic dysfunction and heart failure in the Framingham study: an echocardiographic study over 3 decades. JACC Cardiovasc Imaging 11(1):1–11

33. Ambrosy AP, Gheorghiade M (2017) Real-world dosing of evidence-based medications for heart failure: embracing guideline recommendations and clinical judgement. Eur J Heart Fail 19(11): 1424–1426