Use of loop diuretics in patients with chronic heart failure: an observational overview

Niels TB Scholte,1 Dilan Aydin D,1 Gerard CM Linssen,2 Stefan Koustaal,3 Philip C Rademaker,4 Peter R Geerlings,5 Marco WF van Gent,6 Ismail Aksoy,7 Liane Oosterom,8 Eric Boersma,9,1 Hans-Peter Brunner-La Rocca,9 Jasper J Brugts1

ABSTRACT

Introduction

This study aimed to evaluate the use and dose of loop diuretics (LDs) across the entire ejection fraction (EF) spectrum in a large, ‘real-world’ cohort of chronic heart failure (HF) patients.

Methods

A total of 10 366 patients with chronic HF from 34 Dutch outpatient HF clinics were analysed regarding diuretic use and diuretic dose. Data regarding daily diuretic dose were stratified by furosemide dose equivalent (FDE)>80 mg or ≤80 mg. Multivariable logistic regression models were used to assess the association between diuretic dose and clinical features.

Results

In this cohort, 8512 (82.1%) patients used diuretics, of which 8179 (96.1%) used LDs. LD use was highest among HF with reduced EF (HFrEF) patients (81.1%) followed by HF with mild-reduced EF (76.1%) and HF with preserved ejection fraction EF (73.8%, p<0.001).

Among all LDs users, the median FDE was 40 mg (IQR: 40–80). The results of the multivariable analysis showed that New York Heart Association classes III and IV and diabetes mellitus were one of the strongest determinants of an FDE >80 mg, across all HF categories. Renal impairment was associated with a higher FDE across the entire EF spectrum.

Conclusion

In this large registry of real-world HF patients, LD use was highest among HFrEF patients. Advanced symptoms, diabetes mellitus and worse renal function were significantly associated with a higher diuretic dose regardless of left ventricular ejection fraction.

INTRODUCTION

Loop diuretics (LDs) play a key role in the treatment of chronic heart failure (HF), to prevent congestion, alleviate symptoms and retain euvolemia.1 2 The use of LDs in HF patients is highly recommended (class I) by the European Society of Cardiology (ESC).3 However, the level of objective scientific evidence for its effectiveness is low (level C), and the recommendation is mainly based on expert consensus. Also, factually, the optimal dose and intensity of LDs in HF patients is not well described. Since clinical trials of LDs in HF patients are out of the question, evidence gained from large-scale registrations of representative practices is crucial.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Loop diuretics (LDs) are highly recommended and form a cornerstone medication in the treatment of chronic heart failure (HF).
⇒ LDs help to prevent congestion and maintain euvolemia.
⇒ The vast majority of the HF patients are prescribed LDs.

WHAT THIS STUDY ADDS

⇒ The current objective evidence remains low regarding the description of the usage and dosage of LDs.
⇒ This study offers extensive ‘real-world’ data, providing more insight on this subject across the entire ejection fraction spectrum.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study gives insight on the dose and the determinants related to the dose of LDs.
⇒ Consequently, it provides possible steering on optimisation of diuretics and other HF medication.

METHODS

Study sample, setting and design

The design and methods of the CHECK-HF (Chronisch Hartfalen ESC-richtlijn Cardiologische praktijk Kwaliteitsproject-HartFalen) registry, a large and ‘real-world’ cohort of chronic HF patients in The Netherlands.

Methods

Study sample, setting and design

The design and methods of the CHECK-HF registry have been described in more detail previously.4 In short, the CHECK-HF is a cross-sectional registry consisting of 10 910 unselected chronic HF patients from 34 participating Dutch hospitals, who were
Table 1  Baseline characteristics: loop diuretics use in HFpEF, HFmrEF, HFrEF and semiquantified LVEF

<table>
<thead>
<tr>
<th></th>
<th>HFpEF</th>
<th>HFmrEF</th>
<th>HFrEF</th>
<th>Impaired semiquantified LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LD+</td>
<td>LD−</td>
<td>LD+</td>
<td>LD−</td>
</tr>
<tr>
<td></td>
<td>n=1589</td>
<td>n=564</td>
<td>n=1168</td>
<td>n=367</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years (IQR)</td>
<td>79 (72–85)</td>
<td>70 (61–78)</td>
<td>77 (69–85)</td>
<td>70 (60–77)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>663 (41.9)</td>
<td>314 (55.8)</td>
<td>649 (55.7)</td>
<td>246 (67.0)</td>
</tr>
<tr>
<td>BMI, kg/m² (IQR)</td>
<td>27.8 (24.5–32.2)</td>
<td>26.9 (24.3–30.4)</td>
<td>26.9 (24.0–30.9)</td>
<td>26.2 (23.6–29.2)</td>
</tr>
<tr>
<td>NYHA classification, n  (%)</td>
<td>182 (11.7)</td>
<td>236 (42.1)</td>
<td>128 (11.1)</td>
<td>138 (37.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of HF, n (%)</td>
<td>402 (26.3)</td>
<td>349 (62.0)</td>
<td>524 (46.7)</td>
<td>157 (43.6)*</td>
</tr>
<tr>
<td>Heart rate, beats per minute ±SD</td>
<td>73.5±15.0</td>
<td>70.8±12.3</td>
<td>70.1±11.4</td>
<td>72.5±14.1</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>746 (46.7)</td>
<td>76 (13.6)</td>
<td>455 (39.3)</td>
<td>74 (20.5)</td>
</tr>
<tr>
<td>eGFR, n (%)</td>
<td>120.5±65.5</td>
<td>105.8±67.6</td>
<td>122.0±57.3</td>
<td>95.6±44.2</td>
</tr>
<tr>
<td>Potassium mmol/L ±SD</td>
<td>4.3±0.5</td>
<td>4.4±0.4</td>
<td>4.4±0.4</td>
<td>4.3±0.4*</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL (IQR)</td>
<td>587 (140–1400)</td>
<td>909 (386–1586)*</td>
<td>546 (150–1377)</td>
<td>702 (192–1472)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td>808 (55.1)</td>
<td>284 (45.1)</td>
<td>472 (45.1)</td>
<td>135 (40.4)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>609 (39.3)</td>
<td>314 (55.8)</td>
<td>472 (45.1)</td>
<td>135 (40.4)*</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>598 (36.7)</td>
<td>107 (20.0)</td>
<td>314 (30.0)</td>
<td>78 (23.4)</td>
</tr>
<tr>
<td>COPD</td>
<td>349 (23.8)</td>
<td>63 (11.8)</td>
<td>238 (22.7)</td>
<td>51 (15.3)</td>
</tr>
</tbody>
</table>

Continued
Heart failure and cardiomyopathies recruited between September 2013 and September 2016. All included patients were diagnosed and treated according to the 2012 ESC HF guidelines and seen at the outpatient HF clinic (96%) or general cardiology outpatient clinic (4%). Data regarding patient characteristics, laboratory results, echocardiography and detailed information of HF therapy was collected in the registry.

Data and analysis

The current study included 10,366 HF patients in which data regarding diuretic use and left ventricular ejection fraction (LVEF) was available. Patients were categorised in three groups: HF with preserved ejection fraction (EF) (HFpEF; n=2,153, 20.7%), HF with mild-reduced EF (HFmrEF; n=1,535, 14.8%) and HF with reduced EF (HFrEF; n=5,614, 54.2%), according to the 2016 ESC HF guidelines. In 1,064 patients (10.3%), LVEF was reduced (i.e., <50%) but not exactly measured these patients were stratified as semiquantified LVEF. In patients using LDs other than furosemide (i.e., bumetanide), the LD dose per day was multiplied by 40 to obtain the furosemide dose equivalent per day (FDE). Given that torasemide is unavailable in the Netherlands, this study exclusively involves furosemide and bumetanide. We distinguished patients using an FDE > 80 mg as ‘high’ dose and FDE ≤ 80 mg as ‘low’ dose.

We present the baseline characteristics of LD users and non-LD user in HFpEF, HFmrEF, HFrEF and semiquantified LVEF patients separately. Between-group differences in these characteristics are evaluated by χ² tests and Fisher’s exact tests (continuous data), and as Mann-Whitney U tests and one-way analyses of variances (continuous data). Logistic regression analysis was applied to identify factors related with FDE dosage (‘low’ vs ‘high’), for which we considered age and sex, clinical factors including body mass index (BMI), NYHA class and renal impairment (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m²) and the use of other cardiovascular medication, including beta-blockers, renin-angiotensin-system (RAS) inhibitors and mineralocorticoid receptor antagonists (MRAs). The results are expressed as ORs with 95% CI. Multiple imputation used was applied to account for missing data, applying the monotone method or the Markov chain Monte Carlo method. Finally, in patients with HFrEF, HFmrEF and impaired semiquantified LVEF, we compared high and low FDE with the target dose of guideline-directed medical therapy (GDMT). Statistical analysis was performed using SPSS software V.25.0. P values < 0.05 were considered as statistically significant.

RESULTS

In this cohort of 10,366 HF patients, 8,512 (82.1%) patients used diuretics of which 8,179 (96.1%) LDs. LD use was highest among HFrEF patients (81.1%) followed by HFmrEF (76.1%) and HFpEF (73.8%, p < 0.001). Among patients with an impaired semiquantified LVEF, 81.8% used LDs.
Across the entire LVEF spectrum, patients using LDs were older, were more often men, had a higher BMI and NYHA class, lower systolic and diastolic blood pressure, lower eGFR and more often had diabetes mellitus than the non-LD users (table 1). Also, irrespective of LVEF, patients using LDs more often used MRAs and less often used RAS inhibitors. We found no differences in the use of beta-blockers. Figure 1 shows the distribution of FDE among the three different HF groups and impaired semiquantified group.

Multivariate analysis
Across the entire LVEF spectrum HF patients, using a high dose of LDs were associated with a higher BMI and potassium levels and a lower blood pressure (table 2). Also, these patients had a higher likelihood to have diabetes mellitus, atrial fibrillation and renal impairment. In patients with HFrEF and HFrEF, high FDE was associated with NYHA classes III and IV (table 2). The outcomes of multivariate analysis in the imputed dataset are compared with outcomes of the complete cases analysis, both analysis show the same trends for all variables included in the multivariate analysis.

GDMT target dose in HFmrEF, HFrEF and impaired semiquantified LVEF
Figure 2 shows the difference in the target dose of guideline-recommended HF medication between patients using high FDE versus low FDE in patients with HFmrEF, HFrEF and an impaired semiquantified LVEF, respectively. Figure 2 shows that there is no difference in reaching the target dose of beta-blocker between low and high FDE for patients with HFmrEF and HFrEF (12.7% vs 12.8%, p=0.96 and 14.6% vs 13.4%, p=0.39). However, patients in HFmrEF and those in HFrEF using low FDE more often reach the target dose RAS inhibition (30.0% vs 19.5%, p=0.001 and 36.6% vs 21.5%, p<0.001). The opposite is seen in the use of MRA, in which patients using high FDE more often reach their target dose for both HFmrEF and HFrEF (4.4% vs 16.8%, p<0.001 and 4.2% vs 16.6%, p<0.001).

DISCUSSION
In this study, we evaluated the overall use of diuretics and daily dose in a large cohort of chronic HF patients. The median dose of FDE was relatively low. The highest dose was used in patients with reduced LVEF, and the level of GDMT was negatively influenced by higher diuretic dose. Also, impaired renal function was associated with a higher dose of LD, which important to realise and consider in clinical practice. Furthermore, our analysis show that a higher dose of LD was associated with symptomatic HF. Still, the guidelines are in contrast to these observations as they recommend minimise LD use to preserve renal function. Interestingly, in this regard, diabetes mellitus was among the strongest determinants among LD use which is also related to renal preservation.

In the current literature, large real-world registries describing the use of diuretics and/or daily dose of diuretics in detail are scarce. Data from The EuroHeart Failure Survey programme showed that in patients with
<table>
<thead>
<tr>
<th>Variable</th>
<th>HFrEF OR (95% CI)</th>
<th>P value</th>
<th>HFmrEF OR (95% CI)</th>
<th>P value</th>
<th>HFrEF OR (95% CI)</th>
<th>P value</th>
<th>Impaired semiquantified LVEF OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.00 (0.98 to 1.02)</td>
<td>0.81</td>
<td>0.99 (0.96 to 1.01)</td>
<td>0.23</td>
<td>0.99 (0.98 to 1.00)</td>
<td>0.004</td>
<td>0.98 (0.95 to 1.00)</td>
<td>0.09</td>
</tr>
<tr>
<td>Men</td>
<td>0.92 (0.67 to 1.27)</td>
<td>0.62</td>
<td>0.73 (0.48 to 1.11)</td>
<td>0.14</td>
<td>0.95 (0.79 to 1.15)</td>
<td>0.63</td>
<td>0.74 (0.47 to 1.18)</td>
<td>0.21</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>1.07 (1.04 to 1.10)</td>
<td>&lt;0001</td>
<td>1.06 (1.02 to 1.10)</td>
<td>0.002</td>
<td>1.04 (1.02 to 1.06)</td>
<td>&lt;0001</td>
<td>1.01 (0.96 to 1.07)</td>
<td>0.68</td>
</tr>
<tr>
<td>NYHA classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2.51 (0.95 to 6.60)</td>
<td>0.06</td>
<td>0.92 (0.38 to 2.23)</td>
<td>0.85</td>
<td>1.29 (0.89 to 1.86)</td>
<td>0.18</td>
<td>3.13 (0.69 to 14.17)</td>
<td>0.14</td>
</tr>
<tr>
<td>III</td>
<td>3.94 (1.48 to 10.46)</td>
<td>&lt;0001</td>
<td>1.46 (0.59 to 3.66)</td>
<td>0.41</td>
<td>2.65 (1.82 to 3.87)</td>
<td>&lt;0001</td>
<td>5.32 (1.13 to 24.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>IV</td>
<td>5.68 (1.65 to 19.56)</td>
<td>&lt;0001</td>
<td>8.32 (2.37 to 29.20)</td>
<td>&lt;0001</td>
<td>4.41 (2.47 to 7.87)</td>
<td>&lt;0001</td>
<td>8.11 (0.76 to 86.21)</td>
<td>0.08</td>
</tr>
<tr>
<td>Ischaemic cause of HF</td>
<td>0.93 (0.65 to 1.34)</td>
<td>0.71</td>
<td>0.70 (0.46 to 1.06)</td>
<td>0.09</td>
<td>1.16 (0.95 to 1.40)</td>
<td>0.14</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Systolic BP, per 10 mm Hg</td>
<td>0.89 (0.82 to 0.96)</td>
<td>&lt;0001</td>
<td>0.86 (0.77 to 0.95)</td>
<td>&lt;0001</td>
<td>0.90 (0.85 to 0.94)</td>
<td>&lt;0001</td>
<td>0.95 (0.84 to 1.08)</td>
<td>0.47</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.36 (0.99 to 1.86)</td>
<td>0.06</td>
<td>1.89 (1.24 to 2.86)</td>
<td>0.003</td>
<td>1.44 (1.18 to 1.76)</td>
<td>&lt;0001</td>
<td>1.69 (1.05 to 2.71)</td>
<td>0.03</td>
</tr>
<tr>
<td>QRS duration, ≥130 ms</td>
<td>0.60 (0.41 to 0.88)</td>
<td>0.01</td>
<td>0.61 (0.38 to 0.97)</td>
<td>0.04</td>
<td>0.62 (0.52 to 0.75)</td>
<td>&lt;0001</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>1.65 (1.15 to 2.36)</td>
<td>0.01</td>
<td>1.78 (1.12 to 2.83)</td>
<td>0.01</td>
<td>1.30 (1.04 to 1.64)</td>
<td>0.02</td>
<td>1.56 (0.90 to 2.70)</td>
<td>0.11</td>
</tr>
<tr>
<td>Potassium mmol/L</td>
<td>0.48 (0.34 to 0.66)</td>
<td>&lt;0001</td>
<td>0.47 (0.30 to 0.76)</td>
<td>0.002</td>
<td>0.64 (0.53 to 0.77)</td>
<td>&lt;0001</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.82 (1.31 to 2.53)</td>
<td>&lt;0001</td>
<td>1.74 (1.05 to 2.89)</td>
<td>&lt;0001</td>
<td>2.07 (1.68 to 2.55)</td>
<td>&lt;0001</td>
<td>1.94 (1.20 to 3.13)</td>
<td>0.01</td>
</tr>
<tr>
<td>OSAS</td>
<td>1.44 (0.78 to 2.64)</td>
<td>0.24</td>
<td>1.27 (0.60 to 2.70)</td>
<td>0.53</td>
<td>1.29 (0.92 to 1.82)</td>
<td>0.14</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>0.78 (0.55 to 1.10)</td>
<td>0.15</td>
<td>0.51 (0.32 to 0.81)</td>
<td>0.004</td>
<td>0.78 (0.61 to 0.98)</td>
<td>0.04</td>
<td>0.68 (0.40 to 1.13)</td>
<td>0.13</td>
</tr>
<tr>
<td>RAS inhibition</td>
<td>0.73 (0.54 to 1.01)</td>
<td>0.05</td>
<td>0.63 (0.41 to 0.96)</td>
<td>0.03</td>
<td>0.55 (0.45 to 0.68)</td>
<td>&lt;0001</td>
<td>0.54 (0.34 to 0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>MRAs</td>
<td>1.71 (1.24 to 2.36)</td>
<td>&lt;0001</td>
<td>1.86 (1.21 to 2.85)</td>
<td>&lt;0001</td>
<td>1.57 (1.30 to 1.91)</td>
<td>&lt;0001</td>
<td>1.48 (0.92 to 2.38)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

All bold p-values are considered statistically significant.

BMI, Body Mass Index; BP, blood pressure; HFmrEF, heart failure with mild reduced ejection fraction; HFrEF, heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; OSAS, Obstructive Sleep Apnea Syndrome; RAS, Renin-Angiotensin System.
an LVEF of less than 40%, the use of LDs was higher compared with those with a higher LVEF.9 These results, together with the distribution of furosemide dosages, are in line with the results from our registry. Interestingly, in contrast with our study, the retrospective study of Broschus et al10 showed significantly more use of LDs in HFP EF. Also, the FDE among HFP EF patients tended to be higher in this study compared with HFrEF. Since

Figure 2  Guideline recommended medical therapy low (≤80 mg per day) versus (>80 mg per day) high dose of loop diuretics in (A) heart failure with reduced ejection fraction (HFrEF), (B) heart failure with mild reduced ejection fraction (HFmrEF) and in (C) impaired semiquantified. LVEF, left ventricular ejection fraction; RAS, renin-angiotensin-system; MRA, mineralocorticoid receptor antagonist.
our study had a cross-sectional design, we were unable to investigate clinical outcomes with regard to diuretic use. However, within the current body of literature, a limited number of studies have addressed the relationship between clinical outcomes and LD use. In the study conducted by Faselis et al., the authors showed that patients who receive LDs after hospitalisation for HF decompensation had significantly better 30-day clinical outcomes. Unfortunately, this study did not provide comprehensive information on LD daily doses. In contrast, Nuzzi et al. described the use of LDs in patients with dilated cardiomyopathy. Which showed that LD use and increasing FDE over time is a strong indicator for a clinical event. In addition, in the study of Pellicori et al., worse prognosis towards patients using LDs is also shown. However, after adjusting for severity of congestion neither the use nor the dose of LDs was associated with clinical outcomes. The latter two studies described similar LD daily dose profiles as in the HFrEF group from our study. Current guidelines recommend to prescribe LDs as low as possible to prevent decongestion and to discontinue when possible to preserve renal function. In view of these studies, one might expect that discontinuing LDs will occur more frequently over time. This may be related to the fact that high doses of LDs are more an indication for more advanced HF rather than deleterious per se, which is also in line with the findings of our study.

**Guideline-recommended therapy in HFmrEF and HFrEF**

Our results show that patients using a high FDE in HFmrEF and HFrEF are less likely to reach the target dose of RAS inhibitors and more likely to reach the target dose for MRAs. This finding is in agreement with the ‘Enhanced Feedback for Effective Cardiac Treatment’ (EFFECT) study. Interestingly, comparing the data from the EFFECT study with the current cohort shows that over 10 years, little has changed regarding the use of LDs. The more recent ‘A systems BIOlogy Study to Tailored Treatment in Chronic Heart Failure’ (BIOSTAT-CHF) study showed that higher dosages of LDs limited the up titration of RAS inhibitors in HFrEF patients who were on suboptimal GDMT. Also, at high dosages of LDs, patients tended to use more often MRAs on higher dosages, which is in line with our results.

Another interesting finding is the higher diuretic need in diabetes mellitus. While our cohort has no information on sodium-glucose cotransporter 2 (SGLT2) inhibitors which were not available for HF at that time, it is relevant to note the diuretic and natriuretic effect of SGLT2 inhibitors, but also many pleiotropic, explaining partly their efficacy in recent HF trials. It will be informative to study in HF registries what the effect of SGLT2 inhibitors is in (lowering) daily dose of diuretics in future studies.

**Strengths and limitations**

This registry contains a large number of HF patients in a Western population treated according to European guidelines, which describes the use of LDs across the entire EF spectrum. However, limitations need to be mentioned. As, this registry only contains cross-sectional data, no clinical outcome data was available.

**Future perspective**

As LDs are a cornerstone treatment in alleviating decompensation and maintaining euvolemia in HF patients. It will be informative to observe in HF registries what the effect of angiotensin receptor nephrilysin inhibitor (ARNI) and SGLT2 inhibitors on LDs usage is, particularly when compared with data form CHECK-HF. The ‘Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure’ (PARADIGM-HF) trial already showed that the use of ARNI was associated with a reduction in LD dose, compared with an ACE inhibitor. With the recent evolution of haemodynamic monitoring (eg, CardioMEMS, Cordella) in HF, it offers the opportunity to titrate LDs based on haemodynamic measurements and according to a predefined treatment guideline. The observed benefits of these techniques are mainly driven by changes in LDs.

**CONCLUSIONS**

In this large registry of real-world HF patients, loop diuretic use was highest among HFrEF patients. Advanced symptoms, diabetes mellitus and worse renal function were significantly associated with a higher diuretic dose regardless of LVEF.

**Author affiliations**

1. Department of Cardiology, Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands
2. Department of Cardiology, Hospital Group Twente, Almelo, The Netherlands
3. Department of Cardiology, Groene Hart Hospital, Gouda, The Netherlands
4. Department of Cardiology, ZorgSaam, Terneuzen, The Netherlands
5. Department of Cardiology, St. Jans Gasthuis Weert, Weert, The Netherlands
6. Department of Cardiology, Albert Schweitzer Hospital, Dordrecht, The Netherlands
7. Department of Cardiology, Admiral De Ruyter Hospital, Goes, The Netherlands
8. Department of Cardiology, Dijklander Hospital, Hoorn, The Netherlands
9. Department of Cardiology, Maastricht University Medical Centre, Maastricht, The Netherlands
10. Department of Cardiology, Erasmus MC, Rotterdam, The Netherlands

**Contributors**

NS and DA were equally involved in the data analysis and manuscript writing. GL, SK, PR, PG, MvG, IA, LO, EB, H-PB-LR and JJB were engaged in manuscript preparation and contributed to the thorough review of all manuscript drafts. JJB was responsible for the overall content as the guarantor. All authors read and approved the final manuscript.

**Funding**

This work was supported by Servier, the Netherlands, who funded the inclusion of data and software program. The steering committee (H-PB-LR, GL and JJB) received no funding for this project. This analysis was initiated by the authors and was designed, conducted, interpreted and reported independently of the sponsor. The current study had no other funding source or any with a participating role in outcome assessment or writing of the manuscript. NS is supported by a grant from the Dutch Research Council (NWO), grant number: 628.011.214 (STRAP).

**Competing interests**

MvG has had speaker engagements with Abbott, Novartis and Vifor. H-PB-LR has received research grants and/or fees from AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics and Vifor; and has had speaker engagements with Boehringer Ingelheim and Novartis. JJB received independent research grant from Abbott for ISS and has had speaker engagement or advisory boards in the past 5 years with Astra Zeneca, Abbott, Boehringer Ingelheim, Bayer, Daiichi Sankyo, Novartis and Vifor. All other authors declare to have no conflicts of interest.
Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The study was conducted according to the Declaration of Helsinki and was approved by METC 2017—Maastricht University Medical Center, Maastricht, the Netherlands. No informed consent of the participants in this registry was required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data in this study were obtained from the CHECK-HF registry where restrictions may apply. Such a dataset may be requested from the corresponding author.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Dilan Aydin http://orcid.org/0000-0001-7351-3139
Eric Boersma http://orcid.org/0000-0003-1159-7802

REFERENCES
5. McMurray JJJ, Adamopoulos S, Anker SD, et al. 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 2012;33:1787–847.