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RESEARCH ARTICLE

Contemporary guideline-directed medical therapy in de novo, chronic, and worsening heart failure patients: First data from the TITRATE-HF study

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Aims Despite clear guideline recommendations for initiating four drug classes in all patients with heart failure (HF) with reduced ejection fraction (HFrEF) and the availability of rapid titration schemes, information on real-world implementation lags behind. Closely following the 2021 ESC HF guidelines and 2023 focused update, the TITRATE-HF study started to prospectively investigate the use, sequencing, and titration of guideline-directed medical therapy (GDMT) in HF patients, including the identification of implementation barriers.

Methods and results TITRATE-HF is an ongoing long-term HF registry conducted in the Netherlands. Overall, 4288 patients from 48 hospitals were included. Among these patients, 1732 presented with de novo, 2240 with chronic, and 316 with worsening HF. The median age was 71 years (interquartile range [IQR] 63–78), 29% were female, and median ejection fraction was 35% (IQR 25–40). In total, 44% of chronic and worsening HFrEF patients were prescribed quadruple therapy. However, only 1% of HFrEF patients achieved target dose for all drug classes. In addition, quadruple therapy was more often prescribed to patients treated in a dedicated HF outpatient clinic as compared to a general cardiology outpatient clinic. In each GDMT drug class, 19% to 36% of non-use in HFrEF patients was related to side-effects, intolerances, or contraindications. In the de novo HF cohort, 49% of patients already used one or more GDMT drug classes for other indications than HF.

Conclusion This first analysis of the TITRATE-HF study reports relatively high use of GDMT in a contemporary HF cohort, while still showing room for improvement regarding quadruple therapy. Importantly, the use and dose of GDMT were suboptimal, with the reasons often remaining unclear. This underscores the urgency for further optimization of GDMT and implementation strategies within HF management.

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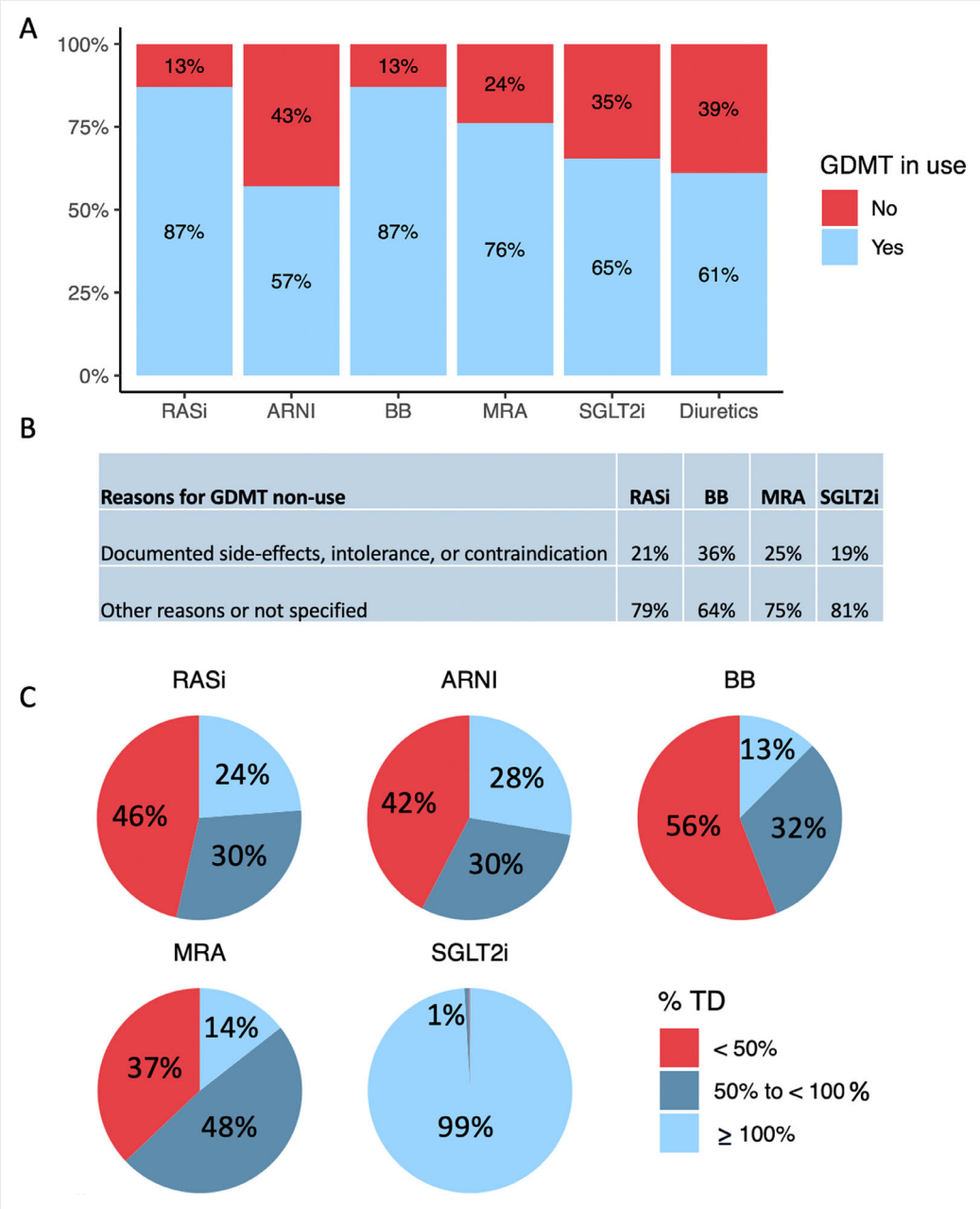
Graphical Abstract



Guideline-directed medical therapy (GDMT) use and dosing in all chronic and worsening heart failure with reduced ejection fraction patients. (*A*) Percentage of patients using GDMT, stratified by drug class. (*B*) Reasons for GDMT non-use. (*C*) Percentage of target dose for each drug class, stratified by <50% of target dose, 50% to 100% of target dose, and ≥100% of target dose. ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor; TD, target dose.

Keywords Registry • Pharmacotherapy • Implementation • Guideline-directed medical therapy • Sequencing • Titration

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Introduction

Guideline-directed medical therapy (GDMT) forms the cornerstone of the treatment for heart failure (HF) with reduced ejection fraction (HFrEF). Hence, the 2021 European Society of Cardiology (ESC) HF guidelines and 2023 focused update recommend timely administration of GDMT at target dose for all eligible HFrEF patients (recommendation level IA), as tolerated.[1,2] Additionally, based on findings from the recent STRONG-HF study, guidelines recommend rapid initiation and up-titration of GDMT within the first 6 weeks post-discharge following acute HF hospitalization.[3]

Despite strong evidence for life-saving drug therapy, previous real-world registries of chronic HF patients have consistently revealed low prescription rates and underdosing of GDMT.[4–8] The reasons for this widespread underutilization of GDMT remain unclear and arise from a variety of implementation barriers related to patients, local hospitals or clinicians, and health care systems.[9]

To gain a better understanding of these implementation barriers, it is imperative to study GDMT sequencing and titration patterns in real-world HF patients during the different stages of their disease. Investigating the start of the titration process in de novo HF patients will provide valuable insights and options to improve HF care. Additionally, exploring why chronic or worsening HF patients do not use one or more GDMT drug classes, despite the fact that they should have already attained optimal GDMT, adds a fundamental layer of understanding to these implementation barriers.

The TITRATE-HF study aims to analyse GDMT sequencing and titration patterns across de novo, chronic, and worsening HF patients, while identifying barriers encountered in the implementation process. In de novo HF patients, the study will additionally investigate the speed and order of initiation and up-titration.

This report presents the first results of TITRATE-HF, discussing the most contemporary use of GDMT and target doses in a large consecutive HF population in the Netherlands, briefly after the publication of the 2021 ESC HF guidelines and the 2023 focused update.

Methods

Study design

The methods of TITRATE-HF have been published earlier.[10] In brief, TITRATE-HF is an ongoing prospective observational HF registry in the Netherlands, aiming at long-term follow-up for up to 10 years of the entire cohort. Between June 2022 and February 2024, the study aimed to consecutively enrol at least 4000 patients with HFrEF, HF with mildly reduced ejection fraction (HFmrEF), and HF with improved ejection fraction (HFimpEF). The current analysis focused on the baseline cross-sectional data of the complete TITRATE-HF cohort. Patients were further categorized into de novo, chronic, and worsening HF groups, according to the ESC guideline definitions as listed in online supplementary *Table S1*. In total, 48 hospitals in the Netherlands participated, including the majority of all general hospitals and university medical centres with a HF outpatient clinic. A full list of participating sites is provided in online supplementary *Table S2*. To ensure the patient population accurately reflected routine clinical practice, the study maintained minimal in- and exclusion criteria and consecutive enrolment. Nonetheless, the diagnostic criteria for HF adhered strictly to the ESC guidelines for HF. Thus, inclusion criteria were diagnosed HF with current or previous left ventricular ejection fraction (LVEF) <50% and written informed consent. Exclusion criteria were an expected life expectancy <1 year, history of a recent major cardiovascular event (myocardial infarction, open heart surgery, or stroke) in the past 2 months, and advanced HF with anticipated left ventricular assist device implantation or heart transplantation within 6 months after study enrolment. The study conforms with the principles outlined in the Declaration of Helsinki, and the study was approved by all ethics committees of the participating sites (MEC-2022-0252). TITRATE-HF ClinicalTrials.gov number, NCT06386042.

Data collection

Data were collected from the electronic patient records at baseline and included demographics, medical history, vital parameters, electrocardiogram, echocardiography, laboratory results, and medication use. Baseline GDMT use was registered in a medication log for all four drug classes, including the dose, as well as all changes made. For de novo HF patients, GDMT utilization prior to HF diagnosis was documented, along with the diagnosis that was the reason for prescription. In chronic and worsening HF patients, the reason for non-use was recorded if a drug was not in use. Changes in GDMT during the last HF hospitalization were registered in case of worsening HF. In addition, the EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire was collected at baseline to capture the self-reported quality of life.[11,12]

Statistical analysis

Continuous variables are summarized using means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on the distribution. The dose of each drug class is expressed as the mean percentage relative to the target dose as specified in the 2021 ESC HF guidelines.[1] Between-group comparisons of baseline characteristics were conducted using the two-sample *t*-test or ANOVA for normally-distributed continuous variables, while the Kruskal–Wallis test was done for continuous variables with a non-normal distribution. The χ^2 test was used for between-group comparisons of categorical variables. The EQ-5D-5L results ranged from level 1 to level 5, with a higher score indicating a poorer quality of life. These results were then dichotomized into 'no problems' (level 1) or 'problems' (levels 2–5), and are presented as an index value according to the value set specific to the Netherlands.[13] To study the effect of confounders on the use of quadruple therapy (simultaneous use of renin–angiotensin system inhibitor [RASi], beta-blocker [BB], mineralocorticoid receptor antagonist [MRA], sodium–glucose cotransporter 2 inhibitor [SGLT2i]), a multivariate model included at least age, sex, body mass index, LVEF, and New York Heart Association (NYHA) class, as well as all variables with a *p*-value <0.10 in univariate models. For the multivariate regression model, missing data were handled by means of multivariate imputation by chained equations. To evaluate the impact of missing data and to test the robustness of the findings, a sensitivity analysis was conducted using only complete cases.

A two-tailed *p*-value <0.05 was considered statistically significant in all analyses. All analyses were performed with SPSS (version 29), R (version 4.3.2.), and RStudio (version 2023.12.0).

Results

Baseline characteristics

A total of 4288 patients from 48 participating sites were included in this analysis. The cohort consists of 1732 de novo HF patients,

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Table 1 Baseline characteristics of de novo, chronic, and worsening heart failure

	De novo HF	Chronic HF	Worsening HF	*p*-value
Patients, *n*	1732	2240	316	
Age, years, median [IQR]	71.0 [62.0–77.0]	71.0 [63.0–78.0]	74.0 [67.0–79.0]	<0.001
Female sex, *n* (%)	539 (31.1)	629 (28.1)	79 (25.0)	0.028
Duration of HF at inclusion, months, median [IQR]	1.0 [0.4–1.9]	44.7 [14.1–105.0]	68.2 [27.8–131.8]	<0.001
EF category, *n* (%)				<0.001
HFrEF	1510 (87.2)	1604 (71.6)	256 (81.0)	
HFmrEF	222 (12.8)	282 (12.6)	36 (11.4)	
HFimpEF	0 (0.0)	354 (15.8)	24 (7.6)	
Non-ischaemic CMP, *n* (%)	1092 (63.8)	1202 (53.7)	153 (48.6)	<0.001
NYHA functional class, *n* (%)				<0.001
I	163 (9.6)	439 (19.7)	13 (4.2)	
II	1180 (69.2)	1463 (65.7)	141 (45.3)	
III	287 (16.8)	311 (14.0)	113 (36.3)	
IV	75 (4.4)	14 (0.6)	44 (14.1)	
BMI, kg/m^2, median [IQR]	26.0 [23.3–29.7]	26.8 [24.2–30.1]	26.5 [23.3–30.1]	<0.001
Systolic BP, mmHg, mean (SD)	127.5 (22.0)	124.0 (19.8)	120.9 (23.1)	<0.001
Diastolic BP, mmHg, mean (SD)	76.2 (13.1)	72.4 (11.3)	71.4 (12.2)	<0.001
Heart rate, bpm, median [IQR]	80.0 [68.0–94.0]	70.0 [62.0–80.0]	77.0 [67.0–89.0]	<0.001
Heart rhythm, *n* (%)				<0.001
SR	1187 (69.9)	1281 (62.9)	141 (45.2)	
AF	468 (27.5)	442 (21.7)	117 (37.5)	
PM	44 (2.6)	315 (15.5)	54 (17.3)	
LVEF, %, median [IQR]	30.0 [25.0–37.0]	35.0 [30.0–42.0]	30.0 [25.0–38.0]	<0.001
History of stroke, *n* (%)	149 (8.6)	231 (10.3)	41 (13.0)	0.029
History of hypertension, *n* (%)	917 (52.9)	1082 (48.3)	186 (58.9)	<0.001
History of hypercholesterolaemia, *n* (%)	623 (36.0)	1007 (45.1)	156 (49.4)	<0.001
Obesity, *n* (%)	387 (22.4)	584 (26.1)	73 (23.1)	0.022
History of diabetes, *n* (%)	362 (20.9)	567 (25.3)	104 (32.9)	<0.001
Smoking, *n* (%)				<0.001
No	729 (43.6)	918 (43.4)	124 (40.4)	
Quit	644 (38.5)	932 (44.1)	137 (44.6)	
Yes	299 (17.9)	264 (12.5)	46 (15.0)	
History of COPD, *n* (%)	184 (10.6)	272 (12.1)	66 (20.9)	<0.001
History of OSAS, *n* (%)	142 (8.2)	289 (12.9)	40 (12.7)	<0.001
eGFR, ml/min/1.73 m^2, median [IQR]	66.0 [53.0–81.0]	60.0 [46.0–75.0]	44.0 [32.0–62.0]	<0.001
eGFR category, *n* (%)				<0.001
<30	60 (3.5)	110 (5.2)	62 (19.7)	
30–59	584 (34.3)	942 (44.1)	165 (52.5)	
>60	1060 (62.2)	1082 (50.7)	87 (27.7)	
NT-proBNP, pmol/L, median [IQR]	217.1 [89.0–519.8]	107.0 [38.4–269.0]	460.5 [208.7–1022.5]	<0.001

AF, atrial fibrillation/flutter; BMI, body mass index; BP, blood pressure; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSAS, obstructive sleep apnoea syndrome; PM, pacemaker; SD, standard deviation; SR, sinus rhythm.

2240 chronic HF patients, and 316 worsening HF patients. The median ages were 71 (IQR 62–77), 71 (IQR 63–78), and 74 years (IQR 67–79), and females were 31.1%, 28.1%, and 25.0%, for de novo, chronic, and worsening HF patients, respectively. Median LVEF was 30% (IQR 25–37) for de novo HF patients, 35% (IQR 30–42) for chronic HF patients, and 30% (IQR 25–38) for worsening HF patients, respectively. On average, chronic HF patients were diagnosed with HF approximately 3.7 years prior to inclusion, while worsening HF patients were diagnosed with HF approximately 5.7 years before inclusion. Among the de novo HF patients, 20.0% were included during HF hospitalization. Of these hospitalizations, 92.0% were also the index hospitalization. In the worsening HF cohort, 50.5% of patients were included during HF hospitalization, while 49.5% were included in the ambulatory setting. Baseline characteristics are summarized in *Table 1* and baseline medication use is summarized in *Table 2*.

De novo heart failure and guideline-directed medical therapy use (naïve)

In the de novo HF cohort, the percentage of GDMT naïve HF patients prior to HF diagnosis was 50.9%. Before HF diagnosis, 29.8% of de novo HF patients already used angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB), 33.0% used BB, 6.4% used MRA, and 3.1% used SGLT2i

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Table 2 Medical therapy prescription rates for de novo, chronic, and worsening heart failure

	De novo HF ($n = 1732$)	Chronic HF ($n = 2240$)	Worsening HF ($n = 316$)	*p*-value*
Guideline-directed medical therapy				
RASi	30%[a]	89%[b]	73%[b]	<0.001
BB	33%[a]	88%	78%	< 0.001
MRA	6%[a]	75%	71%	0.115
SGLT2i	3%[a]	64%	56%	0.005
Other medication				
Loop diuretics	56%	56%	82%	<0.001
Digoxin	11%	11%	17%	0.003
Ivabradine	2%	4%	2%	0.064
Amiodarone	5%	10%	21%	<0.001
Sotalol	2%	5%	3%	0.050
Anticoagulation, indication:	50%	63%	74%	<0.001
HF/LV thrombus	14%	18%	12%	
Atrial fibrillation/flutter	63%	61%	71%	
Mechanical heart valve	2%	4%	5%	
Pulmonary embolus/deep vein thrombosis	5%	3%	6%	
Unknown	16%	15%	6%	
Statin	45%	58%	52%	0.052

BB, beta-blocker; HF, heart failure; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor.
[a]In use due to other indication than HF.
[b]Angiotensin receptor–neprilysin inhibitor use is 57.9% in chronic HF, and 36.9% in worsening HF.
*p-value for the difference between chronic and worsening HF.

based on other indications than HF. ACEi and ARB were most commonly used due to hypertension, while BB were most commonly used due to hypertension, coronary artery disease, or other indications such as atrial rhythm disorders.

Guideline-directed medical therapy use in chronic and worsening heart failure patients

At baseline, for all LVEF types (HFrEF, HFmrEF, and HFimpEF) together, 87.1% of chronic and worsening HF patients were prescribed RASi, which is a composite of ACEi, ARB, and angiotensin receptor–neprilysin inhibitors (ARNI). In total, 55.3% of the chronic and worsening HF patients used ARNI. Furthermore, baseline GDMT use in chronic and worsening HF patients was 87.1% for BB, 74.9% for MRA, and 63.0% for SGLT2i. The use of generic drug names within each drug class, including the mean percentage of target dose is provided in online supplementary *Table S3*. In total, 43.2% of patients were prescribed quadruple therapy (RASi, BB, MRA, SGLT2i). Additionally, 33.3% of chronic and worsening HF patients simultaneously used ARNI, BB, MRA, and SGLT2i.

Guideline-directed medical therapy use stratified by left ventricular ejection fraction type

Within the chronic and worsening HF cohorts ($n = 2556$), 1860 patients (72.8%) had HFrEF, 318 patients had HFmrEF (12.4%) and 378 patients had HFimpEF (14.8%). Percentages of GDMT use, quadruple therapy, and other medication use within chronic and worsening HF, stratified by LVEF type, is presented in *Table 3*.

Of the chronic and worsening HFrEF patients ($n = 1860$), 87.0% used RASi, 87.1% used BB, 76.2% used MRA, and 65.4% used SGLT2i. Of these patients, 44.4% used quadruple therapy (RASi, BB, MRA, SGLT2i), with only 0.8% at target dose for all drug classes. In this cohort, 57.1% used ARNI and 34.7% of patients simultaneously used ARNI, BB, MRA and SGLT2i. An overview of GDMT use in chronic and worsening HFrEF patients is presented in *Graphical Abstract*. Depending on the drug class, only 19% to 36% of GDMT non-use in chronic and worsening HFrEF patients could be linked to side-effects, intolerances, or contraindications. The most common side-effects listed as the reasons for non-use were hypotension for RASi, bradycardia and dizziness for BB, hyperkalaemia for MRA, and urogenital infection for SGLT2i (online supplementary *Table S4*). There were substantial differences between sites regarding GDMT prescription rates in chronic and worsening HFrEF patients (*Figure 1*). This was especially notable for quadruple GDMT prescription (RASi, BB, MRA, SGLT2i), which varied from 20% to 79% across different sites. In addition, there was a significant difference in the prescription rates of quadruple therapy for patients treated in a dedicated HF outpatient clinic versus a general cardiology outpatient clinic. In chronic and worsening HFrEF patients, 47.2% of those treated at a dedicated HF outpatient clinic received quadruple therapy (RASi, BB, MRA, SGLT2i). Notably, 37.2% of this cohort received simultaneous prescriptions of ARNI, BB, MRA, and SGLT2i. In contrast, in a general cardiology outpatient clinic, 32.5% of patients were prescribed quadruple therapy (RASi, BB, MRA, SGLT2i), with simultaneous usage of ARNI, BB, MRA, and SGLT2i being observed in 23.9% of cases (all $p < 0.001$).

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Table 3 Medical therapy prescription rates for chronic and worsening heart failure patients, stratified by left ventricular ejection fraction type

	Chronic and worsening HF ($n = 2556$)			Chronic HF ($n = 2240$)			Worsening HF ($n = 316$)		
	HFrEF ($n = 1860$)	HFmrEF ($n = 318$)	HFimpEF ($n = 378$)	HFrEF ($n = 1604$)	HFmrEF ($n = 282$)	HFimpEF ($n = 354$)	HFrEF ($n = 256$)	HFmrEF ($n = 36$)	HFimpEF ($n = 24$)
Guideline-directed medical therapy									
RASi	87.0%	83.6%	90.7%	89.0%	86.5%	91.5%	73.8%	61.1%	75.0%
ARNI	57.1%	38.2%	61.3%	59.6%	41.6%	63.2%	40.9%	11.1%	33.3%
BB	87.1%	84.5%	89.7%	88.5%	85.4%	90.4%	77.7%	77.8%	79.2%
MRA	76.2%	69.5%	72.9%	76.9%	68.8%	73.7%	71.5%	75.0%	62.5%
SGLT2i	65.4%	55.5%	57.6%	66.5%	57.7%	58.1%	58.8%	38.9%	50.0%
Quadruple therapy									
RASi, BB, MRA, SGLT2i	44.4%	35.8%	43.4%	46.5%	37.9%	44.6%	32.4%	19.4%	25.0%
ARNI, BB, MRA, SGLT2i	34.7%	24.5%	33.6%	36.7%	27.0%	35.6%	22.8%	5.6%	8.3%
Other medication									
Loop diuretics	60.3%	60.1%	54.8%	57.1%	56.0%	52.5%	80.1%	91.7%	87.5%
Digoxin	11.8%	12.3%	9.5%	10.7%	12.8%	9.9%	18.8%	8.3%	4.2%
Ivabradine	3.5%	1.6%	6.6%	3.7%	1.8%	7.1%	2.3%	0.0%	0.0%
Amiodarone	12.7%	6.0%	6.6%	11.0%	6.0%	5.9%	23.4%	5.6%	16.7%
Sotalol	4.9%	5.0%	6.1%	5.2%	5.3%	6.5%	3.1%	2.8%	0.0%
Anticoagulation, indication:	65.6%	62.6%	59.3%	63.9%	61.7%	57.4%	76.2%	69.4%	87.5%
HF/LV thrombus	18.1%	11.1%	17.0%	18.9%	12.6%	18.2%	13.8%	0.0%	4.8%
Atrial fibrillation/flutter	60.2%	72.4%	64.7%	58.5%	70.1%	63.5%	68.7%	88.0%	76.2%
Mechanical heart valve	4.2%	3.0%	3.1%	4.0%	3.4%	2.5%	5.1%	0.0%	9.5%
Pulmonary embolus/deep vein thrombosis	3.5%	2.0%	1.3%	2.9%	1.1%	1.5%	6.2%	8.0%	0.0%
Unknown	14.1%	11.6%	13.8%	15.6%	12.6%	14.3%	6.2%	4.0%	9.5%
Statin	59.3%	52.2%	51.9%	60.3%	51.8%	52.5%	52.7%	55.6%	41.7%

ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitors.

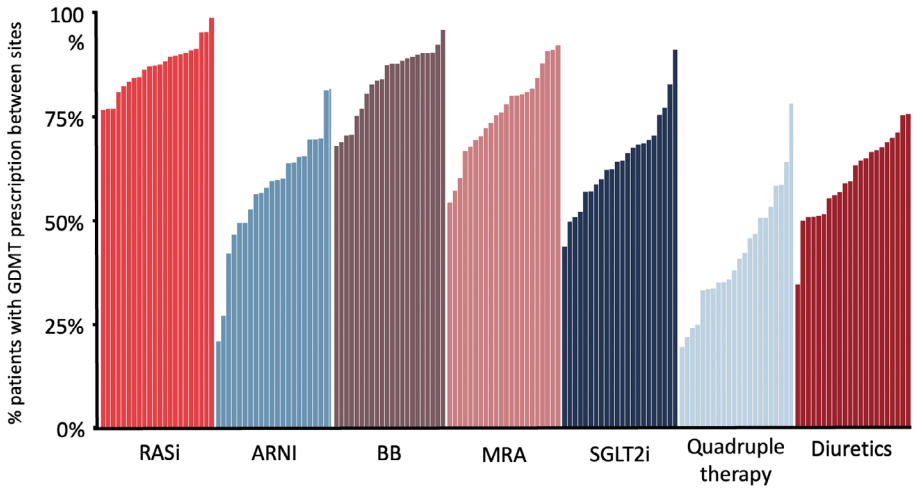

Figure 1 Differences in guideline-directed medical therapy (GDMT) use in heart failure with reduced ejection fraction patients between participating sites with ≥50 enrolled patients. ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

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In chronic and worsening HFmrEF, GDMT use was 83.6%, 84.5%, 69.5%, and 55.5% for RASi, BB, MRA, and SGLT2i, respectively. Of the HFmrEF patients, 38.2% used ARNI. In this cohort, 35.8% used quadruple therapy (RASi, BB, MRA, SGLT2i). Simultaneous prescription of ARNI, BB, MRA, and SGLT2i occurred in 24.5% of patients. In the chronic and worsening HFimpEF group, RASi use was 90.7%, BB use was 89.7%, MRA use was 72.9%, and SGLT2i use was 57.6%. In addition, 61.3% used ARNI. In the HFimpEF cohort, 43.4% patients used quadruple therapy (RASi, BB, MRA, SGLT2i). In total, 33.6% of the HFimpEF patients simultaneously used ARNI, BB, MRA and SGLT2i.

An overview of GDMT use and non-use in chronic and worsening HF patients, stratified by all LVEF types together (HFrEF, HFmrEF, and HFimpEF), HFmrEF and HFimpEF, is presented in online supplementary *Figure S1*. In addition, percentages of target dose for each drug type are summarized in online supplementary *Figure S2*.

Multivariate prediction for guideline-directed medical therapy use in heart failure with reduced ejection fraction

Multivariate predictors for the use of quadruple therapy (RASi, BB, MRA, SGLT2i) in chronic and worsening HFrEF patients are summarized in online supplementary *Table S5*. In summary, higher age, higher NYHA class, higher systolic blood pressure, and higher heart rate were significantly and independently associated with decreased odds of being prescribed quadruple therapy (all $p \leq 0.019$). In contrast, a higher body mass index was significantly associated with increased odds of being prescribed quadruple therapy ($p = 0.007$). Sensitivity analysis yielded similar results. In addition, the relation between systolic blood pressure and GDMT use is summarized in online supplementary *Table S6*.

Changes in guideline-directed medical therapy during admissions for worsening heart failure

Changes in diuretics were most frequent and occurred in 73.9% of patients. In the context of worsening HF hospitalizations, changes in GDMT were also prevalent but much less compared to diuretics. SGLT2i were initiated in 34.2% of patients during hospitalization, and 13.7% switched from ACEi or ARB to ARNI. BB changes occurred in 30.0%, while MRA changes occurred in 38.8% of patients.

With the exception of MRA ($p = 0.115$), GDMT use in worsening HF patients was significantly lower in comparison to chronic HF patients (all $p \leq 0.005$). In contrast, use of diuretics, anticoagulation, digoxin, and amiodarone was significantly higher in the worsening HF cohort (all $p < 0.001$). Furthermore, markers of disease progression such as atrial fibrillation, reduced estimated glomerular filtration rate, and higher NT-proBNP were significantly more prevalent in worsening HF patients compared to chronic HF patients (all $p < 0.001$).

Quality of life

The percentage of patients reporting problems per dimension of the EQ-5D-5L differed significantly between de novo, chronic, and worsening HF ($p < 0.001$) (online supplementary *Figure S3*). Index scores were 0.77 ($\pm$ 0.21) for de novo HF, 0.78 ($\pm$ 0.20) for chronic HF, and 0.67 ($\pm$ 0.26) for worsening HF ($p < 0.001$). In addition, visual analogue scale scores were 69.0 ($\pm$ 17.3) for de novo HF, 71.4 ($\pm$ 15.7) for chronic HF, and 61.5 ($\pm$ 19.6) for worsening HF patients ($p < 0.001$).

Discussion

These first cross-sectional results of the TITRATE-HF study show relatively high use of GDMT in HF patients in the Netherlands. However, the average doses for RASi, BB, and MRA were still substantially lower than those recommended by the guidelines. In addition, a large variation in the use of pharmacological HF therapy was seen between different sites, as well as between general cardiology and dedicated HF outpatient clinics. This study brings valuable insights in the use of evidence-based pharmacological HF treatment; however, it also underlines that significant gaps in GDMT use and dosing remain.

Since the introduction of the 2021 ESC HF guideline and 2023 guideline update,[1,2] TITRATE-HF presents the first and most contemporary data of GDMT use and achieved target doses in de novo, chronic, and worsening HF patients. This registry presents novel data on GDMT naïve patients among de novo HF patients prior to HF diagnosis. Almost 50% of de novo HF patients were already using at least one GDMT drug class for indications other than HF. This prior use was predominantly driven by conditions like hypertension and coronary artery disease, which are common comorbidities in HF patients. Right after HF diagnosis, up-titration of these medications to target dose as tolerated is important because optimal dosages for other comorbidities may be insufficient for the treatment of HF. Additionally, our results indicate that patients treated in dedicated HF outpatient clinics are more frequently prescribed quadruple therapy compared to patients treated in a general cardiology outpatient clinic. Based on these findings, it might be beneficial to structure the care for HFrEF patients within such dedicated HF outpatient clinics to ensure optimized therapeutic strategies and guideline implementation.

Recent randomized controlled trials such as PARADIGM-HF, DAPA-HF, and EMPEROR-Reduced have introduced new drug classes into the HF guidelines. As a result, the arsenal for the treatment of HFrEF has increased steadily and substantially. However, this has also increased the difficulty to achieve optimal GDMT.[14–16] In this evolving landscape, there is a major role for real-world registries to better understand guideline implementation in daily clinical practice. Identifying barriers encountered during implementation in the real-world is crucial to get all HF patients on life-saving drug therapy. Registries do not only help to identify these treatment barriers, but also provide a sense of urgency to improve upon areas lacking in GDMT prescription.[17] In addition, an analysis of the Swedish HF registry (SwedeHF) demonstrated that enrolment in a registry by itself may improve guideline implementation.[18]

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Unique to TITRATE-HF is that it comprehensively documents the speed and order of GDMT initiation, as well as reasons behind non-use, down-titrations, and discontinuations across all GDMT drug classes. This first report of TITRATE-HF focused on the reasons for GDMT non-use in chronic and worsening HF and revealed that only 19% to 36% of instances of non-use in HFrEF patients could be attributed to side-effects or intolerances. Despite the fact that these patients should have attained optimal GDMT (class IA indication in the ESC HF guideline), the reasons for GDMT non-use remain largely unclear. This significant gap in prescription rates raises critical questions. Importantly, healthcare costs are not a likely hindrance in the Netherlands, as all patients have mandatory health insurance with minimal out-of-pocket expenses.[19]

Several factors potentially contribute to the unexplained non-use of GDMT. Firstly, non-documentation of medical conditions in the past might be an explanation. To address this issue, it is essential for clinicians to be encouraged to consistently document their reasons for not initiating, reducing, or discontinuing medical therapy in patient records, a practice that is frequently missing. This documentation process would also avoid accidental re-prescription of contraindicated drugs with possible serious side-effects.[20] Second, the large differences in GDMT prescription rates between participating sites may be due to physician clinical inertia, referring to the failure of treatment intensification or adjustment in the absence of reasonable contraindications or other barriers.[21] A major reason for physician clinical inertia is the misperception of 'stable HF', a disputed term, misleadingly implying no need for further optimization of GDMT in patients who are seemingly clinically stable.[22] Another possible reason for physician clinical inertia is the so-called 'risk treatment paradox', referring to the phenomenon where high-risk patients with more severe symptoms receive fewer or lower doses of HF medication. This undertreatment is possibly caused by concerns for potential adverse side-effects, as well as lower expectations of benefits with higher doses of GDMT.[23] It is important that HF clinicians weigh not only the potential negative effects of prescribing HF medication, but also the risks associated with not prescribing GDMT.[24]

TITRATE-HF shows higher GDMT prescription rates in HFrEF patients in comparison to previous large-scale HF registries, such as CHECK-HF, CHAMP-HF, and ASIAN-HF (*Figure 2*).[4–6,8] However, prescribed doses were still significantly below target dose. In comparison with SwedeHF, GDMT prescription rates were similar for RASi and BB, although TITRATE-HF shows higher uptake of MRA, because SwedeHF also included patients before MRA were recommended for all HFrEF patients since the 2012 ESC HF guideline. In CHAMP-HF, triple therapy of RASi, BB, and MRA at target dose was only achieved in about 1% of patients, comparable to the use of quadruple therapy (RASi, BB, MRA, SGLT2i) at target dose in TITRATE-HF. A comparative analysis with the CHECK-HF registry, a cross-sectional study conducted almost a decade earlier in similar Dutch clinics, underscores the strides made in MRA use. While CHECK-HF showed good prescription rates of RASi and BB, MRA were only prescribed to 56% of HFrEF patients, compared to 76% in TITRATE-HF. Despite guidelines recommending MRA use for a broader range of HF patients since 2012, the slow implementation of MRA emphasizes the prolonged trajectory required before

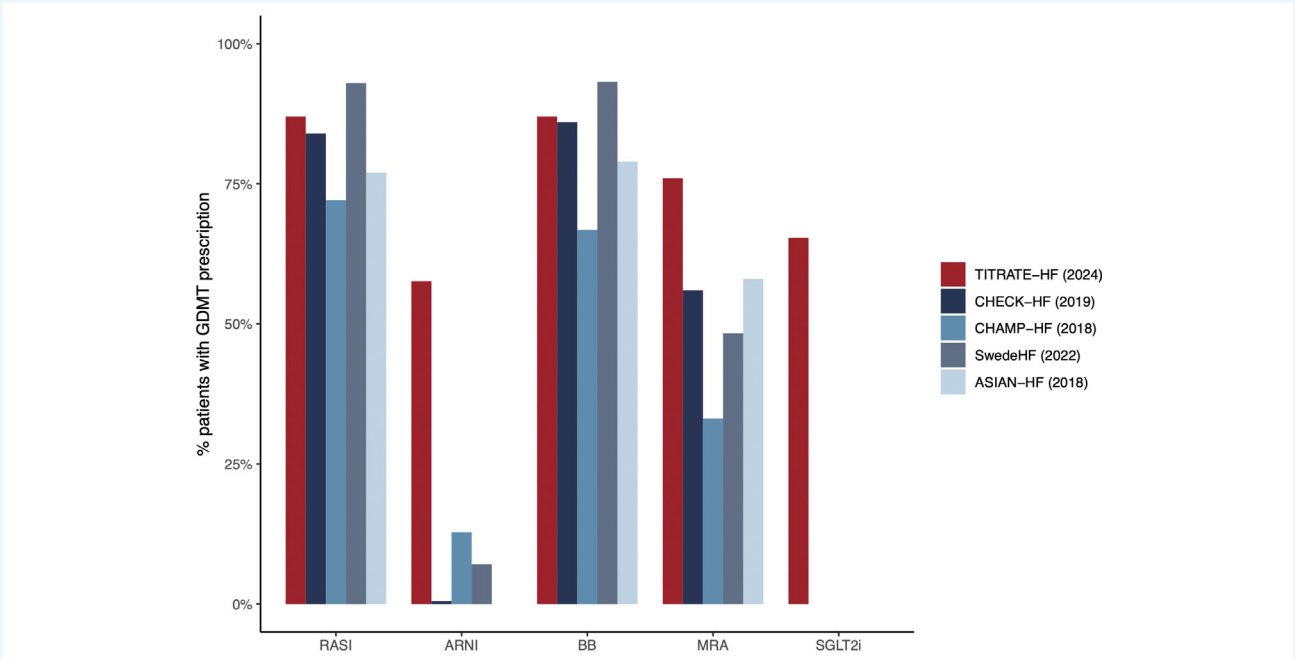

Figure 2 Comparison of guideline-directed medical therapy (GDMT) use in heart failure with reduced ejection fraction patients between heart failure registries. ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

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a new guideline-recommended drug class is implemented well. This is in line with findings from the multinational EVOLUTION-HF, which also demonstrated delayed initiation of novel drug classes compared to older drug classes.[7] Another conclusion when comparing CHECK-HF and TITRATE-HF, is that GDMT prescription levels (either three or four drug classes) slightly improved from 39% to 44%. However, this is in perspective of the ESC guideline recommendations that have become stronger. In addition, it may be worthwhile to point out that the uptake of SGLT2i seems to be faster than previous classes of drugs. One may speculate whether this is related to the fact that there is only one dose used with no need for further up-titration, or that adherence to guidelines is indeed improving.

In chronic and worsening HFrEF patients, patients with lower systolic blood pressure were more frequently prescribed quadruple therapy in comparison to patients with higher systolic blood pressure. These findings are in line with previous findings of an analysis of CHECK-HF.[25] A possible explanation for this association might be that the low blood pressure is a sign of more severe disease or better use of the drug classes of GDMT.

The TITRATE-HF study has multiple strengths worth mentioning. The study consists of a large-scale cohort of 4288 HF patients representing three distinct phases of disease progression in HF, namely de novo, chronic, and worsening HF that are prospectively monitored in terms of GDMT use, dose changes, side-effects, and long-term prognosis for the coming 10 years. Patients were included prospectively and consecutively to minimize selection bias and to enrol a cohort reflective of the population seen in daily clinical practice. Also, the vast majority of Dutch hospitals with a dedicated HF outpatient clinic participated in this registry (>70%). TITRATE-HF offers a representative overview of the quality of care for HF patients in the Netherlands. To our knowledge, TITRATE-HF is one of the first studies to identify pre-HF diagnosis GDMT use (naïve) in a large set of de novo HF patients. It is also the most contemporary study describing the uptake of the latest guideline-recommended drug classes, ARNI and SGLT2i. Study enrolment started after both drug classes were already recommended by guidelines, therefore making TITRATE-HF able to accurately assess the uptake of these drug classes including the speed and order of up-titration—when more follow-up data are available—to compare with the guideline recommendations based upon STRONG-HF.

This study also has limitations to consider. First of all, the study was conducted solely in the Netherlands, which could limit external generalizability. However, it is unlikely that barriers encountered and side-effects experienced by patients would differ significantly in other Western countries. Secondly, the large number of participating hospitals and the relatively lower number of inclusions in a site may lead to selection bias and subsequently overestimate the use of GDMT. However, to minimize the impact of this limitation, the inclusion process was designed to be consecutive. Thirdly, many reasons for GDMT non-use were well-documented but it is of note that in many occasions healthcare providers have not reported clear reasons for non-use in the patient health records. Consequently, a sizeable knowledge gap currently remains of where barriers occur in the implementation process. To fill this gap, TITRATE-HF will analyse every GDMT titration step in de novo HF patients prospectively. Detailed records of titration patterns, including reasons for down-titration or discontinuation, will provide valuable insights into implementation barriers.

Future perspectives

For the coming years, TITRATE-HF will be very helpful to prospectively study the impact of sequencing, order and target dose of GDMT in HF patients. In the context of guideline recommendations for rapid sequencing, the real-world TITRATE-HF study will show urgently-needed data on the titration process across the different stages of HF, including the order and speed of GDMT initiation and up-titration. This includes long-term prognoses for de novo, chronic, and worsening HF patients, with data on implementation barriers and a detailed assessment of relevant subgroups, such as women, elderly, and patients with comorbidities.

Conclusion

In this contemporary real-world HF population in the Netherlands, GDMT prescription rates were relatively higher compared to previous registries. However, the average doses were below the target doses recommended by the guidelines. This report serves as the foundation and starting point for the TITRATE-HF study, focusing on analysing GDMT sequencing and titration patterns, while identifying implementation barriers.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

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steering committee received no funding for this project. All authors have approved the manuscript before submission.

Conflict of interest: M.E.E. reports speaker fees from Astra Zeneca, Vifor, Boehringer Ingelheim, and Novartis. S.K. reports speaker engagements with Novartis, Boehringer Ingelheim, and Astra Zeneca. J.S. received an educational grant and speaker/consultancy fees from Boehringer Ingelheim, Daiichi Sankyo, AstraZeneca, General Electric and Novo Nordisk, all not related to this work. A.M. received speaker fee from Novartis. S.v.W. received grants and/or speaker fees from Boehringer Ingelheim, Novartis, Artazenica, Roche, Pfizer. C.J.W.B. reports speaker engagements with Abbott, AstraZeneca, Boehringer Ingelheim, and Novartis. S.L.M.A.B. reports speaker fees from Boston Scientific and Medtronic Trading BV and consulting fees from Boston Scientific. R.v.K. received grant from Dutch Heart Foundation, and speaker fees from Novartis Pharma and Bayer, and is voting nucleus member of ESC WG on Aorta and Peripheral Artery Disease. O.C.M. reports speaker engagement or advisory board fees from AstraZeneca, Abbott, Boehringer Ingelheim, Daiichi Sankyo, Novartis, Novo Nordisk, Siemens and Vifor. R.M.A.v.d.B. reports grants from Abbott and Boehringer Ingelheim and speaker fees from Abbott, Boehringer Ingelheim, Bayer, and Health Investment, all not related to this work. C.E.E.v.O. board member NVVC, board member MSBD/FMSD diakonessenhuis, and member audit committee FMS. A.F.M.K. reports Amgen advisory board and national Lead Surmount study Eli-Lilly. L.K. reports speaker fees from Bayer, Boehringer Ingelheim, Amgen, and Novartis. M.L.H. reports grants from Dutch Heart Foundation, Netherlands CardioVascular Research Initiative and Vifor Pharma, and consulting or speaker fees from Boehringer Ingelheim, Vifor Pharma, AstraZeneca, Bayer, MSD, Novartis, and Abbott. M.K.S. reports speakers fee from AstraZeneca. F.W.A. reports grants from Heart4Data Consortium, funded by the Dutch Heart Foundation and ZonMw. P.M. reports grant support from Novartis, Pharma Nord, Pfizer, Eidos, AstraZeneca, Vifor Pharma, and Pharmacosmos. H.P.B.R. reports grants from Roche Diagnostics and Vifor Pharma, consulting fees from Novartis, Boehringer Ingelheim, Vifor Pharma, and Roche Diagnostics, and payment for export testimony from Novartis, participation in board of CeleCor Therapeutics, and leadership for IHI project iCARE4CVD. R.A.d.B. reports research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals GmbH, Novo Nordisk, and Roche; speaker engagements with and/or fees from and/or served on an advisory board for Abbott, AstraZeneca, Bristol Myers Squibb, Cardior Pharmaceuticals GmbH, NovoNordisk, and Roche; and received travel support from Abbott, Cardior Pharmaceuticals GmbH, and NovoNordisk. J.J.B. reports speaker engagements for invited lectures or advisory board fees from AstraZeneca, Abbott, Boehringer Ingelheim, Bayer, Daiichi Sankyo, Novartis, and Vifor in the past 5 years. All other authors have nothing to disclose.

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