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Factors associated with non-use and sub-target dosing of medical therapy for heart failure with reduced ejection fraction

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Abstract

In clinical practice, many patients with heart failure with reduced ejection fraction (HFrEF) are either not prescribed guideline-directed medical therapies for which they are eligible or are prescribed therapies at sub-target doses. The objective of this study was to examine the factors associated with not receiving guideline-directed medical therapies or receiving sub-target doses. We conducted a systematic review of articles published between January 2014 and May 2019 that described dosing patterns and factors associated with non-use and sub-target dosing of HFrEF therapies in clinical practice. Thirty-seven studies were included. The percentages of patients reaching target doses for angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, sacubitril/valsartan, beta-blockers, and mineralocorticoid receptor antagonists ranged from 4 to 55%, 11 to 87%, 4 to 60%, and 22 to 80%, respectively. Older age and worsening renal function were associated with non-use and sub-target dosing, lower body mass index was commonly associated with non-use, and hyperkalemia and hypotension were commonly associated with sub-target dosing. In conclusion, several common patient characteristics are associated with non-use and sub-target dosing of medical therapy for HFrEF. These high-risk groups are in particular need of further studies to improve implementation of available medications and to define the role of novel therapies.

Keywords Heart failure · Systolic heart failure · Drug therapy · Maximum tolerated dose · Guideline adherence

Introduction

Heart failure (HF) affects about 64 million people globally [1, 2] and is associated with substantial morbidity, mortality, and economic burden [3–5]. Medical therapy is the cornerstone of treatment for heart failure with reduced ejection fraction (HFrEF), and multiple medications have been proven to significantly increase survival, reduce hospitalizations, and improve quality of life [6]. These guideline-directed medical therapies (GDMT) include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan, beta-blockers, and mineralocorticoid receptor antagonists (MRAs), with selective adjunctive use of diuretics, hydralazine, isosorbide dinitrate, ivabradine, and digoxin [7–9]. Newer trials have also shown improved clinical outcomes with dapagliflozin, empagliflozin, vericiguat, and omecamtiv mecarbil [10–13].

Despite substantial benefits in clinical trials and strong guideline recommendations, there remain major gaps in the use and dosing of GDMT in real-world practice [14–17]. These treatment gaps have been demonstrated repeatedly in the literature and have not meaningfully improved over the past decade [18]. It is important to understand the root causes of non-use and sub-target dosing of guideline-recommended HF therapies to best inform clinical care, research initiatives, and policy decisions. We sought to systematically review real-world studies that reported the reasons or factors associated with non-use and sub-target dosing of GDMT for HFrEF.

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Methods

Information sources and search methods

This review was conducted according to PRISMA guidelines [19]. MEDLINE and Embase were searched via ProQuest using the search strategies shown in Online Tables 1 and 2. The first search focused on research regarding use of HFrEF medical therapy and the second focused on dosing patterns. Since a previous literature review published in 2016 examined real-world treatment regimens and dosing patterns among HFrEF patients during 2000–2015 [15], our review focused on articles published since 2015.

Study selection

Non-duplicate results of the literature searches were screened first by title and abstract and then by a review of the full text. At each screening step, study eligibility was based on pre-defined PICOS criteria (Table 1), as recommended in the PRISMA guidelines [19]. Non-interventional studies of patients with HF or HFrEF published in English between January 1, 2014, and May 15, 2019, were included. Studies were excluded if they were clinical trials or economic modeling studies, or if they included exclusively patients with HF with preserved ejection fraction or acute HF, or non-pharmacological treatments for HF. Two independent reviewers screened and reviewed the articles, and a third reviewer oversaw the process and resolved any discrepancies between the first two reviewers. Institutional review was not needed for this review.

Data Collection and definitions

Variables extracted included study details (e.g., design and data source, time frame, objective), patient characteristics, proportions of patients receiving various doses of GDMT, and the reasons for and characteristics associated with non-use or sub-target dosing of GDMT. GDMT data included ACEIs/ARBs/ARNI, beta-blockers, and MRAs. Sub-target dosing was defined as less than the target dose described in the guidelines from the European Society of Cardiology [7, 20, 21] or the American College of Cardiology/American Heart Association [9], with the following exceptions: Martens et al. published their own table of target doses, with slight variations from the European Society of Cardiology

Table 1 Study inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Patients with HF or HFrEF	Cohorts of patients with exclusively HFpEF or acute heart failure Patients at risk of HF
Interventions	Any HF pharmacologic treatment	Non-pharmacological treatments for HF, including behavioral or surgical interventions
Comparators	Any or none	Not applicable
Outcomes	Characteristics/variables associated with patients treated versus not treated with guideline-recommended therapy (safety included) Factors associated with suboptimal dosing/non-guideline therapy Reasons why guideline-recommended therapies are not prescribed Dosing patterns	Studies without outcomes of interest
Study design	Observational studies (prospective or retrospective) Survey studies Registry studies Literature reviews of observational studies	Randomized controlled trials Modeling studies
Publication type	Journal articles Reviews/perspectives Practice guidelines Health technology assessment reports	Not applicable
Location	Not applicable	Not applicable
Language	English	Non-English
Time period	January 1, 2014- May 15, 2019	Not applicable

HF heart failure, *HFpEF* heart failure with preserved ejection fraction *HFrEF* heart failure with reduced ejection fraction *PD* pharmacodynamics *PK* pharmacokinetics

Table 2 Rates of use of guideline-directed medical therapies

	No. studies	Range	References
ACEI/ ARB	19	55–97%	[14, 15, 23–25, 27, 28, 31, 33, 37–40, 44, 45, 48, 50, 51, 53]
ARNI[a]	3	0.5–14%	[39, 40, 48]
Beta-blocker	24	51–99%	[14, 15, 17, 22–25, 27, 28, 30, 31, 33, 37–41, 44, 45, 48–51, 53]
MRA	20	18–90%	[14, 15, 17, 22, 24, 25, 27, 28, 30, 31, 33, 38–41, 44, 45, 48, 49, 53]
ACEI/ARB + beta-blocker	7	34–69%	[27, 28, 31, 33, 47, 48, 51]
ACEI/ARB + beta-blocker + MRA	5[b]	12–39%	[27, 31, 33, 39, 48]

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor-neprilysin inhibitor, *MRA* mineralocorticoid receptor

[a]Antol et al. 2018 [30], Atallah et al. 2019 [25], and Martens et al. 2018 [22] specifically analyzed patients treated with sacubitril/ valsartan and therefore were not included in this row of the table. And in Brunner-La Rocca et al. 2019 [48], sacubitril/valsartan use was 0.5%, which may be because it was collected only in the last couple of months

[b]Greene et al. 2018 [39] found the % of ACEI/ARB/ARNI + beta-blocker + MRA to be 22.1%

guidelines [22]; Gilstrap et al. defined dosing as "less or no" therapy at discharge compared with hospital admission [23].

Data analysis

The 2 primary outcomes of interest were factors associated with non-use and with sub-target dosing of GDMT. Included studies were grouped based on their reporting of quantitative versus qualitative data for the outcomes of interest. Quantitative data were defined as results of multivariate logistic regression analysis, whereas qualitative data were defined as physician- or patient-reported reasons for non-use or sub-target dosing, obtained from the medical record or physician/patient surveys. Tables were constructed to provide a comprehensive listing of these findings, whereas the text emphasizes factors reported consistently by multiple studies and/or across multiple drug classes. Descriptive statistics were used to describe findings regarding rates of GDMT use and target-level dosing. We tabulated the range of reported prescription/use rates for each drug class and the range of reported percentages of patients receiving 100% and 50% of the target dose for each drug class.

Results

Summary of included studies

A total of 1060 unique articles were identified and screened from the literature searches (Fig. 1). After applying the predefined PICOS criteria, 919 articles were excluded by screening the title and abstract, and 104 additional articles were excluded after full-text review, leaving 36 included articles. These studies and their key characteristics are listed in Online Table 3 and included 14 retrospective cohort studies [22, 24–36], 13 prospective cohort studies [14, 17, 23, 37–46], 5 cross-sectional studies [47–51], 2 review studies [15, 52], and 2 studies with mixed methods [53, 54]. Population sizes varied from 52 [35] to 93,074 patients [28].

Rates of use of guideline-directed medical therapies

The percentages of patients using ACEIs/ARBs, ARNI, beta-blockers, and MRAs ranged from 55 to 97%, 0.5 to 14%, 51 to 99%, and 18 to 90%, respectively (Table 2). When restricted to studies reporting rates of use specifically among eligible patients, rates of use for ACEIs/ARBs, ARNI, beta-blockers, and MRAs ranged from 60 to 94% [15, 28, 38–40], 13 to 14% [39, 40], 67 to 97% [15, 28, 38–40], and 28 to 77% [15, 28, 37–40], respectively. ACEI/ARB + beta-blocker combinations were used by 34–69% of patients, whereas triple combinations of ACEIs/ARBs, beta-blockers, and MRAs were used by 12–39% (Table 2).

Factors associated with non-use of HF therapies

Five studies reported logistic regression analyses of factors associated with non-use of GDMT [14, 33, 39, 48, 51] (Table 3). Four of these studies found an association between older age and non-use of GDMT [14, 33, 39, 48]. Lower body mass index [14, 39, 48], higher ejection fraction [14, 39], worsening renal function [14, 39, 48], and higher New York Heart Association (NYHA) functional class [39, 48, 51] were also associated with non-use. In the USA, Hispanic ethnicity and atrial fibrillation were associated with non-use [39] and, in the Netherlands, hypertension was associated with use of several drug classes [48]. Chang et al. found that use of ACEIs/ARBs increased the likelihood of using beta-blockers, and vice versa [14]. Two studies reported factors associated with non-use of

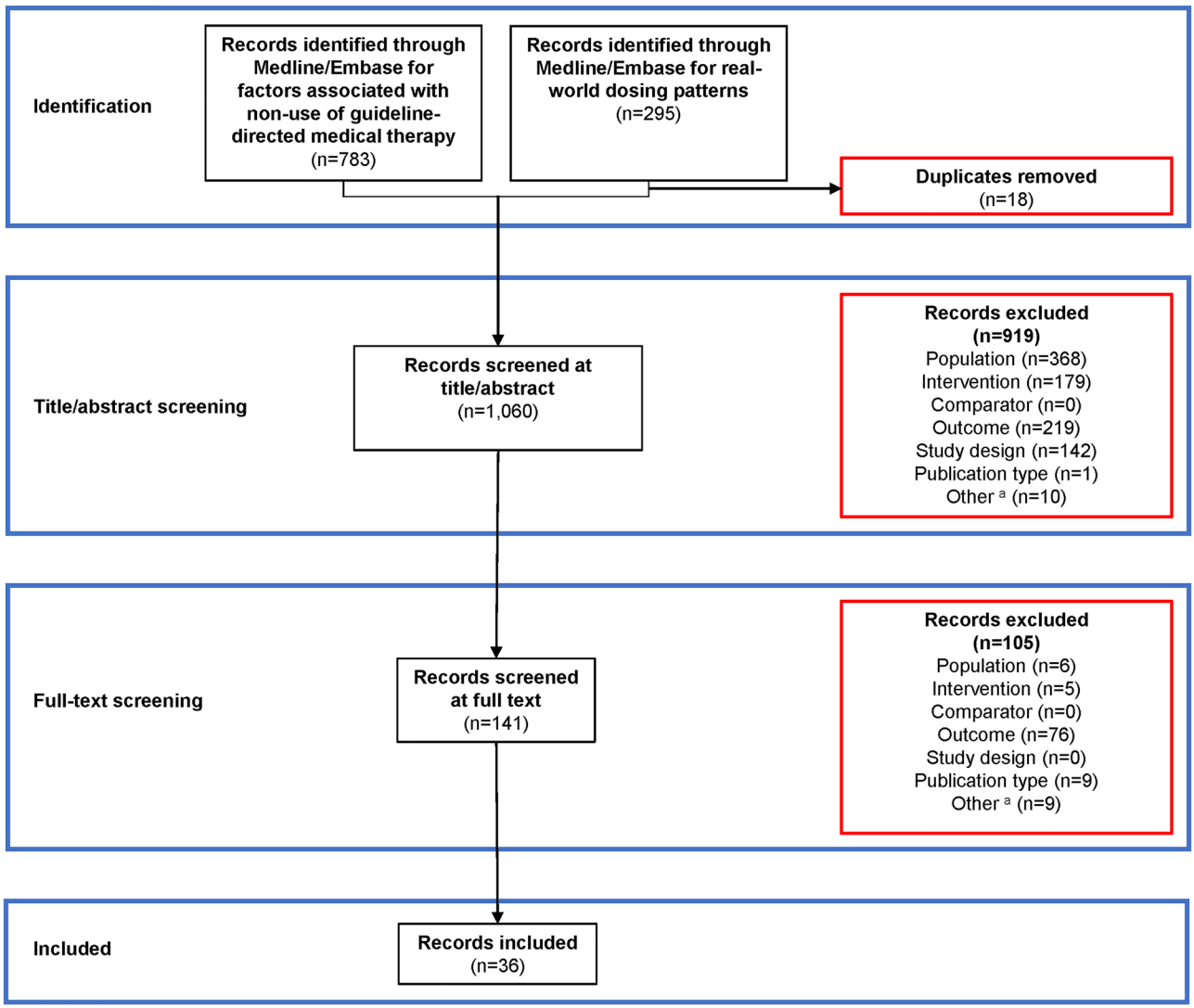

Fig. 1 Selection of included studies. ([a]Non-English studies, duplicates, small sample size, and full-text articles not available)

GDMT using qualitative data [45, 53]. Clinical factors identified by both studies included worsening renal function, hypotension, and lower heart rate (Table 3). Hirt et al. combined reviews of electronic medical records with physician and patient interviews [53]. Physician reasons for not prescribing therapy included not seeing an indication, concerns about adverse effects, and forgetting to prescribe. Patient reasons included not being physically active, perceptions of ineffectiveness, forgetting to take medications, and information from third parties such as magazines.

Rates of target dose achievement

The percentages of patients reaching target doses for ACEIs/ARBs, ARNI, beta-blockers, and MRAs ranged from 4 to 55%, 11 to 87%, 4 to 60%, and 22 to 80%, respectively (Table 4). Studies based on data from specialized HF treatment programs or from single centers tended to report high percentages of patients reaching the target dose [22, 24, 35].

Factors associated with sub-target dosing of HF therapies

Three studies reported logistic regression analyses of factors associated with sub-target dosing of GDMT [39, 40, 43] (Table 5). Ouwerkerk et al. [43] assessed dosing of ACEIs/ARBs and beta-blockers on a continuous scale. Factors associated with lower ACEI/ARB dosing included female gender, lower body mass index, worsening renal function, and higher alkaline

Table 3 Factors associated with non-use of guideline-directed medical therapies

Factors	ACEI/ARB	ARNI	Beta-blocker	MRA
Sociodemographic characteristics				
Older age	Brunner-La Rocca 2019 [48]* Chang 2017 [14]* Hirt 2016 [53]*** [a] Kruik-Kolloffel 2019 [33]*	Greene 2018 [39]*	Brunner-La Rocca 2019 [48]* Greene 2018 [39]* Chang 2017 [14]* Kruik-Kolloffel 2019 [33]*	Brunner-La Rocca 2019 [48]* Greene 2018 [39]* Chang 2017 [14]* Kruik-Kolloffel 2019 [33]*
Female	Greene 2018 [39]*			
Male			Brunner-La Rocca 2019 [48]*	Greene 2018 [39]*
Hispanic		Greene 2018 [39]*	Greene 2018 [39]*	Greene 2018 [39]*
Clinical characteristics				
Worsening renal function	Greene 2018 [39]* Chang 2017 [14]* Opolski 2017 [45]**	Greene 2018 [39]*	Brunner-La Rocca 2019 [48]*	Greene 2018 [39]* Chang 2017 [14]* Opolski 2017 [45]** Hirt 2016 [53]***
Hyperkalemia				Opolski 2017 [45]**
NYHA functional class	Greene 2018 [39] (III and IV vs. I)* Brunner-La Rocca 2019 [48] (per higher class)* Niriayo 2019 (III vs. I) [51]*			
Higher ejection fraction		Greene 2018 [39]*	Greene 2018 [39]*	Chang 2017 [14]* Greene 2018 [39]*
Lower body mass index	Chang 2017 [14]* Brunner-La Rocca 2019 [48]*		Chang 2017 [14]* Brunner-La Rocca 2019 [48]*	Brunner-La Rocca 2019 [48]* Greene 2018 [39]*
Atrial fibrillation	Greene 2018 [39]*		Greene 2018 [39]*	
Asthma/obstructive pulmonary disease			Chang 2017 [14]* Greene 2018 [39]* Opolski 2017 [45]**	
Cough	Opolski 2017 [45]**			
Valvular heart disease	Niriayo 2019 [51]*			
Non-sinus rhythm				
Pacemaker dependence				
QRS duration	Brunner-La Rocca 2019 [48]*		Brunner-La Rocca 2019 [48]*	
Higher blood pressure				Chang 2017 [14]*
Absence of hypertension	Brunner-La Rocca 2019 [48]* Niriayo 2019 [51]*		Brunner-La Rocca 2019 [48]*	Brunner-La Rocca 2019 [48]*
Hypotension	Opolski 2017 [45]** Hirt 2016 [53]***		Opolski 2017 [45]**	
Higher heart rate	Brunner-La Rocca 2019 [48]*		Chang 2017 [14]*	
Bradycardia/lower heart rate			Opolski 2017 [45]** Hirt 2016 [53]***	
Diabetes			Hirt 2016 [53]***	
Absence of diabetes	Niriayo 2019 [51]*			
Gynecomastia				Opolski 2017 [45]**
Fatigue			Opolski 2017 [45]**	
Worsening of claudication related to PAD			Opolski 2017 [45]**	
Atrioventricular conduction disorders			Opolski 2017 [45]**	

Table 3 (continued)

Factors	ACEI/ARB	ARNI	Beta-blocker	MRA
Physician-related factors				
Physicians do not see an indication	Hirt 2016 [53]***			Hirt 2016 [53]***
Physician forget to prescribe	Hirt 2016 [53]***		Hirt 2016 [53]***	
Physician's concerns about AE				Hirt 2016 [53]***
Other patient-related factors				
Forgetfulness	Hirt 2016 [53]***			
Patient was not physically active			Hirt 2016 [53]***	
Patient perception of ineffectiveness	Hirt 2016 [53]***			
Information from a third party such as magazines	Hirt 2016 [53]***			

ACEI angiotensin-converting enzyme inhibitor, *AE* adverse event, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor-neprilysin inhibitor, *HF* heart failure, *MRA* mineralocorticoid receptor antagonist, *NYHA* New York Heart Association, *PAD* peripheral artery disease

*Chart review/electronic medical record/registry/other database with a regression analysis; **Chart review with reasons obtained from chart; ***Electronic medical record + survey input from doctors and patients

[a]Hirt et al. [53] did not specify drug classes for patient-related factors

phosphatase levels. Factors associated with lower beta-blocker dosing were older age, lower heart rate and diastolic blood pressure, and signs of pulmonary congestion. Greene et al. [40] showed lower likelihood of up-titration/initiation of GDMT with older age (beta-blockers and ARNI), history of ventricular tachycardia/fibrillation (beta-blockers), higher ejection fraction (ARNI and MRAs), hyperlipidemia (MRAs), and lower annual household income (ARNI). Higher Kansas City Cardiomyopathy Questionnaire score was associated with lower likelihood of up-titration/initiation of MRAs. Greene et al. [39] assessed the likelihood of dosing at target and/or half-target levels and found a wide variety of sociodemographic and clinical factors to be associated with sub-target dosing of GDMT (Table 5).

Several studies assessed reasons for sub-target dosing qualitatively [22, 23, 26, 32], while Hirt et al. [53] assessed sub-target dosing via patient and physician interviews. Worsening renal function and hypotension were reported across multiple studies as reasons for not achieving target doses (Table 5). Physicians not seeing the importance of achieving the target dose, forgetting to prescribe, or planning to up-titrate the therapy later were reasons for sub-target dosing. Patient-related reasons included being in hospice [23, 53].

Table 4 Proportion of patients reaching target dose, by medication class

Therapeutic class	Percentage of patients reaching 100% of the target dose			Percentage of patients reaching 50% of the target dose		
	No. studies	Range	References	No. studies	Range	References
ACEI/ARB	11	4–55%	[14, 26, 27, 38–40, 43–45, 48, 51]	14	24%—86%	[14, 15, 17, 31, 37, 39–41, 43–45, 49, 50, 52]
ARNI	10	11–87%	[22, 25, 30, 32, 35, 36, 39, 40, 42, 46]	8	41–94%	[30, 32, 35, 36, 39, 40, 42, 46]
Beta-blocker	11	4–60%	[14, 24, 26, 27, 38–40, 43–45, 48]	14	21%—84%	[14, 15, 17, 31, 37, 39–41, 43–45, 49, 50, 52]
MRA	9	22–80%	[14, 17, 38–41, 44, 45, 48]	8	67%—100%	[14, 31, 39, 40, 44, 45, 49, 52]

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor-neprilysin inhibitor, *MRA* mineralocorticoid receptor antagonist

Table 5 Factors associated with sub-target dosing

Factors	ACEI/ARB	ARNI	Beta-blocker	MRA
Sociodemographic characteristics				
Older age		Greene 2019 [40]*	Ouwerkerk 2017 [43]* Greene 2019 [40]* Greene 2018 [39]*	
Female	Ouwerkerk 2017 [43]*			
Male				Greene 2018 [39]*
Other vs. Caucasian	Greene 2018 [39]*			
Hispanic			Greene 2018 [39]*	
Annual household income < $50,000		Greene 2019 [40]*		
Clinical characteristics				
Prior HF hospitalization (within 12 month)	Greene 2018 [39]*		Greene 2018 [39]*	
Greater severity of HF (NYHA class III and IV)	Greene 2018 [39]*			
Lower body mass index and lower weight	Ouwerkerk 2017 [43]*			
Higher alkaline phosphatase value	Ouwerkerk 2017 [43]*			
Coronary artery disease		Greene 2018 [39]*	Greene 2018 [39]*	
History of ventricular tachycardia/ fibrillation			Greene 2019 [40]*	
Higher heart rate		Greene 2018 [39]*	Greene 2018 [39]*	
Lower heart rate			Ouwerkerk 2017 [43]*	
Smoking			Greene 2018 [39]*	
Lower diastolic blood pressure			Ouwerkerk 2017 [43]*	
Pulmonary congestion			Ouwerkerk 2017 [43]*	
Atrial fibrillation				Greene 2018 [39]*
Higher ejection fraction		Greene 2019 [40]*		Greene 2019 [40]* Greene 2018 [39]*
Worsening renal function	Ouwerkerk 2017 [43]* Gilstrap 2018 [23]**,a Hirt 2016 [53]***	Martens 2018 [22]** Du 2019 [32]**	Gilstrap 2018 [23]**	
Hyperkalemia	Barywani 2015 [26]**	Moliner-Abós 2019 [54]** Du 2019 [32]** Martens 2018 [22]**		Hirt 2016 [53]***
Asthma/obstructive pulmonary disease	Greene 2018 [39]*		Barywani 2015 [26]** Greene 2018 [39]* ΔGilstrap 2018 [23]	
Hypotension	Barywani 2015 [26]** Gilstrap 2018 [23]** Hirt 2016 [53]***	Martens 2018 [22]** Moliner-Abós 2019 [54]** Du 2019 [32]**	Hirt 2016 [53]*** Gilstrap 2018 [23]** Barywani 2015 [26]**	
Inotropic therapy/cardiogenic shock	Gilstrap 2018 [23]**		Gilstrap 2018 [23]**	
Bradycardia			Hirt 2016 [53]*** Gilstrap 2018 [23]** Barywani 2015 [26]**	
Depression			Hirt 2016 [53]***	
Itching		Martens 2018 [22]**		
Blurred vision		Martens 2018 [22]**		
Diarrhea		Martens 2018 [22]**		
Develop rash and/or fatigue		Du 2019 [32]**		
Normal blood pressure	Hirt 2016 [53]***		Hirt 2016 [53]***	
Physician-related factors				
Physician's lack of awareness of the importance of reaching target dose	Hirt 2016 [53]***		Hirt 2016 [53]***	

Table 5 (continued)

Factors	ACEI/ARB	ARNI	Beta-blocker	MRA
Physician forgot to increase dose	Hirt 2016 [53]***		Hirt 2016 [53]***	
Plan to up-titrate			Gilstrap 2018 [23]**	
Other patient-related factors				
In hospice	Gilstrap 2018 [23]**			
Patient non-compliance or failing to complete bloodwork		Du 2019 [32]**		
KCCQ overall summary score				Greene 2019 [40]*

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor-neprilysin inhibitor, *HF* heart failure, *KCCQ* Kansas City Cardiomyopathy Questionnaire, *MRA* mineralocorticoid receptor antagonist, *NHYA* New York Heart Association

*Chart review/electronic medical record/registry/other database with a regression analysis. These studies reported the odds of up-titration/initiation (Greene 2019 [40]), the likelihood of achieving a lower percentage of the target dose (Ouwerkerk 2017 [43]), or the odds of attaining the maximal or half-maximal target dose (Greene 2018 [39]); **Chart review with reasons obtained from chart; ***Electronic medical record + survey input from doctors and patients

[a]Gilstrap et al. [23] did not distinguish between no medication and down-titration of medication; however, most patients were on medication at discharge

Discussion

In order to implement effective and safe interventions to improve the treatment of HFrEF patients, understanding the causes and modifiable factors associated with suboptimal treatment is important. This review of recent studies shows that use of GDMT continues to be suboptimal and variable, with large proportions of HFrEF patients not reaching target doses. Across studies, we found multiple factors associated with non-use and sub-target dosing of GDMT. Factors most frequently associated with non-use were older age, lower body mass index, higher ejection fraction, worsening renal function, and more severe NYHA functional class. For sub-target dosing, the most frequent associations were with older age, worsening renal function, hyperkalemia, and lower blood pressure. Some of these findings, such as the associations with hypotension and decreased renal function, suggest that side effects, concerns for intolerability, and/or real or perceived relative contraindications to GDMT are significant contributors to patients not receiving GDMT or reaching target doses (Fig. 2).

The low rates of medication use and target dosing in clinical practice raise concerns that the efficacy of GDMT established in landmark clinical outcome trials may not generalize to real-world settings. The protocols for these trials generally specified that the study drug undergo gradual, tolerance-limited up-titration every few weeks [40, 55]. Following these protocols, in general, most patients achieved the target dose and sub-target doses were only prescribed when target doses could not be tolerated. For example, 49% of patients reached target doses of enalapril in the SOLVD trial [56], 60% with eplerenone in the EMPHASIS-HF trial [57], and 65% with carvedilol in the COPERNICUS trial [58]. Although differences between clinical trial and real-world populations have been proposed as an explanation for underuse and underdosing of GDMT, these differences may be less drastic than previously thought [59, 60]. Importantly, the magnitude of the gaps seen in routine practice is unlikely to be explained by population differences and supports opportunities for improving quality of care. For example, in the CHAMP-HF registry, very few medication changes occurred during1-year follow-up [40], suggesting clinical inertia. Data from several of the included studies support the importance of medication dosing for improved outcomes. For example, Ouwerkerk et al. found that using < 50% of the recommended ACEI/ARB and beta-blocker dose was associated with an increased risk of death and/or HF hospitalization, compared with target dosing [43]. Teng et al. observed a dose-dependent decrease in the hazard of a 1-year risk of all-cause death or HF hospitalization with increasing doses of ACEIs/ARBs and beta-blockers [44]. However, multiple other studies not meeting criteria for inclusion in our review have also found an association between higher doses of GDMT and improved clinical outcomes [61, 62]. Although important to acknowledge that observational studies are inherently vulnerable to residual confounding and cannot definitively prove cause-effect relationships, these results are generally concordant with randomized evidence and clinical guidelines supporting incremental benefits with target or maximally tolerated doses.

Our results suggest that comorbidities and concern for patient intolerance are two main types of patient factors associated with sub-target dosing, which is consistent with a recent study of gaps in adherence to HF guidelines [63]. It is notable that patients with more advanced comorbidities are often excluded from HFrEF trials, and such patients may be less likely to reach target dosing.

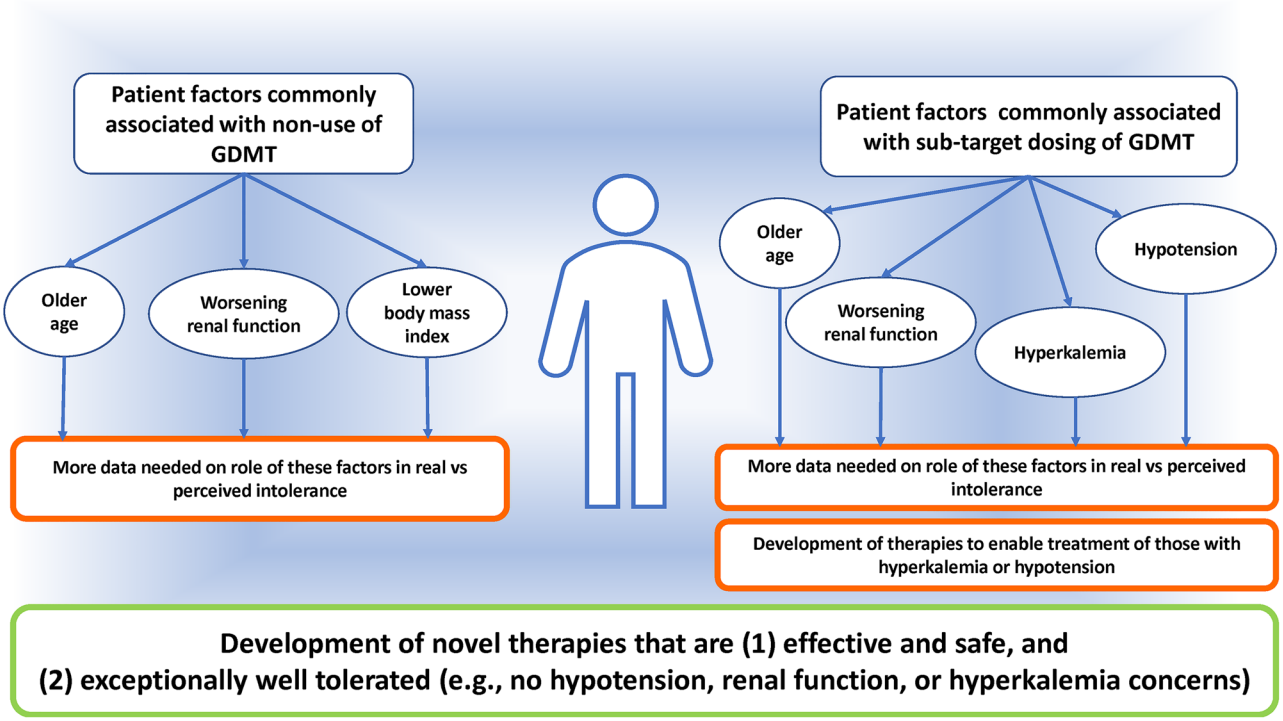

Fig. 2 Optimizing medical treatments for patients with heart failure with reduced ejection fraction. The figure illustrates a patient-centered approach to improving the implementation of currently available therapies (orange boxes) and highlights the need for new therapies for specific groups of patients (green box). (*GDMT* guideline-directed medical therapy)

Barring non-compliance issues, lack of or suboptimal use of GDMT due to intolerance or comorbidities may put patients at higher risk, necessitating a need for novel therapies that are effective and well-tolerated. However, failure of physicians to see the importance of achieving the target dose remains a barrier and clinical inertia is a multi-factorial problem with contributions from healthcare providers, patients, and the healthcare system. Strategies with the potential to alleviate clinical inertia include education of physicians in conjunction with performance evaluations, dissemination of guidelines in a way that improves physician understanding and implementation, and team-based healthcare that includes patients in the decision-making process [64]. For example, we found history of lung disease to be repeatedly associated with higher likelihood of beta-blocker non-use and sub-target dosing. Although this certainly could reflect bronchospasm and true intolerance, it is notable that multiple studies and meta-analyses have found beta-blockers associated with improved survival in patients with HFrEF and comorbid COPD and to not result in significant differences in pulmonary function [65–68]. Thus, the scenario of beta-blockers in lung disease may be an example where clinician education regarding newer data and clinical guidelines may help alleviate more historical concerns over a perceived high risk for patient intolerance. Likewise, patient education will be critical, as many HF patients in practice may be unfamiliar with GDMT, express concerns regarding efficacy and safety, and over-estimate their individual survival [69]. Practical strategies include spacing medication dosing to avoid fluctuations in blood pressure that lead to symptoms of hypotension and simplifying the dosing regimen [70]. Quality improvement initiatives integrating scorecards and performance measures could also provide physicians with quantitative feedback on their achievement of clinical goals.

Limitations of our study should be noted. The determination of patient eligibility and contraindications for the various GDMT varied across studies. Analyses that did account for eligibility generally found rates of absolute contraindications to be low. For sub-target dosing, the proportion of patients at the maximally tolerated dose versus those receiving suboptimal care is unclear. Data on whether patients were challenged with initiation or higher doses of therapies were not available. Our review summarized factors associated with the outcomes of use and dosing of GDMT but was not quantitative at the patient level and did not assess the relative strength of individual associations.

In conclusion, in contemporary real-world clinical practice, there remain sizeable proportions of patients with HFrEF who

do not receive GDMT or who receive therapies at sub-target doses. Several factors are associated with non-use and sub-target dosing, including age, comorbidities, and characteristics that could increase risk for intolerance such as hypotension and impaired renal function. Quality improvement initiatives are needed to improve titration of GDMT to maximally tolerated or target doses. An unmet need remains for patients who cannot reach target doses and face significant residual risk for mortality and morbidity. For patients who cannot tolerate target doses of GDMT, further development of pharmacotherapies that are both effective and well-tolerated is warranted.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s10741-021-10077-x.

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Compliance with ethical standards

Conflict of interests Stephen J. Greene has received a Heart Failure Society of America/ Emergency Medicine Foundation Acute Heart Failure Young Investigator Award funded by Novartis; has received research support from the American Heart Association, Amgen, AstraZeneca, Bristol-Myers Squibb, Merck, and Novartis; has served on advisory boards for Amgen and Cytokinetics; and serves as a consultant for Amgen and Merck. Xi Tan and Mei Yang are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and stockholders of Merck & Co., Inc., Kenilworth, NJ, USA. Yu-Chen Yeh, Mark Bernauer, and Omer Zaidi are employees of Pharmerit, which received research support from Merck & Co., Inc. to conduct the study. Javed Butler serves as a consultant to Abbott, Array, Amgen, Applied Therapeutics, Astra Zeneca, Bayer, Boehringer Ingelheim, CVRx, Eli Lilly, G3 Pharma, Impulse Dynamics, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Sequana Medical, V-Wave Limited, and Vifor.

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