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REVIEW

Optimization of GDMT for patients with heart failure and reduced ejection fraction: can physiological and biological barriers explain the gaps in adherence to heart failure guidelines?

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Abstract

Heart failure is a growing epidemic with high mortality rates and recurrent hospital admissions that creates a burden on affected individuals, their caregivers and the whole healthcare system. Throughout the years, many randomized trials have established the effectiveness of several pharmacological therapies and electrophysiological devices to reduce hospitalizations and improve quality of life and survival, mostly for patients with heart failure with reduced ejection fraction (HFrEF). These studies led to the publication of national societies' recommendations to guide clinicians in the management of HFrEF. Yet, many reports have shown significant care gaps in adherence to these recommendations in clinical practice, highlighting suboptimal use and/or dosing of evidence-based therapies. Adherence to guidelines has been shown to be associated with the best prognosis in HFrEF, with patients presenting with intolerances or contraindications having the highest risk of events; however, it remains unclear whether this association is causal or merely a marker of more advanced disease. Furthermore, individual characteristics may limit the possibility of reaching the targeted dosage of specific agents. Herein, we provide a comprehensive overview of clinicians' adherence to heart failure guidelines in a specialized real-life setting, particularly regarding use and optimization of guideline-derived medical therapies, as well as the implementation of more recent agents such as sacubitril/valsartan and SGLT2 inhibitors. We seek potential explanations for suboptimal treatment and its impact on patient outcomes.

Keywords: drug therapy, guideline adherence, heart failure, outcome measures, reduced ejection fraction.

Citation

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Introduction

There are currently over 64 million people living with heart failure (HF) worldwide,[1] causing an important burden on patients, their caregivers and healthcare systems, leading to recurrent hospitalizations and increased mortality.[2] Whilst HF with preserved ejection fraction is on the rise due to the ageing of the population and the increase in prevalence of risk factors, such as obesity, hypertension and diabetes mellitus,[3,4] its treatment is less well defined than its counterpart, HF with reduced ejection fraction (HFrEF). Robust evidence exists for the use of a combination of four drugs for the treatment of HFrEF, namely a beta-blocker, an angiotensin receptor–neprilysin inhibitor (ARNI) or angiotensin-converting enzyme inhibitor (ACEI)/angiotensin-receptor blocker (ARB), a mineralocorticoid receptor antagonist (MRA), and a sodium–glucose cotransporter 2 inhibitor (SGLT2i).[5–7] Nevertheless, despite the publication of national societies' guidelines supporting the prescription of a combination of these pharmacological agents at target doses for patients with HFrEF,[8,9] poor adherence to these recommendations has been demonstrated in real life.[10–13]

In this review, we discuss the importance and benefits of pharmacological optimization for the treatment of HFrEF by focusing on individual characteristics causing physiological and biological limitations to target doses.

Methods

We examine the prescription rates and optimization of drugs for the treatment of HFrEF in real-life ambulatory settings and their impact on mortality and morbidity. The literature search was performed from October 2022 to April 2023 on PubMed and Google Scholar using the following keywords: "HFrEF therapy", "guideline adherence heart failure", "clinical inertia heart failure" and "ambulatory care management heart failure". The literature selection strategy consisted of all clinical trials (including randomized, non-randomized and open trials), observational studies (excluding case reports and case series) and reviews (including narrative reviews, clinical guidelines and meta-analyses) published within the last 15 years. Only articles published in English were selected with no focus on specific countries or world regions.

Review

Use and optimization of pharmacotherapies for the treatment of outpatients with HFrEF in ambulatory care

The pharmacological treatment of HFrEF has evolved over the last two decades from the prescription of diuretics, beta-blockers, renin-angiotensin system (RAS) inhibitors and MRA to a more sophisticated regimen including sacubitril/valsartan and, more recently, SGLT2i;[8] ivabradine can be added in selected patients. Hence, a combination of four classes of guideline-derived medical therapies (GDMT), comprised of a beta-blocker, an ARNI (or alternatively an ACEI/ARB), an MRA and an SGLT2i, is now the cornerstone of treatment to improve survival and reduce hospitalization of patients with HFrEF.[7] Furthermore, newer agents recently showed beneficial effects on patient prognosis, including the cardiac myosin activator omecamtiv mecarbil,[14] and vericiguat,[15] an oral soluble guanylate cyclase stimulator. Thus, implementation of this complex pharmacological regimen has become an important challenge, with significant care gaps being observed between guidelines and clinical practice, including delays in both drug prescription and optimization, which may ultimately lead to suboptimal patient outcomes.[16] Many hypotheses have been suggested to explain this care gap, with clinical inertia being proposed as a major factor.[12,17,18]

Prescription rates of evidence-based therapies in clinical practice: status quo

Great variability exists in the prescription rates of each class of agent comprising GDMT for ambulatory patients with HFrEF (Table 1).[10–13,18–26] In 2008, the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) evaluated 167 outpatient cardiology clinics and showed high prescription rates of beta-blockers (86%) and RAS inhibitors (ACEI or ARB; 80%) in eligible patients but much lower use of MRAs (36%); this was believed to be due to a perceived risk of increased mortality or hospitalization associated with hyperkalaemia as shown after the publication of the RALES and the subsequently wide use of MRAs.[19,27] Moreover, an analysis from the Swedish Heart Failure Registry showed that use of beta-blockers improved from 85% to 93% (p=0.008) between 2003 and 2012, whereas use of RAS inhibitors remained unchanged (88% *versus* 86%; p=0.091) and the use of MRAs decreased (53% *versus* 42%; p<0.001) after adjusting for 38 clinically significant baseline variables.[22] Yet, 10 years after the publication of IMPROVE HF, these patterns remained unchanged, with prescription rates in the Change the Management of Patients with Heart Failure (CHAMP-HF) registry as low as 33.4% for MRAs and 73.4% for RAS inhibitors, including the newer ARNI (13%), and suboptimal for beta-blockers (67% of eligible patients). In fact, concomitant use of all three recommended classes of drugs merely reached 22%.[10] Accordingly, whilst beta-blockers and ACEI/ARBs seem to be well implemented in current clinical practice, the use of other pharmacotherapies, such as MRA and the relatively newer sacubitril/valsartan, remains unsatisfactory. By contrast, in a retrospective analysis of 511 patients with HFrEF followed in a multidisciplinary HF clinic with access to granular clinical and para-clinical data, prescription rates of ARNI and MRAs amongst eligible patients were markedly higher than in previous reports, reaching 91.4% and 93.4%, respectively; triple therapy was prescribed to 76.5% of eligible patients. These findings suggest that greater use of newer classes of agents is achievable in real-life practice, especially with a multidisciplinary and more personalized approach to evaluate adherence to GDMT.[12]

Additionally, the setting in which these patients with HFrEF are followed seems important. For instance, results from a secondary analysis in the CHAMP-HF Registry showed that evidence-based therapies were more often prescribed to eligible patients seen in cardiology settings compared with those seen in the family medicine/internal medicine setting (ACEI/ARB/ARNI: 73.2% *versus* 65.4; beta-blockers: 70.5% *versus* 42.3%; MRAs: 35.2 *versus* 14.4%, respectively).[10] Whilst no statistical tests were conducted, it is of no surprise that specialized healthcare providers tend to prescribe GDMT more frequently than general practitioners (GPs) in real-world practice. In fact, another study that compared the management of patients with HFrEF when treated by cardiologists *versus* when treated by GPs came to a similar conclusion, stipulating that GPs are less likely than cardiologists to prescribe beta-blockers or MRAs to patients with HFrEF;

Table 1. Prescription rates and target doses of recommended therapies of all included studies.

Authors (year)	Study short name	Setting	Patients included	Prescription and rates	%	At target dose (%)
Fonarow GC, et al. (2008)[19]	IMPROVE HF	167 outpatient cardiology practices	15,381	BB ACEI/ARB MRA	86.0 80.0 36.0	NA
Komajda M, et al. (2016)[13]	QUALIFY	547 outpatient clinics	7092	BB ACEI/ARB MRA	86.7 86.7 69.3	14.8 27.9/6.9 70.8
Ouwerkerk W, et al. (2017)[18]	BIOSTAT-CHF	69 outpatient centres	2100	BB ACEI/ARB	90.5 85.5	13.5 26.2
Greene SJ, et al. (2018)[10]	CHAMP-HF	150 primary care and cardiology outpatient practices	3518	BB ACEI/ARB/ARNI ARNI MRA	67.0 73.4 13.0 33.4	27.5 16.8 14.0 76.6
Brunner-La Rocca HP, et al. (2019)[11]	CHECK-HF	34 HF outpatient clinics	5701	BB ACEI/ARB MRA	86.0 84.0 56.0	18.9 43.6 52.0
Jarjour M, et al. (2020)[79]	Care Gaps in Adherence to HF Guidelines	1 HF outpatient clinic	511	BB Vasodilators ARNI MRA	98.6 90.3 91.4 93.4	29.9 38.5 50.6 39.1
de Frutos F, et al. (2020)[24]	The Linx Registry	14 outpatient cardiology clinics	1056	BB ACEI/ARB/ARNI ARNI MRA	91.8 86.9 23.9 72.7	25.4 24.9/7.7 8.1 19.7
Cowie MR, et al. (2021)[25]	QUALIFY	549 outpatient clinics (89.5% cardiologists, 10.5% GP)	4368	BB ACEI/ARB MRA	Baseline 87.9 90.3 70.6	12-months follow-up 18.0 34.8/3.2 53.7
Pierce JB, et al. (2022)[46]	HF-ACTION	82 outpatient centres in the US, Canada, France	1999	BB ACEI	85.6 70.4	35.6 28.5
Maggioni AP, et al. (2013)[23]	ESC-HF-LT	211 cardiology inpatient and outpatient centres	4792 outpatients	BB ACEI/ARB MRA	92.7 92.2 67.0	NA
Crespo-Leiro MG, et al. (2016)[20]	ESC-HF-LT-R	211 cardiology inpatient and outpatient centres	7173 outpatients	BB ACEI/ARB MRA	89.1 86.5 59.1	NA
Thorvaldsen T, et al. (2016)[22]	SwedeHF	2003–2005: 32 sites 2009–2012: 104 sites (inpatient and outpatient)	5908	BB ACEI/ARB MRA	2003–2012 84.8–93.4 88.4–86.0 52.5–41.7	2003–2012 33.0–40.8 46.8–47.9
Teng TK, et al. (2018)[21]	ASIAN-HF	46 medical, cardiology and HF inpatient and outpatient centres	5276	BB ACEI/ARB MRA	79.0 77.0 58.0	13.0 17.0 29.0

(*Continued*)

Table 1. (Continued)

Teng TK, et al. (2023)[26]	Titration of medications and outcomes in HF cohorts from Singapore and New Zealand	Four centres in New Zealand and six centres in Singapore (inpatient and outpatient)	1110	BB ACEI/ARB	Baseline 88.0 86.5	6 months 14.5 16.5

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; GP, general practitioner; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NA, not available.

a combination of ACEI/ARB, beta-blocker and MRA was also more frequently prescribed by cardiologists.[28] As for the use of ivabradine, all reports suggest that this agent is more suited for a niche population, especially following beta-blocker optimization in patients in sinus rhythm.[11–13,23,24]

Regarding SGLT2i, few studies have documented their prescription for patients with HFrEF in clinical practice. An observational study performed in Japan, Sweden and the USA (EVOLUTION HF: *Utilization of Dapagliflozin and Other Guideline Directed Medical Therapies in Heart Failure Patients: A Multinational Observational Study Based on Secondary Data*)[29] showed delayed initiation of more recent agents, such as ARNI (USA: 62.0% 30-day after discharge; Japan: 72.7%; Sweden: 59.5%) and dapagliflozin (USA: 37.3%; Japan: 74.6%; Sweden: 54.9%), after an HF hospitalization compared with beta-blockers, RAS inhibitors and MRAs, despite their rapid onset of action and significant benefits as reported in PARADIGM-HF,[30] DAPA-HF[31] and EMPEROR-REDUCED.[32] These treatment gaps are concerning as HF hospital admission should represent an opportunity to prescribe or up-titrate GDMT.[33] Likewise, a single-centre European report showed that 19.6% of patients with HFrEF were prescribed SGLT2i at discharge following a hospitalization for HF; interestingly, patients prescribed an SGLT2i were more likely to also receive concomitant therapy with sacubitril/valsartan, a beta-blocker and an MRA compared with those not being prescribed an SGLT2i. The prescription rate of SGLT2i increased dramatically following the publication of the landmark clinical trials, from 6.8% in 2017 to 56.6% in 2022 (p_{trend}<0.0001).[34] Furthermore, the INitiation of SGlt2i in Hospital for HFrEF (INSIGHT-HF) study demonstrated that, among the 150 patients with HFrEF analysed, 57% received an SGLT2i within the first-month post-discharge, with 87% of these being initiated during hospitalization, highlighting the importance of in-hospital prescription of novel therapies.[35] Nevertheless, ambulatory implementation is still lacking, with only 4% of octogenarians with HFrEF receiving SGLT2i in an outpatient setting,[36] despite shown benefits in patients with HFrEF, regardless of the presence of diabetes.[37] Finally, these treatment gaps have prognostic implication, with patients receiving at least two classes of drugs (beta-blocker and ACEI/ARB/ARNI) at 50–99% of target dose having a lower risk of cardiovascular mortality or hospitalization for HF compared with those being prescribed only one class at target dose (HR 0.86, 95% CI 0.74–0.99).[38]

Optimization of pharmacotherapies for the management of HFrEF and associated challenges

Initiation and up-titration of recommended evidence-based therapies in a timely matter is the fundamental basis of the management of patients with HFrEF to improve outcomes[39] but remain suboptimal in clinical practice. Besides the prescription of pharmacological agents for eligible patients with no documented intolerance or contraindication, guidelines recommend the achievement of target doses that have been used and proven beneficial in the landmark trials.[8,9] Hence, despite high prescription rates of most classes of drugs included in GDMT,[10–13,18–24,40] up-titration to target doses continue to be a challenge[41] and these gaps in adherence appear to have a significant impact on the prognosis of patients with HFrEF (Table 2).[18,42–45]

Achievement of recommended target doses

Previous studies have shown that a significant proportion of patients remain on suboptimal doses of GDMT despite no obvious intolerance or contraindication (Table 1).[10–13,18,21,22,24–26,46] An analysis from CHAMP-HF showed that very little up-titration occurs in clinical practice, with less than 1% of eligible patients being treated with the triple combination at target doses of a beta-blocker, RAS inhibitor and MRA combination over 12 months. Noteworthy, there were minimal or no changes in dosage at each 3-month visit during follow-up, with most patients

Table 2. Management of HFrEF and associated patient outcomes of all included studies.

Authors (year)	Study short name	Patients included	Follow-up duration	Outcomes	Hazard ratio (95% CI)		
Ouwerkerk W, et al. (2017)[18]	BIOSTAT-CHF	2100	Median: 21 months	Mortality Mortality and/or HF hospitalization	**Compared with TD of ACEI/ARB**		
					0% 1.76 (1.54–1.98) 1.77 (1.61–1.94)	**1–49%** 1.50 (1.33–1.67) 1.23 (1.09–1.36)	**50–99%** 0.82 (0.61–1.02) 0.86 (0.71–1.00)
					Compared with TD of beta-blockers		
					2.41 (2.13–2.68) 1.51 (1.29–1.72)	1.91 (1.74–2.08) 1.27 (1.15–1.39)	1.29 (1.07–1.51) 1.04 (0.89–1.20)
Komajda M, et al. (2016)[13]	QUALIFY	6669	6 months	HF mortality and/or HF hospitalization	**Compared with good adherence score[a]**		
					Poor 1.36 (1.08–1.71)		**Moderate** 1.22 (1.01–1.47)
Ouwerkerk W, et al. (2018)[61]	BIOSTAT-CHF	1802	24 months	All-cause death or HF hospitalization ACEI/ARB Beta-blockers MRA	**Estimated event reduction compared with scenario C (<50% TD), *n* (95% CI)**		
					A (Up-titration to ≥50% TD) 177 (128 to 227) 24 (-54 to 103) 222 (147 to 298)		**B (Up-titration according to a biomarker model)** 178 (130 to 226) 84 (40 to 128) 236 (170 to 303)
Greene SJ, et al. (2022)[42]	CHAMP-HF	4832	24 months	All-cause mortality HF hospitalization	**Compared with TD of ACEI/ARB/ARNI**		
					0% 1.75 (1.32–2.34) 1.29 (1.04–1.60)	**1–49%** 1.37 (1.05–1.79) 1.23 (1.04–1.47)	**50–99%** 1.16 (0.87–1.55) 1.08 (0.90–1.30)
					Compared with TD of beta-blockers		
					1.24 (0.92–1.67)	1.41 (1.11–1.79)	1.30 (1.00–1.69)
					p=0.085		
					Compared with TD of MRA		
					p=0.962		
					p=0.983		
Pierce JB, et al. (2022)[46]	HF-ACTION	1999	Median: 30.1 months	CV death and/or HF hospitalization	**Compared with stable TD of ACEI**		
					Stable sub-TD *p*=0.57	**Dose escalation** *p* =0.12	**Dose de-escalation** *p* =0.06
					Compared with stable TD of beta-blockers		
					1.49 (1.18–1.87)	1.18 (0.84–1.65)	1.98 (1.36–2.87)
D'Amario D, et al. (2022)[38]	SwedeHF	17,809	Median: 2.06 years	CV death and/or HF hospitalization	**Compared with no use of ACEI/ARB/ARNI**		
					1–49% TD 0.83 (0.76–0.91)	**50–99%** 0.78 (0.71–0.86)	**≥100%** 0.73 (0.67–0.80)
					Compared with no use of beta-blockers		
					0.86 (0.79–0.95)	0.81 (0.74–0.89)	0.74 (0.68–0.82)

(*Continued*)

Table 2. (Continued)

Jarjour M, et al. (2023)[45]	Optimization of HFrEF therapy improves outcomes	511	12 months	All-cause death and/or HF events (hospitalization, emergency consultation or intravenous diuretic)	**Compared with optimal triple therapy (beta-blocker, ACEI/ARB/ARNI/hydralazine-nitrate and MRA)**		
					Intolerant/ contraindicated	**Undertreated**	**In titration**
					4.60 (2.23–9.48)	3.45 (1.78–6.67)	1.99 (0.97–4.06)

[a]The QUALIFY study group proposed an adherence score that was calculated for each patient: 0 points were attributed if medication was not prescribed in the absence of contraindications, 0.5 points if <50% of target doses were prescribed or 1 point for the prescription of ≥50% of target dose of GDMT. Three levels of adherence were then established: good adherence (score =1); moderate (>0.5 to <1) or poor (≤0.5).[43]

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; HF, heart failure; MRA, mineralocorticoid receptor antagonist; TD, target dose.

remaining at stable but sub-target doses for all classes of agents.[47] Similarly, a recent report from the Swedish Heart Failure Registry found very low achievement of target doses of GDMT (44% for RAS inhibitors/ARNI, 36% for beta-blockers and 16% for MRAs), which was inversely proportional to age,[48] illustrating the risk–treatment paradox in which those at higher risk of adverse events receive the least aggressive regimen.[49] As expected, in an organized environment such as in clinical trials, achievement of GDMT is markedly higher, ranging from 66% to 84%.[50–53] Whilst these discrepancies can be partly explained by the controlled and monitored setting in which trials are conducted, the difficulty to translate their findings into clinical practice may also be explained by reduced tolerability, as these patients often present with comorbidities, frailty and polypharmacy, limiting further up-titration of GDMT.[41] Yet, an analysis from the systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) showed that achievement of target doses of ACEI/ARB in patients with HFrEF is associated with improved outcomes, regardless of their age (i.e. ≥70 *versus* <70 years old).[54] These findings are in line with those reported in the Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) study,[55] suggesting that optimization of GDMT should be pursued even in seemingly fragile patients. However, higher doses of beta-blockers in older patients did not provide incremental benefit over intermediate doses.[54] In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS), patients who achieved a dose of 5 mg of nebivolol showed similar outcomes to those at target doses of 10 mg.[56] This can be explained by the altered beta-adrenergic sensitivity in older patients, necessitating potentially lower-than-target doses of beta-blockers to control heart rate (HR).[57] Finally, Savarese et al. reported that 75.7% of patients initiated on dapagliflozin within 12 months of discharge from an HF hospitalization would achieve target doses, although this agent does not usually require up-titration.[29] Therefore, a one-size-fits-all approach may be unrealistic in real-life settings and calls for a shift toward a more personalized treatment.

Achievement of a maximally tolerated dose

Achieving the target doses used in the landmark trials seem difficult when applied to the general population, probably due to side-effects and intolerance. Indeed, up-titration of GDMT may be limited by factors such as blood pressure (BP), HR, renal function, electrolyte abnormalities or comorbidities.[41] For instance, beta-blockers may be prescribed at appropriate but sub-target doses in patients with chronic obstructive pulmonary disease and asthma, as they may increase risk of hospitalization,[58] or in the presence of a low HR, limiting further up-titration. In most observational studies based on registry data, the only achievement of target doses, percentages or median doses reached were reported because of the non-availability of more granular data, such as HR, systolic BP (SBP) or laboratory results (renal function, potassium levels), leading to the conclusion that the large observed gaps in adherence to HF guidelines were due to clinical inertia.[11,19,21,22,24,29,40,47,48] The Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT) trial evaluated whether optimization of GDMT based on specific NT-proBNP levels may improve outcomes of patients with HFrEF when compared with usual care, aiming at target doses only. Despite clear objectives and involvement of experienced HF cardiologists, optimization rates of pharmacotherapies remained low at 6 months in both groups, with patients in the intervention arm not receiving a more intensive regimen than controls. The most commonly reported reason for the absence of changes in treatment was that the patient was 'at the maximally tolerated dose';

whilst this was not clearly defined, it was likely based on perceived physiological parameters that may have included HR, SBP, potassium levels and eGFR, limiting further up-titration.[17] Recently, we reported on 511 patients with HFrEF and showed that inertia was much less prevalent than previously described when optimization of GDMT was based not only on target doses reached but also on patient physiological (i.e. HR, SBP and NYHA class) and biological (i.e. serum potassium and creatinine) parameters as well as on clinician intent to up-titrate or not GDMT. Such an approach showed optimization rates reaching 67.5% for beta-blockers, 63.4% for vasodilators (ACEI/ARB/ARNI or hydralazine nitrates) and 58.9% for MRAs. This high rate of optimization can be attributed to many factors. First, we had access to granular data to characterize the optimization of treatment, which were unavailable to previous authors; in addition, this cohort was followed by a multidisciplinary specialized HF team of cardiologists, pharmacists and nurse-practitioners, a unique setting that is not always available in all healthcare systems. Nevertheless, one-fifth of patients were still undertreated or in titration after 6 months of follow-up despite no apparent intolerance, contraindications, or physiological and/or biological limitations, suggesting that, whilst these parameters may explain, at least partly, this non-adherence, some clinical inertia still persist in the management of patients with HFrEF even in specialized settings.[12]

By contrast, an analysis from the CHAMP-HF registry suggested that SBP is not an important barrier to drug intensification, with only slightly more patients with an SBP of ≥110 mmHg being on target doses of beta-blockers and ACEI/ARB/ARNI (9.7%) compared with those with an SBP of <110 mmHg (5.8%); the overall pattern was similar for higher SBP (≥120 or ≥130 mmHg). Comparable results were obtained when performing a sensitivity analysis that excluded patients with an HR of <60 bpm, suggesting that bradycardia may not have solely precluded the dose intensification of beta-blockers in CHAMP-HF.[59] Likewise, a Dutch registry of 8246 patients with HFrEF showed that (1) the percentage of patients at target doses of beta-blockers and RAS inhibitors was slightly lower in the group with SBP of <110 mmHg compared with the group with SBP of ≥110 mmHg and (2) doses prescribed were still suboptimal even in patients with potential room for up-titration (BP ≥130 mmHg).[60] Interestingly, a study comparing three scenarios for the management of HFrEF, namely doses of ACEI/ARB, beta-blocker, or MRA up-titrated (A) to ≥50% of target dose, (B) according to a biomarker-selection model, or (C) to <50% of target dose, showed that the lowest number of adverse events (all-cause death or HF hospitalization) occurred in scenario B, followed by A, with C having the worst outcomes.[61] Whilst specialized multidisciplinary care could at least partly explain our high rate of adherence to guidelines, considerable gaps persist in the management of patients with HFrEF in clinical practice, suggesting that every patient cannot probably receive all agents at target doses but every effort should be made to titrate them to their individual maximally tolerated dosage to improve outcomes.

Prolonged period of up-titration and subtarget doses of GDMT

Despite the rapid clinical benefits (within a month) of the newer HFrEF agents (i.e. ARNI and SGLT2i),[30,31] prolonged up-titration may be necessary for some patients who may be older, with comorbidities, frail or 'unstable' (e.g. more susceptible of side-effects caused by medications such as hypotension, renal dysfunction or bradycardia).[36,41,62] For instance, one-third of patients were still being up-titrated beyond 1 year in the European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT) study.[23] Interestingly, the one-fifth of patients still being up-titrated after 6 months in our cohort[12] exhibited a lower 1-year risk of all-cause death or HF events (hospitalization, emergency consultation or ambulatory administration of intravenous diuretic) than those undertreated (HR 0.58, 95% CI 0.35–0.95; p=0.0304), yet tended to have poorer outcomes than patients on triple therapy (beta-blocker, ACEI/ARB/ARNI and MRA) at target or maximally tolerated doses (p=0.0588); those intolerant or with contraindications to triple therapy had the worst prognosis (HR 4.60, 95% CI 2.23–9.48; p<0.0001), highlighting a particular population necessitating closer attention.[45]

Indeed, the line between inertia and necessary careful optimization of fragile patients is difficult to define retrospectively but, in both CHAMP-HF and Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) most patients on sub-target doses had no changes in their GDMTs over a follow-up of 12 and 6 months, respectively, despite eligibility to intensification, suggesting a predominance of the former over the latter.[46,47] Likewise, in a multi-ethnic HF cohort from Singapore and New Zealand (n=1110), only a minority of eligible patients had their ACEI/ARBs (10%) and beta-blockers (16%) up-titrated over a period of 6 months, despite 56% and 48% of patients being on low doses (<50% of target) of GDMT over time, with no apparent contraindications. Lower levels of NT-proBNP were actually associated with a higher likelihood of up-titration for ACEI/ARBs and beta-blockers, reflecting either difficulty to treat the sicker patients or the risk–treatment paradox.[26] These gaps in adherence have a significant impact on patient outcomes. First, in CHAMP-HF, patients receiving subtarget doses had an increased risk of all-cause mortality proportional to the level of target dose of RAS inhibitors (0%: HR 1.75, 95% CI 1.32–2.34; 1–49%: 1.37, 1.05–1.79; 50–99%: 1.16, 0.87–1.55) and beta-blockers achieved (0%: 1.24, 0.92–1.67; 1–49%: 1.41, 1.11–1.79; 50–99%:

1.30, 1.00–1.69) compared with patients receiving target doses over a 24 months. Lower doses of RAS inhibitors were also associated with a greater risk of HF hospitalization.[42] Findings from the HF-ACTION trial also showed a dose–response relationship, meaning that, compared with patients at stable target doses of a beta-blocker, those at stable sub-target doses had an increased risk of cardiovascular mortality or hospitalization for HF (HR 1.49, 95% CI 1.18–1.87), whilst the risk of events was not significantly higher for those still being up-titrated; patients at highest risk of outcomes were those who required a dose de-escalation (HR 1.98, 95% CI 1.36–2.87).[46] Finally, results of the BIOSTAT-CHF study, which focused on the titration of beta-blockers and ACEIs/ARBs and its impact on outcomes of patients with HFrEF, were consistent with those previously described: prescription of <50% of target dose is associated with an increased risk of hospitalization due to HF and/or all-cause death (ACEI/ARBs 0%: HR 1.77, 95% CI 1.61–1.94; 1–49%: 1.23, 95% CI 1.09–1.36 and beta-blockers 0%: 1.51, 95% CI 1.29–1.72; 1–49%: 1.27, 95% CI 1.15–1.39), whilst patients at highest risk of adverse events are those intolerant to treatment. Intriguingly, patients who achieved 50–99% of the target dose seem to share the same risk of outcomes with those on target doses.[18] Perhaps, it could potentially be that these patients have reached a maximally tolerated dose, or possibly, a physiological or biological limitation preventing further dose intensification, meaning that these patients were optimally treated. Hence, it is of utmost importance to titrate GDMT in a timely manner for all eligible patients presenting with no apparent limitations in order to fully benefit from these therapies.

Factors associated with suboptimal treatment: potential causes and ways to improve

Several reasons have been suggested for the low prescription rate and/or dose intensification of GDMT in clinical practice related to (1) the patient; (2) the healthcare provider and (3) the healthcare system.[62]

Many patient features may represent a challenge to drug optimization; these include advanced age, declining health status, advanced symptoms (NYHA class III–IV and prominent congestion), comorbidities (diabetes, impaired renal function, pulmonary disease, etc.), female sex, lower body habitus/body mass index (BMI), HR, SBP and serum potassium level.[18,26,47,62–66] These parameters may be perceived as an individual's fragility, leading to either careful up-titration of GDMT or no intent at all.[25] Indeed, there was an independent association between obesity (BMI ≥30 kg/m^2) and likelihood of prescription/up-titration to target doses of GDMT in the Swedish Heart Failure Registry.[67] This phenomenon may at least partially explain the 'obesity paradox' in HF, where patients with overweight/obesity seem to have better outcomes than those with lower BMI.[68]

The presence of comorbidities also seems an important obstacle in the optimization of GDMT for patients with HFrEF.[12,13,23] In fact, patients with coronary artery disease are less likely to receive optimal doses of beta-blockers[25,47] or MRA[12], which perhaps reflects the lower likelihood of optimal treatment in patients at higher risk of adverse events,[49] with the possible exception of diabetes.[12] These findings illustrate the real or perceived fragility of these patients, who are often older, with more advanced disease and more likely to receive multiple drugs for their comorbidities, which altogether may contribute to the difficult optimization of GDMT.[62] Defined in the literature as the prescription of five medications or more,[69] patients with HFrEF approach this criterion for polypharmacy by considering only the number of HF drugs prescribed. Nevertheless, though polypharmacy increases the risk of drug–drug interactions, adverse events and poor compliance, the significant benefits on morbidity and mortality of the quadruple therapy for HFrEF highlights the importance of finding the right balance between risks and benefits in these patients.[62,70]

Other factors associated with suboptimal treatment of HFrEF are related to the physician or team caring for the patient, including a lack of knowledge of the most recent HF guidelines and perception of frailty.[62] Moreover, some clinicians might lack motivation or may be reluctant to use novel effective drugs by fear of decompensating what they consider a stable patient, or perhaps due to their uncertainty in the effectiveness of these therapies.[13,44,59,62] Hence, continuous education is central to improving the management of this complex syndrome, emphasizing the underestimation of the real risk of their so-called stable patient and their overestimation of potential side-effects.

Lastly, some barriers to GDMT optimization depend on the healthcare system infrastructure itself, including the type and number of healthcare professionals, time constraints, type of medical environment (inpatient, emergency department, HF or general cardiology clinics) and access to healthcare facilities (minorities/socioeconomic status, rural areas).[2,13,71] Other limitations involve reimbursement policies and insurance coverage systems in place in different world regions. Moreover, completeness of and access to patient data across the healthcare system are also important factors to consider in the comanagement of HFrEF as they may limit interdisciplinary teamwork. Finally, guidelines and recommendations pose a challenge to the optimization of treatment because they are not particularly patient-centred and do not necessarily acknowledge the challenges of a real-world population.[72,73] Hence, understanding and addressing these components might improve overall outcomes of patients with HFrEF.

Clinical inertia

Many of these factors will lead to clinical inertia, a phenomenon first described in 2001 and which remains a major barrier for the optimal management of chronic diseases such as hypertension, diabetes and HF.[74] Some authors reporting on adherence of clinicians to HF guidelines claimed that clinical inertia accounts for the majority of measured care gaps in the management of patients with HFrEF.[29,47] Inertia is defined as the failure to prescribe an evidence-based therapy, to up-titrate it to achieve a recommended target dose or to substitute a pharmacotherapy by a more potent agent[30] in patients who are deemed eligible with no documented intolerance or contraindication.[75] It oversees the three main intertwined components previously discussed.[71] First, it can be due to the perceived complexity or lack of knowledge of the guidelines. Patient factors revolve mostly around compliance to treatment whilst those related to the healthcare system may involve the lack of practice models focusing on the optimization of treatment, timely access to care and time management.[71,75] In our analysis of adherence to HF guidelines in an outpatient specialized HF clinic, results showed that 15% of patients prescribed an ACEI or ARB were eligible to alternatively receive an ARNI yet were not switched accordingly.[12] Similarly, a report from the *Utilization of Dapagliflozin and Other Guideline Directed Medical Therapies in Heart Failure Patients: A Multinational Observational Study Based on Secondary Data (EVOLUTION HF)* in the USA showed that only 3.1% of patients were switched from an ACEI to an ARNI.[29]

Finally, whilst some patients require slower up-titration for tolerability, others may remain in a prolonged up-titration phase despite no documented intolerance, contraindications or apparent physiological/biological parameters limiting further dose intensification; this situation reflects an insidious form of clinical inertia. Beyond non-adherence to HF guidelines and suboptimal use and dosing of evidence-based therapies, clinical inertia has a direct impact on the morbidity and mortality of the affected patients;[76] therefore, it is important to recognize it and put in place strategies to tackle it to improve the management of patients with HFrEF and possibly reduce the rates of hospitalizations and deaths.[71,75]

Potential strategies to improve the management of patients with HFrEF

Given the results presented previously and the care gaps that persist in clinical practice, an opportunity arises for the development of interventional programmes with the aim of potentially improving the management of patients with HFrEF. One interesting avenue is specialized HF clinics integrating multidisciplinary teams comprised of cardiologists, pharmacists and nurse-practitioners in which patients with HFrEF may be followed. The importance of such patient care has long been reflected in the literature,[77,78] and was, in fact, highlighted by our analysis of 511 patients with HFrEF followed by a multidisciplinary team in Canada, with considerably higher optimization rates compared with similar studies.[79] The Role of a Multidisciplinary Heart Failure Clinic in Optimization of Guideline-Directed Medical Therapy (HF-Optimize) study drew the same conclusion, with significant improvement of GDMT use and outcomes in patients with HFrEF followed at an HF clinic by a multidisciplinary team of pharmacists, HF cardiologists, nurses and nutritionists.[80] In the same vein, a multinational, open-label, randomized trial, the Safety, Tolerability and Efficacy of Up-titration of Guideline-directed Medical Therapies for Acute Heart Failure (STRONG-HF) study, recently showed the efficacy of an intensive interventional programme aimed at optimizing treatment within 2 weeks post-discharge followed by four ambulatory visits within the next 2 months for monitoring (i.e. clinical status, laboratory results and NT-proBNP levels). By day 90, a higher proportion of patients in the high-intensity care group was optimized to maximally tolerated doses of GDMT than the usual care group, followed with a higher decrease in NT-proBNP levels in the former than the latter group.[39] Altogether, these findings suggest that better adherence to GDMT is achievable with the implementation of optimization-based interventional programmes intended for the management of outpatients with HFrEF.

Furthermore, over the past decade, numerous controlled trials have shed light on the usefulness of a clinical decision support system in clinical practice, having demonstrated significant improvement in patient care and clinical outcomes when implemented directly into the electronic medical record.[81–83] Briefly, the electronic medical record is questioned about individual patient characteristics, which are then matched to a clinical knowledge base, resulting in patient-specific recommendations generated to support the clinician's decision.[84] Although these support systems allow the standardization of care and improvement of the management of chronic diseases,[85–87] they still have not been broadly established in specialized HF settings.

Conclusion

The marked progress in the management of patients with HFrEF in landmark clinical trials has not translated into dramatically improved prognosis in the overall population mainly due to the existence of care gaps between what is recommended and what the patients are actually receiving. Whilst prescription rates of beta-blockers and RAS inhibitors are rather satisfactory, under-prescriptions of MRAs and ARNI still persist. Moreover, under-dosing

remains common and recommended target doses or maximally tolerated doses are not always achieved, even in patients who seem eligible. Finally, some patients may remain in a prolonged up-titration phase. Many factors at the patient, physician and system levels are intertwined and contribute to this clinical inertia encountered in clinical practice; strategies should be developed to tackle these barriers to improve prognosis at a population level.

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