Navigating between Scylla and Charybdis: challenges and strategies for implementing guideline-directed medical treatment in heart failure with reduced ejection fraction

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Abstract

Guideline-directed medical therapy (GDMT) has the potential to reduce the risks of mortality and hospitalisation in patients with heart failure (HF) with reduced ejection fraction (HFrEF). However, real-world data indicate that many patients with HFrEF do not receive optimised GDMT, which involves several different medications, many of which require up-titration to target doses. There are many challenges to implementing GDMT, the most important being patient-related factors (comorbidities, advanced age, frailty, cognitive impairment, poor adherence, low socioeconomic status), treatment-related factors (intolerance, side-effects) and healthcare-related factors that influence availability and accessibility of HF care. Accordingly, international disparities in resources for HF management and limited public reimbursement of GDMT, coupled with clinical inertia for treatment intensification combine to hinder efforts to provide GDMT.

In this review paper, authors aim to provide solutions based on available evidence, practical experience, and expert consensus on how to utilise evolving strategies, novel medications, and patient profiling to allow the more comprehensive uptake of GDMT. Authors discuss professional education, motivation, and training, as well as patient empowerment for self-care as important tools to overcome clinical inertia and boost GDMT implementation. We provide evidence on how multidisciplinary care and institutional accreditation can be successfully used to increase prescription rates and adherence to GDMT. We consider the role of modern technologies in advancing professional and patient education and facilitating patient-provider communication. Finally, authors emphasise the role of novel drugs (especially sodium-glucose cotransporter-2 inhibitors), and a tailored approach to drug management as evolving strategies for the more successful implementation of GDMT.

Key words: heart failure, guideline directed medical therapy, optimal treatment, medication adherence, quality of care, health education**,** sodium-glucose cotransporter-2 inhibitors

Introduction

Heart failure (HF) is a global epidemic associated with significant disability, mortality, and healthcare costs. Data from a recent Heart Failure Association (HFA) survey, the HFA Atlas, indicate that there are presently ~14 million patients with HF, and ~2.5 million HF-related hospitalisations per year in the 42 participating European Society of Cardiology (ESC) member countries. These countries encompass a broad geographical region (Europe, Mediterranean, Middle East, and several former Soviet Union countries) with a population of ~800 million people [1]. Furthermore, it is estimated that each year ~2.4 million new cases will add to the burden of HF in this region [1]. The 2021 HFA/ESC guidelines on the management of HF have identified multiple disease modifying therapies with beneficial effects on survival and health status of patients with HF with reduced ejection fraction (HFrEF) [2]. They included sodium-glucose co-transporter-2 (SGLT2) inhibitors as a novel class of medications that can reduce mortality in patients with HFrEF [2]. Accordingly, optimal guideline-directed medical therapy (GDMT) involves a combination of several medications, up-titrated to evidence-based target doses [2]. However, many challenges exist in the implementation, up-titration and adherence to GDMT in real-world clinical practice [3-5], despite evidence that optimal GDMT can save lives and prevent hospitalisations [4, 6]. Indeed, GDMT use was associated with a decline in HF mortality over the past decades, but early post-discharge mortality and hospital readmission rates remained stable due to the complexity of comorbidities, the ageing of patients with HF, and failure to implement or optimise GDMT [7, 8]. There are multiple reasons for underutilisation of GDMT, which could be grouped into 3 equally important categories: patient-related factors (i.e. comorbidities, frailty, advanced age, cognitive impairment, poor adherence, greater severity of HF symptoms, low socioeconomic status, poor health literacy etc.), treatment-related factors (poor tolerance, side-effects) and healthcare-related factors [3, 5]. Amongst the latter, variability in resources for HF management and drug

reimbursement policies across the ESC member countries, as well as a lack of proficiency in up-titration and clinical inertia play significant roles [1].

Accumulating clinical trial evidence suggests that SGLT2 inhibitors provide beneficial treatment effects that are complementary to standard HFrEF medications and extend beyond type 2 diabetes [9, 10]. Of note, these medications offer simple, once-daily dosing without the need for up-titration, have an early onset of treatment benefits and a favourable safety profile, and therefore, should be considered in the majority of HFrEF patients. Several position papers [11, 12] and recent guidelines have already endorsed [2, 13], SGLT2 inhibitors as an additional novel class of GDMT in HFrEF with an anticipation that their use will improve outcomes and facilitate optimisation of GDMT.

This review paper aims to summarise gaps and challenges to the implementation and optimisation of GDMT in daily practice. It also attempts to propose solutions based on available evidence, practical experience, and expert consensus on how to utilise evolving strategies and novel medications to allow more comprehensive uptake of GDMT.

Real-world data on implementation of guideline-directed medical therapy for heart failure

Retrospective analysis of observational studies clearly demonstrated that increasing treatment intensity reduces the risk of death and rehospitalization among patients hospitalised for HFrEF [14-17]. However, international observational surveys and registries consistently reported that initiation, up-titration, and adherence to GDMT among patients with HFrEF was significantly lower in daily practice compared to clinical trials [15]. Although prescription rates have improved over the past decade [18], under-dosing of standard HF medications is still frequent. Indeed, several contemporary surveys and registries from Europe and elsewhere documented significant gaps in the prescription and attainment of the recommended doses of GDMT in eligible patients (**Table 1**). In the QUALIFY survey, not only were the prescription rates for angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARB), beta-blockers and mineralocorticoid receptor

antagonists (MRA) lower than expected, but almost a third of patients on ACEIs and a half of those on ARBs or beta-blockers received <50% of target doses [3]. Similarly, in the ASIAN-HF registry, recommended doses were attained in only 17% of patients on ACEIs/ARBs, 13% of patients on beta-blockers and 29% of those on MRAs [19]. More recently, the ESC Heart Failure Long-term Registry showed that in HFrEF patients managed by cardiologists, despite high prescription rates of GDMT, less than a third of patients received medications at recommended doses [18]. This registry showed that in in ambulatory and hospitalised patients with HF there was no significant improvement in the rates of drug prescription at 1-year follow-up [18]. Also, in the CHAMP-HF registry, only a minority of patients from primary care and cardiology practices in the United States of America (US) attained target doses of ACEIs/ARBs (17%), sacubitril/valsartan (14%) and beta-blockers (28%) [20]. Similar results were shown in other multinational registries [4, 21, 22]. Even more worrying is the fact that target doses of all recommended drugs were simultaneously achieved in only 1% of eligible patients and only modest improvements (6-10%) in drug prescription or up-titration occurred at 12 months, while at the same time, similar proportion of prescribers either discontinued or de-escalated their patient's treatment [20]. A recent analysis of 68,172 new users of GDMT with a recent hospitalisation for HF retrieved from Sweden, United Kingdom and US healthcare databases showed target dose achievement over 12 months in 15%, 10%, 12%, 30% of the patients receiving ACEIs, ARBs, beta-blockers and sacubitril/valsartan respectively, whereas, at the same time, discontinuation rates were as high as 55%, 33%, 24% and 27%, respectively [23].

The importance of implementing, optimising, and adhering to GDMT is borne out by clinical trials and prospective observational studies. It was consistently documented that those patients attaining <50% of the target doses of ACEIs/ARBs, sacubitril/valsartan and beta-blockers have a greater risk of death or hospitalisation for HF compared with patients on optimal GDMT [3, 4, 24]. Conversely, more comprehensive, and optimised GDMT is associated with an improvement in outcomes [6]. A meta-analysis of 58 relevant clinical

trials conducted between 1987 and 2017, has shown that the combination of disease-modifying medications, i.e. ACEIs/ARBs, beta-blockers, MRAs, ivabradine and sacubitril/valsartan provided progressive improvement in mortality and hospitalisation outcomes in individuals with HFrEF [6]. The IMPROVE-HF registry involving a cohort of 4,128 patients with a 2-year follow-up, showed that incremental use of GDMT was associated with a long-term survival benefit, with a potential plateau at 4 to 5 therapies [16]. Importantly, sustained adherence to GDMT conferred lower long-term all-cause and cardiovascular mortality in HFrEF patients [25].

Reasons for underutilisation of guideline-directed medical therapy in heart failure

Multiple reasons were put forward to explain underutilisation of GDMT [26]. Broadly, they could be grouped into 3 categories: 1) patient-related factors, including medical and socio-demographic characteristics and challenges inherent to managing comorbidities and polypharmacy, 2) treatment-related aspects including actual or perceived tolerability concerns or medication side-effects (e.g. bradycardia with beta-blockers, hyperkalaemia with MRAs, hypotension etc.), and 3) healthcare-related factors with an impact on delivery and quality of care for patients with HF [27]. These issues are summarised in **Figure 1**.

Patient characteristics consistently associated with lower prescription or up-titration of GDMT include female sex, advanced age, lower blood pressure, heart rate or body mass index, and greater severity of HF (more advanced New York Heart Association class and more pronounced congestion) [4, 5, 28]. In some instances, racial differences and lack of full-time employment were associated with under-utilisation of GDMT [5]. Other relevant factors include low socioeconomic status, limited formal education, chronic mental stress and low health literacy [29]. Comorbidities also play a significant part by increasing the risk of intolerance and side-effects. Registry data indicated that severe renal dysfunction and hyperkalaemia were the most frequent reasons for withholding or discontinuing ACEIs/ARBs and MRAs, respectively [3, 18, 30, 31]. Asthma and bradycardia were the

most frequent contraindications or reasons for discontinuation of beta-blockers [3, 18]. Concerns about intolerance and side-effects are particularly important in the elderly and frail patients, where comorbidities, cognitive impairment, polypharmacy, and limited social support impose significant obstacles. In the CHECK-HF registry, advanced age (≥75 years) was associated with a lower rate of GDMT prescription and optimisation to target doses [32]. In this study, contraindications and intolerance were the main contributors to under-prescription in the elderly, but in ~60% of patients, the reasons for under-prescription remained unspecified [32]. Ageing and other patient characteristics identify vulnerable populations in need of the more attentive follow-up and greater efforts to optimise therapies. However, even under specialist care, attaining target doses may be slow and difficult, as evidenced by the ESC Heart Failure Long-Term Registry, where key reasons for under-dosing were ongoing up-titration, drug intolerance or contraindications, but in ~30% of patients the reasons remained unknown [18, 33]. A risk-treatment paradox was identified whereby higher-risk patients with HF are less likely to receive recommended therapy. This may reflect that higher-risk patients may have a higher prevalence of contraindications, rendering them ineligible for evidence-based therapies (evidence gap), or that higher-risk patients may be less likely to receive therapies even when eligible for the treatment (treatment gap) [34]. Lower rates of target dosing in routine practice compared with clinical trials are usually attributed to differences in patient characteristics [4, 5, 28]. The greater success in up-titration in clinical trials is partially explained by inclusion of younger, more motivated patients with fewer comorbidities, which could have resulted in an overestimation of the potential for GDMT optimisation. Most recent trials also strongly encouraged selection for the inclusion of patients already receiving standard of care medications. However, a recent comparison between the PARADIGM-HF trial and CHAMP-HF registry showed that patients included in the PARADIGM-HF trial had similar characteristics to those encountered in routine practice, and yet, the latter were less likely to receive sacubitril/valsartan, which points to a treatment rather than evidence gap in the real world practice [35]. In order to close this gap, non-medical reasons (i.e. healthcare-related

factors) need to be considered in addition to patient- and drug-related factors.

An insight into how differences and inequalities in healthcare for patients with HF might hinder delivery of GDMT in the ESC member countries has come from the HFA Atlas [1]. Firstly, the HFA Atlas underlies considerable variation in reimbursement policies for standard HF medications. Although full or partial public healthcare reimbursement for ACEIs/ARBs, beta-blockers and MRAs was offered in most countries, still several countries provided no public funding for these essential drugs [1]. Furthermore, public reimbursement for sacubitril/valsartan was available in less than a half of the member countries and full reimbursement in only a minority [1]. Limited reimbursement may be an important barrier to the provision of GDMT, which may explain regional differences in drug prescription rates noted in previous surveys, particularly in the middle-income countries of central and eastern Europe [4]. Secondly, the HFA Atlas demonstrated considerable international disparities in the availability of specialised centres for multidisciplinary HF management (i.e. HF centres), that likely reflected differences in national healthcare polices, funding and service organisation. Accordingly, most ESC member countries reported less than 3 HF centres per million people, which is probably insufficient to accommodate growing demands and complexities of contemporary HF management [1]. Limited availability or accessibility of HF centres may preclude regular visits to cardiologists or HF specialists, where GDMT optimisation may be more likely to be prioritised. This may divert the task of GDMT optimisation to non-specialists, such as primary care practitioners, who may lack training and confidence in the management of HF [36]. In addition, insufficient communication during the transition from hospital-based specialist care to primary care, and involvement of multiple prescribers with no clear allocation of responsibility, favours clinical inertia and makes it less likely that treatment intensification will occur. In general, continuity of physician care was associated with better clinical outcomes [37]. In patients with HF, early follow-up after an episode of HF exacerbation was shown to decrease the risk of death and hospital readmission, particularly if performed by a familiar physician (i.e., a physician previously involved in patient care) [38]. However, even among familiar and experienced

physicians, clinical inertia was recognised as an important contributor to a care gap, defined as a discrepancy between processes of care considered as best practice (based on of high-quality evidence) and the care given in routine clinical practice [39, 40]. Lack of motivation, time constraints imposed by a busy practice, lack of awareness/knowledge, insufficient self-confidence to perform a given recommendation, overemphasis on tolerability or side-effect issues and competing promotional influences are some of the most important modifiable factors associated with clinical inertia [39]. Furthermore, nurses specialising in HF, who may support and facilitate efforts at GDMT optimisation are also scarce. According to the HFA Atlas data, approximately a half of ESC member countries lack specialised nurses involved in HF care [1]. The HFA Atlas also pointed to unmet needs in improving professional education and training in the management of HF and developing multidisciplinary collaboration at all levels of care [1].

Evolving strategies to improve implementation of GDMT

Several strategies can be proposed with a prospect of overcoming the barriers in the implementation, adherence, and optimisation of GDMT as summarised in **Figure 2.**

Education of healthcare professionals and patients

Firstly, significant progress could be achieved by promoting professional education and raising awareness of good practice in implementing GDMT among all practitioners involved in HF management. As the physicians play a critical role in implementing GDMT, they need to become aware that implementation and up-titration of all mandatory classes of HF medications is their obligation. A stronger effort from the National Heart Failure Societies/Working Groups at providing educational courses and seminars adapted for practitioners at different levels of care (from primary to tertiary), as well as dissemination of educational material (e.g. translated version of ESC guidelines, national guidelines, treatment update leaflets and alerts) might help in improving GDMT implementation. Harnessing benefits of e-Learning platforms, mobile applications and social media can aid

in enhancing educational efforts and facilitating professional communication. This is particularly relevant for boosting the competence and confidence of non-specialists involved in HF care, who need easily available sources of information and precise guidance on how to overcome difficulties in GDMT optimisation. Several of the more successful strategies in overcoming clinical inertia include face-to-face educational visits by influential local specialists and established key opinion leaders, real-time clinical reminders (computerised or on-paper) about treatment optimisation, critical reappraisal of treatment schemes on staff meetings with an emphasis on comprehensive, evidence-based and holistic approach, and audit and comparison with local peers [39, 40]. Ambulatory visits need to be taken as an opportunity to reassess and optimise the treatment, even in patients perceived as “clinically stable” [2].

It is equally as important to raise awareness and improve self-care among patients, and family members. Patients need to be provided the information that will help them to understand their condition better, follow the treatment plan and make necessary life-style modifications to decrease symptom burden and improve outcomes. It was shown that patient empowerment for self-care can significantly increase adherence to GDMT and reduce mortality and hospitalisations in patients with HF [41]. Patient education needs to be the responsibility of all practitioners involved in the process of care, beginning with predischarge counselling for hospitalised patients, and continuing through educational efforts carried out by other providers (e.g. general practitioners, internal medicine specialists, pharmacists, nurses and others) [42]. This task can be facilitated by printed material (brochures, flyers, leaflets) available at patient desks, mobile phone applications, video education, and educational websites in different languages (e.g. ‘heartfailurematters.org’) [43]. Patient self-care and support can be further advanced by patient organisations. Their role is essential in advocacy activities directed to regulatory issues on resource allocation and reimbursement of HF therapies. Advocating for the full public reimbursement and other measures that support funding of HF medications (including novel drugs with proven outcome advantages) needs to be prioritised to relieve

the financial burden from the patients and enable the more widespread implementation of GDMT.

Improving standards of care, addressing gaps in evidence, and implementing novel technologies

Gaps in quality of HF management can be substantially reduced by improving standards of care though the provision of multidisciplinary team management from primary to tertiary levels [44, 45]. Standardised multidisciplinary team management can ensure easier communication between healthcare providers and seamless transition of care across different levels (from primary to tertiary and vice versa). The hospitalisation for HF should be an opportunity to introduce and/or optimise already prescribed HF medications. A post-discharge plan including a schedule for up-titration visits and guidance about how to monitor and manage drug intolerance and side-effects can also help in overcoming clinical inertia in optimising GDMT [2]. Of note, interventions aimed at providing standardised management protocols and institutional accreditation have proven effective in boosting prescription rates and adherence to evidence-based therapies [46, 47]. To meet this goal, ESC/HFA initiated a project of Quality-of-Care Centres (QCC), defined as healthcare institutions offering multidisciplinary HF management (from primary to tertiary levels) in accordance with the academic accreditation protocols from ESC/HFA [48]. These centres will be embedded into the existing healthcare systems across ESC member countries. The project will also support QCC networking, professional education, knowledge building and exchange of experience, which is expected to help in advancing quality of care for patients with HF.

Although subgroup analyses in most clinical trials did not show evidence of heterogeneity in treatment effects of HF medications, it need to be noted that patients of advanced age, women and some ethnic/racial groups were under-represented (especially in older trials), whilst individuals with severe comorbidities or advanced frailty were excluded.

This creates an uncertainty about tolerability, dosing, and side-effects of HF drugs in older and sicker patients that entrenches clinical inertia in GDMT implementation. An important step forward would be to foster more inclusive clinical trials, and registry-based pragmatic trials [49], that would provide evidence-based data from diverse patient populations, as well as assessment of different protocols of drug initiation and intensification.

Telemedicine also offers promise for improving implementation of GDMT. In the randomised TIM-HF2 trial, remote patient monitoring and physician-led medical support demonstrated the potential to reduce HF hospitalisations and mortality compared with standard care [50]. More recently, lockdown restrictions and limited access to medical services during the COVID-19 outbreak have prompted a global acceleration in the use of telemedicine. It was shown that broadly available communication technologies (e.g. telephone calls, smartphone or web-channelled virtual visits etc) can be employed in suitable patients to adjust medical therapies and reduce the risk of hospitalisation due to worsening HF [51].

Novel medications and tailored treatment plan in HFrEF

SGLT2 inhibitors have gained recognition as a novel class of HFrEF medications with a favourable impact on cardiovascular and renal outcomes, regardless of diabetes status. In the landmark DAPA-HF trial, dapagliflozin demonstrated a significant attenuation in cardiovascular mortality or worsening HF (unplanned HF hospitalisation or urgent visit for intravenous HF therapy) with a 26% risk reduction compared to placebo [9]. Similar risk reduction (by 25%) in cardiovascular mortality or HF hospitalisation was observed with empagliflozin in the EMPEROR-Reduced trial [10]. Most recently, the SOLOIST-WHR trial with sotagliflozin (combined SGTL2 and SGLT1 inhibitor), in patients with recently decompensated HF and diabetes, confirmed risk reduction of cardiovascular mortality and worsening HF [52], previously observed with dapagliflozin and empagliflozin.

SGLT2 inhibitors are unique amongst HFrEF medications as they do not affect

blood pressure, heart rate, or potassium levels, and require no dose adjustment or up-titration. They have proven beneficial in patients with moderate kidney dysfunction (i.e. estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 for dapagliflozin, and eGFR ≥20 mL/min/1.73 m^2 for empagliflozin) [9, 10]. Despite a mild and transient drop in eGFR that can occur soon after treatment initiation, they offer long-term kidney protection [53]. Treatment benefits with SGLT2 inhibitors occur soon (within weeks) after drug initiation, and independently of age, sex, or background medical therapy. In a sub-analysis of the DAPA-HF trial, the effectiveness of dapagliflozin was similar irrespective of whether patients received ≥50% of the target doses of background HF medications. [54]. Effectiveness of dapagliflozin and empagliflozin was maintained in vulnerable and frequently undertreated patient populations, such as those with signs of congestion, recent HF hospitalisation, and the elderly [28, 55-57]. In EMPEROR-Reduced trial, empagliflozin treatment was associated a lower requirement for intensification of diuretic treatment even in patients with overt signs of congestion [58]. Furthermore, empagliflozin treatment appeared to facilitate the use of MRAs, since patients on empagliflozin and taking MRA's are less likely to discontinue the MRAs or experience severe hyperkalaemia [59]. All these characteristics, and a favourable safety profile (i.e. low risk of hypoglycaemia, lower limb amputations, bone fracture and diabetic ketoacidosis), provide a rationale for an easy and early implementation of SGLT2 inhibitors into GDMT.

Moreover, an indirect comparison of 3 pivotal trials assessing the efficacy of an MRA (EMPHASIS-HF), sacubitril/valsartan (PARADIGM-HF) and an SGLT2 inhibitor (DAPA-HF) indicated that comprehensive medical therapy with sacubitril-valsartan, beta-blocker, MRA and SGTL2 inhibitor may further reduce the risk of death and worsening HF compared with standard treatment (ACEI or ARB and beta-blocker) [60]. Patients who commence comprehensive therapy aged 55 years were projected to gain an additional 8.3 years free of CV mortality or first HF hospitalisation, compared with patients starting conventional therapy [60].

Current 2021 ESC/HFA guidelines on HF management recommend that

contemporary pharmacotherapy of HFrEF should include ACEIs or sacubitril/valsartan (or ARBs if intolerant to ACEI or sacubitril/valsartan), beta-blockers, MRAs, and SGLT2 inhibitors, as core treatments suitable for all patients [2]. Diuretic should be given if needed to control congestion. Additional evidence-based therapies (i.e. ivabradine, vericiguat, omecamtiv mecarbil, ferric carboxymaltose etc) can be considered in selected patients. A tailored approach was recently proposed by ESC/HFA to facilitate GDMT implementation and optimisation, with provision of core HFrEF medications (sacubitril-valsartan or ACEi/ARB, beta-blockers, MRAs, SGTL2 inhibitor and diuretics) and dose-adjustments according to the patient's clinical characteristics [61]. Accordingly, all patients should be started on core HFrEF medications, whilst dose modifications should be performed considering blood pressure, heart rate, presence of congestion, atrial fibrillation, and kidney (dys)function. This strategy is expected to be more successful in providing comprehensive therapy for each individual patient compared with the traditional, step by step, up-titration of each drug class before commencing treatment with the next. It remains to be observed whether these novel concepts will translate into better implementation and adherence to GDMT in the real-world practice.

Conclusions

With the growing burden of HF, it has become imperative to provide effective disease-modifying therapies and to ensure their availability and implementation in a broad spectrum of patients with HF. Improving delivery of healthcare, changing clinical practices, raising awareness about clinical inertia, integrating innovative technologies and new therapies and advocating for broader public reimbursement of HF medications can prove successful in a wider implementation of GDMT.

Available data suggest that building professional skills and supporting patient empowerment for self-care could be important steps in overcoming clinical inertia and improving adherence to GDMT. Involvement of patient organisations can provide valuable support to patient education and promote advocacy activities aimed at delivering resources

and therapies that can improve management of HF. Broader implementation of structured multidisciplinary care though the establishment of academically accredited QCCs could be another essential part in improving accessibility and quality of care. Wider application of technologies that can modernise GDMT implementation, and improve patient-provider communication, can also facilitate this task. Finally, the use of novel, easier-to-prescribe drugs, and a tailored approach to the comprehensive medical management could also prove beneficial for the implementation, optimisation, and adherence to GDMT.

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TABLE LEGEND:

Table 1. Real-world data on implementation of guideline-directed medical therapies in heart failure with reduced ejection fraction

Table 1. Real-world data on implementation of guideline-directed medical therapies in heart failure with reduced ejection fraction

Registry/period of data collection	No. of patients/ Patient characteristics	LVEF (%)	Age and comorbidities (%)	Therapy (%)	≥ 50% of target doses (%)
QUALIFY 2013-2014	6118/CHF	33±10.8	Age 63.2 ± 12.6/78 HTA (64.4) DM (34.4) CAD (56.8) CKD (17.8)	ACEI (65.2) ARB (22.0) BB (86.5) MRA (69.2)	ACEI (72.4) ARB (49.5) BB (51.4) MRA (76.1)

ESC Heart Failure Long-Term Registry 2011-2013	12 440/ 40.5% with AHF 59.5% with CHF	AHF 38 (30–51) CHF 35 (28-45)	AHF AHF 71 (61–79)/63.7 HTA (64.5) DM (38.9) CAD (54.0) CKD (26.4) CHF Age 66 (57–75)/72.2 HTA (58.2) DM (31.8) CAD (43.0) CKD (18.2)	ACEI (70.7) ARB (23.5) BB (92.7) MRA (67.0)	ACEI (29.3) ARB (24.1) BB (17.5) MRA (30.5)
ASIAN-HF 2012-2015	5005/CHF	27	Age 59.6 [13.2)/77 HTA (46-56) DM (39-42) CAD (44-48) CKD (38-57)	ACEI/ARB (77) BB (79) MRA (58)	ACEI/ARB (17) BB (13) MRA (29)
CHAMP-HF 2017-2018	3518/CHF	29±8	Age 66±13/71 HTA (78-93.2) DM (37.6-44.5) CAD (61.1-63) CKD (16.1-42.5)	ACEI/ARB (61) BB (67) MRA (34.2)	ACEI/ARB (17) BB (28) MRA (77)

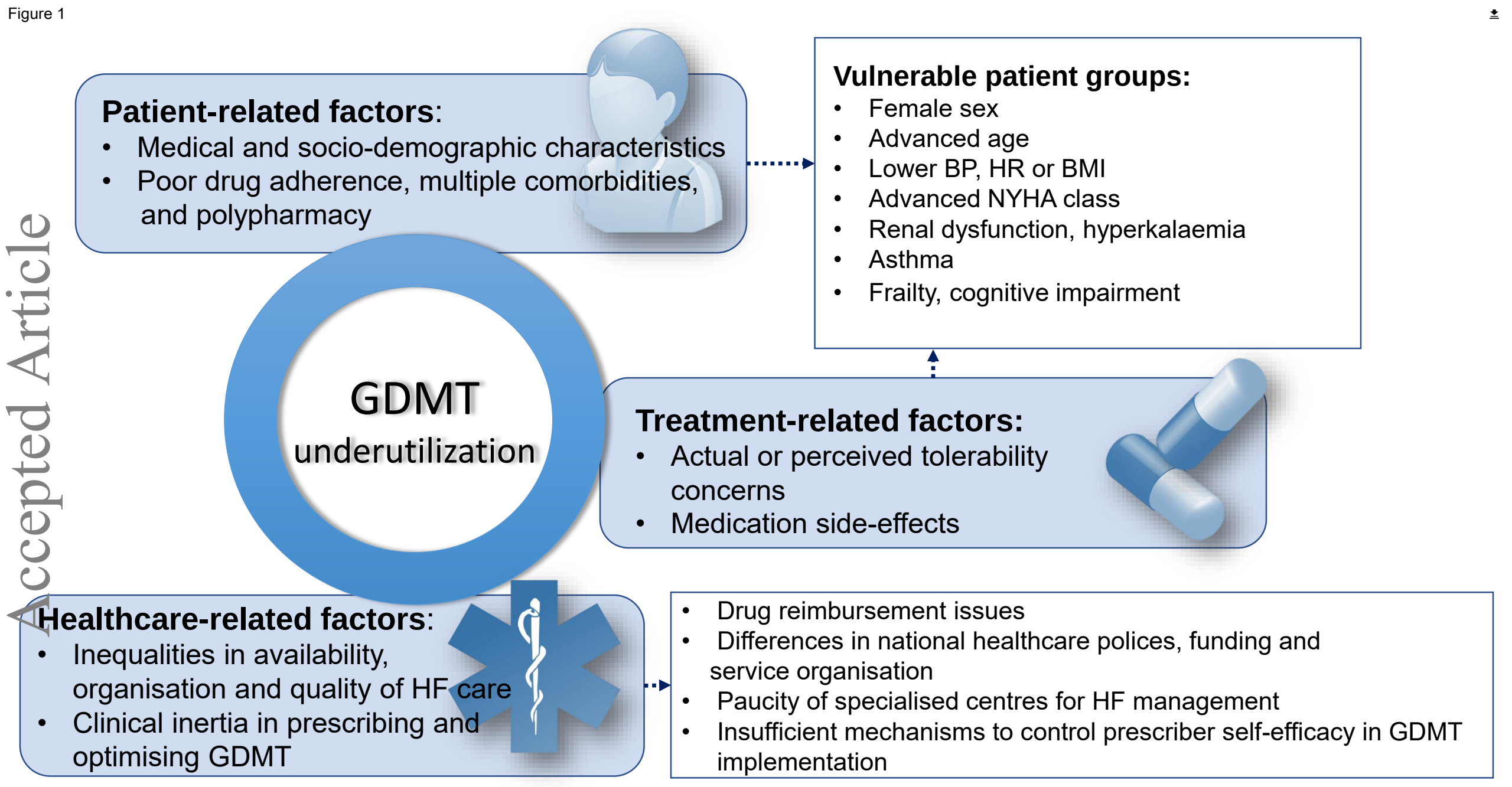
*Values are mean ± standard deviation, median (interquartile range), range or n (%). ACEI, angiotensin-converting enzyme inhibitor; AHF, acute heart failure; ARB, angiotensin receptor blocker; BMI, body mass index; BB, beta-blocker; CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; HF, heart failure; HR, heart rate; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; TD, target dose.

FIGURE LEGEND:

Figure 1. Reasons for underutilisation of guideline-directed medical therapies in heart failure with reduced ejection fraction

Figure 2. Evolving strategies to improve implementation of guideline-directed medical therapies in heart failure with reduced ejection fraction

Figure 1



BP,blood pressure; BMI, body mass index; GDMT, guideline-directed medical treatment; HR, heart rate; NYHA, New York Heart Association

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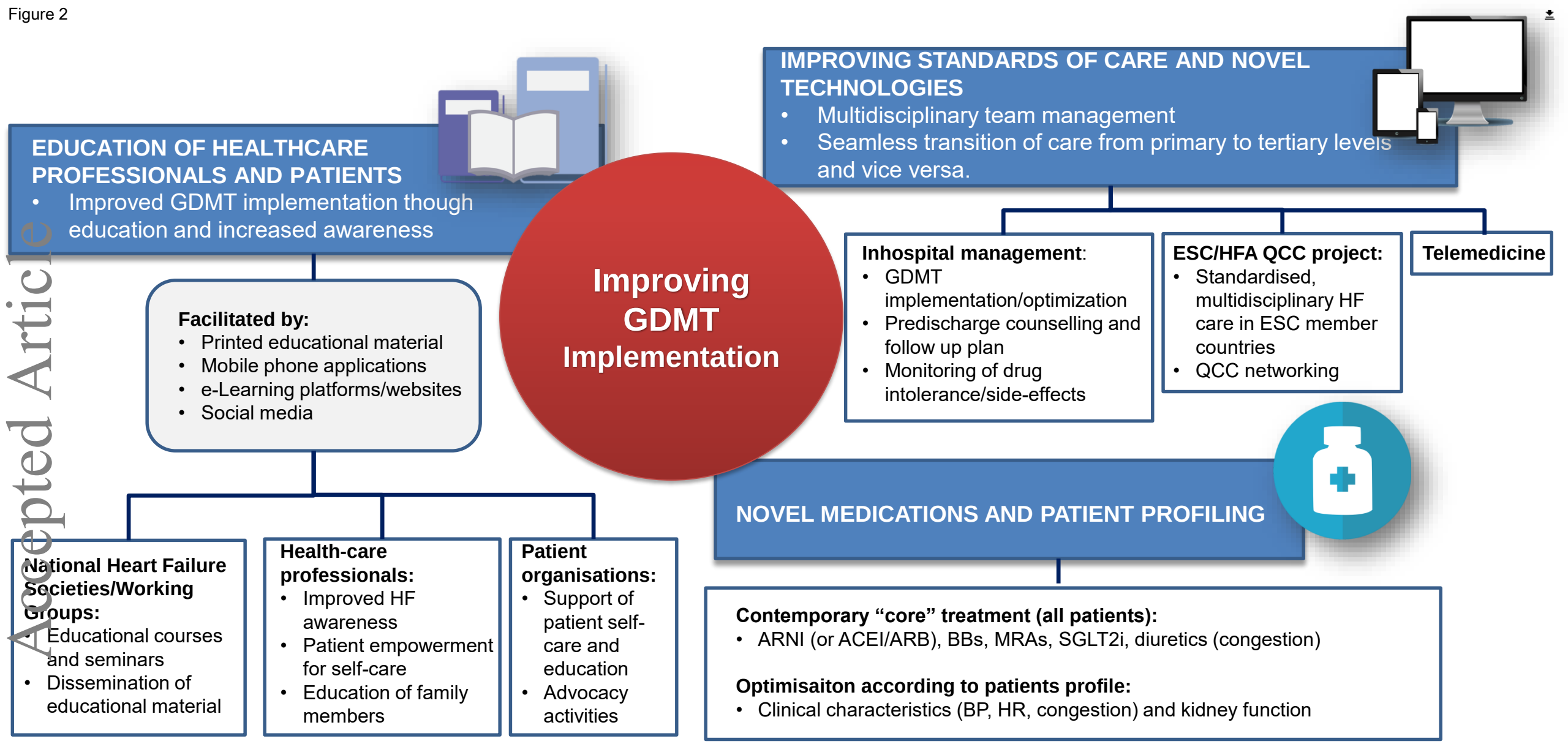
Figure 2



ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; BP, blood pressure; ESC, European Society of Cardiology, GDMT, guideline-directed medical treatment; HFrEF, heart failure with reduced ejection fraction; HF, heart failure, HR, heart rate; MRA, mineralocortiocoid receptor antagonist; SGLT2i, Sodium-glucose co-transporter-2 inhibitors; QCC; Quality of care