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POSITION PAPER

How to tackle therapeutic inertia in heart failure with reduced ejection fraction. A scientific statement of the Heart Failure Association of the ESC

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Guideline-directed medical therapy (GDMT) in patients with heart failure and reduced ejection fraction (HFrEF) reduces morbidity and mortality, but its implementation is often poor in daily clinical practice. Barriers to implementation include clinical and organizational factors that might contribute to clinical inertia, i.e. avoidance/delay of recommended treatment initiation/optimization. The spectrum of strategies that might be applied to foster GDMT implementation is wide, and involves the organizational set-up of heart failure care pathways, tailored drug initiation/optimization strategies increasing the chance of successful implementation, digital tools/telehealth interventions, educational activities and strategies targeting patient/physician awareness, and use of quality registries. This scientific statement by the Heart Failure Association of the ESC provides an overview of the current state of GDMT implementation in HFrEF, clinical and organizational barriers to implementation, and aims at suggesting a comprehensive framework on how to overcome clinical inertia and ultimately improve implementation of GDMT in HFrEF based on up-to-date evidence.

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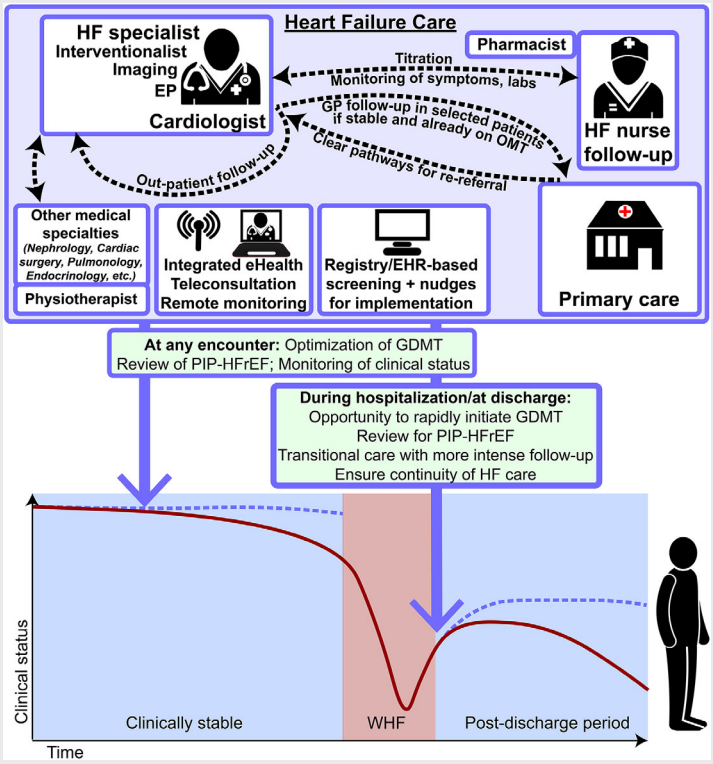
Graphical Abstract



Heart failure (HF) care to promote implementation of HF with reduced ejection fraction (HFrEF) guideline-directed medical therapy (GDMT). EHR, electronic health record; EP, electrophysiologist; GP, general practitioner; OMT, optimal medical therapy; PIP, potentially inappropriate prescription; WHF, worsening heart failure.

Keywords Clinical inertia • Guidelines-directed medical therapy • Heart failure • Heart failure with reduced ejection fraction • Implementation

Preamble

Heart failure (HF) is characterized by significant morbidity and mortality, and impaired quality of life.[1,2] It is associated with a 1-year mortality ranging between 15% and 30%,[3–7] and represents the leading cause of hospitalization in individuals aged >65 years.[8]

Over the last four decades, randomized controlled trials (RCTs) in HF with reduced ejection fraction (HFrEF) have demonstrated the efficacy and safety of several pharmacological and device therapies in terms of mortality and morbidity reduction and improvement of quality of life.[9–20] It is estimated that patients receiving the 'four pillars' of the pharmacological treatment for HFrEF, that is, a combination of a sodium–glucose cotransporter 2 inhibitor (SGLT2i), an angiotensin receptor–neprilysin inhibitor (ARNi), a beta-blocker and a mineralocorticoid receptor antagonist (MRA), may have a 61% reduction in risk of all-cause mortality, a 67% reduction in risk of cardiovascular (CV) mortality, and a 64% reduction in risk of CV mortality or HF hospitalization.[21] Despite these encouraging data and the clear and consistent guidance from international guidelines highlighting the need for a rapid establishment of the quadruple therapy in patients with HFrEF,[22,23] there is evidence of poorly implemented use of guideline-directed medical therapies (GDMT) in clinical practice.[24–27] Although in a proportion of patients the lack of treatment optimization might be partially explained by side effects and tolerability issues, the magnitude of this phenomenon as observed in registries and large real-world databases indicates that clinical inertia might play a significant role.[28,29]

This scientific statement of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) aims to raise awareness on the need of GDMT implementation, identify factors that might contribute to clinical inertia and act as barriers to implementation, summarize recent evidence supporting potential approaches to improve implementation and counteract clinical inertia, and

propose strategies for optimizing GDMT use in clinical practice (*Graphical Abstract*).

Status of guideline-directed medical therapy implementation in major national and multi-national registries

The extent of GDMT implementation in patients with HFrEF has been widely explored in large national and multi-national registries, including the ESC HF Long-Term (ESC-HF-LT) registry (21 European and Mediterranean countries),[30] the Swedish HF Registry (SwedeHF),[26,31] the CHECK-HF (Netherlands),[32] the CHAMP-HF (United States),[33] and the ASIAN-HF (11 countries in Asia).[34] Although any use (irrespective of dose) has been reported in 73–93% of patients with HFrEF for renin–angiotensin system inhibitors (RASi) and 67–93% for beta-blockers, only 33–68% were treated with MRA,[26,30,32–34] and a minority reached the target dose (TD) for RASi/ARNi (17–40%) and beta-blockers (13–40%) (*Figure 1*).[31–34] Data on the implementation of SGLT2i are more scarce due to their recent introduction; in 2022, ~50% of patients with HFrEF in SwedeHF received a SGLT2i.[35] The most recent multi-national data on GDMT implementation come from the EVOLUTION HF study, which enrolled 266 589 patients initiating any GDMT within 12 months of a hospitalization for HF in Sweden, Japan and US during 2020–2022.[24] This study showed a different perspective on the limited implementation of GDMT, which is the delayed initiation of SGLT2i and ARNi as compared with traditional drugs, despite the strong recommendation from guidelines to rapidly implement the full treatment combination.[23] Overall there were high discontinuation rates at 1 year, that is, 23% for dapagliflozin, 26% for ARNi, 33–38% for RASi, 25% for beta-blockers and 42% for MRA, with TD achieved and maintained only in a minority of patients.[24]

When analysing treatment use, it is important to consider that although more unselected than RCTs, registries are still prone to selection bias due to their selective and incomplete coverage, with most patients enrolled in specialized centres and therefore more likely to receive better treatment/follow-up.[36] This leads to overestimating the use of optimal medical therapy (OMT), and therefore GDMT implementation in real-world clinical practice is likely even more needed than what registry-based studies suggest. On the other hand, registry data may not fully reveal clinical conditions and contraindications limiting GDMT implementation in real-life praxis which may instead lead to some overestimation.

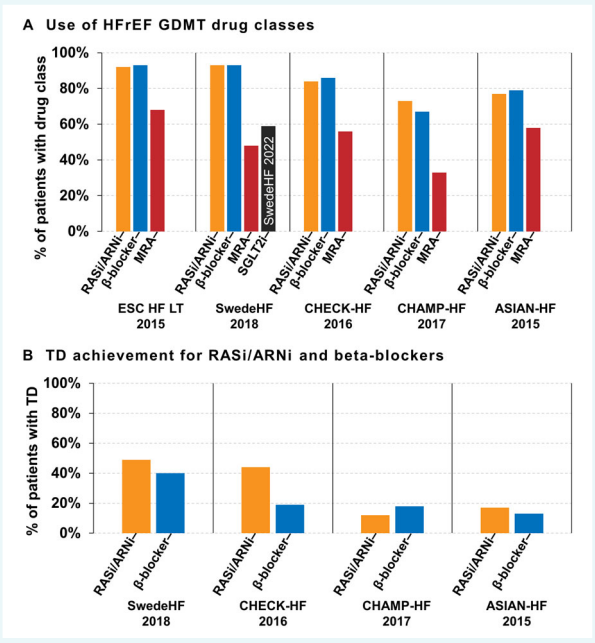


Figure 1 State of guideline-directed medical therapy (GDMT) implementation in heart failure with reduced ejection fraction (HFrEF) (*A*) and achievement of target dose (TD) (*B*) – data from large registries. ARNi, angiotensin receptor–neprilysin inhibitor; ASIAN-HF, Asian Sudden Cardiac Death in Heart Failure; CHAMP-HF, Change the Management of Patients With Heart Failure; CHECK-HF, Chronic Heart Failure ESC-guideline based Cardiology practice Quality project; ESC HF LT, European Society of Cardiology Heart Failure Long-Term registry; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SwedeHF, Swedish Heart Failure registry; TD, target dose.

Advocated/potential reasons for lack of implementation

Clinical inertia: general and contextualized definition

In physics, inertia is the resistance of an object to undergo change. In clinical practice, it has been defined as 'the resistance or the lack of treatment intensification in patients not on optimized therapy'.[37] In the setting of HFrEF, clinical inertia might result in a delayed or missed initiation of treatments. Inertia can be triggered by factors that make treatment intensification more challenging and/or cumbersome, which can be related to the specific characteristics of the patient or of the healthcare system where the patient is encountered and followed up.[38] Patient-related factors might include clinical (e.g. age, sex, blood pressure, renal function, potassium levels, comorbidity burden, frailty), socioeconomic (e.g. income, cultural background, family context, isolation) and psychological (e.g. mental disorders, dementia) components. Healthcare-related factors include the accessibility to a structured follow-up and the availability of pre-/post-discharge strategies, and physicians' lack of time and awareness.[39] Key factors that might precipitate clinical inertia, as well as potential related mitigation strategies, will be discussed below.

Hypotension

Hypotension predicts poor outcomes in patients with HF.[40–42] In a large cohort of 39 372 patients included in the Meta-analysis

Global Group in Chronic Heart Failure (MAGGIC) programme, lower systolic blood pressure (SBP) was an independent predictor of mortality, with an even greater role in patients with lower ejection fraction.[43] Actual or anticipated hypotension is one of the most frequent causes of GDMT underuse, contributing to explain its unfavourable prognostic role.[44] Development of haemodynamic intolerance to angiotensin-converting enzyme inhibitors (ACEi) identifies patients with more severe disease and poorer prognosis.[45] In the ESC-HF-LT registry, hypotension was reported as the reason for not achieving TD in 26% of patients undertreated with ACEi/angiotensin receptor blockers (ARB), and 17% of those undertreated with beta-blockers.[29] In the CHAMP-HF registry, lower SBP predicted missed initiation or dose optimization of ACEi/ARB and beta-blockers.[33,44]

An SBP <90–100 mmHg was an exclusion criterion in major clinical trials, and therefore limited evidence supporting the initiation of GDMT in patients with lower blood pressure might be considered a barrier to implementation. In addition, excessively low blood pressure may increase the risk of CV events in certain subgroups of patients (e.g. those with coronary artery disease). However, it is important to acknowledge that no GDMT has been linked with harm or lack of benefit even in the lower range of blood pressure levels.[46–51] Moreover, the association between hypotension and poor outcomes is diminished if hypotension is related to GDMT implementation.[52] Therefore, in case of non-severe and asymptomatic hypotension, the 2021 ESC guidelines recommend to maintain the same dose as the recommended GDMT in HFrEF.[23,53]

In patients with symptomatic or severe persistent hypotension (SBP <90 mmHg), several strategies should be considered. Reducing or withdrawing vasodilating agents not indicated in HFrEF, as well as reassessing the indications for drugs with hypotensive effects (e.g. nitrates, calcium-channel blockers, and alpha-blockers), might be helpful to address hypotension without impacting GDMT use. In the absence of congestion, dose reduction/withdrawn of diuretics might be attempted. Device therapies and procedures demonstrated to increase cardiac output (i.e. cardiac resynchronization therapy [CRT], percutaneous correction of severe mitral regurgitation) might act as enablers to GDMT initiation/dose up-titration by increasing blood pressure.[54–56] Pre-discharge initiation/optimization of GDMT together with a close post-discharge follow-up visit might facilitate the achievement of OMT in a setting where symptomatic hypotension could be recognized and timely addressed.[57] Blood pressure is a dynamic parameter reflecting the haemodynamic status at a specific time point, and therefore initiation/optimization of GDMT should be re-evaluated at each medical encounter. Importantly, in patient profiles characterized by hypotension limiting the optimization of the treatment with RASi/ARNi and specific beta-blockers, a prompt initiation of treatments such as SGLT2i and MRA could be prioritized given their limited hypotensive effect, particularly in those patients with low baseline blood pressure.[46–48,58] Use of ivabradine could favour the achievement of target heart rate value without a significant impact on blood pressure in patients on RASi/ARNi and MRA unable to tolerate further up-titration of beta-blockers.[59] Additionally, beta-blockers have been shown to be effective and safe in trials including patients with blood pressures ≥85 mmHg.[14,50] If the implementation of the treatment with beta-blockers is still limited by hypotension, the selection of specific agents with a better blood pressure/heart rate lowering profile can be considered (e.g. bisoprolol, metoprolol or nebivolol, instead of carvedilol).[60] If de-escalation of HFrEF GDMT is ultimately deemed necessary, hypotension associated with bradycardia might contribute to identifying beta-blocker as the causal agent.

Impaired kidney function

Chronic kidney disease (CKD) is highly prevalent in HFrEF (up to ∼50%) and is independently associated with increased mortality/morbidity.[61] Worsening renal function is one of the most frequent causes of underuse of RASi/ARNi and MRA.[62] In the ESC-HF-LT registry, worsening renal function was the reason for non-achievement of TD for ARB and MRA in ∼10% of patients.[29] Guidelines recommend the discontinuation of ACEi/ARB and MRA only when estimated glomerular filtration rate (eGFR) <20 ml/min/1.73 m^2, and of ARNI when eGFR <30 ml/min/1.73 m^2.[23] However, real-world data show that even lesser degrees of impaired eGFR (30–60 ml/min/1.73 m^2) are associated with lower use and higher discontinuation rates of ACEi/ARB and MRA, despite evidence on efficacy and safety of HF treatments in this eGFR range from RCTs.[62–64]

First, it should be noted that the benefit of GDMTs in HFrEF is well-established also in patients with CKD. Major RCTs included patients with an eGFR ≥20 ml/min/1.73 m^2 for ACEi/ARB and SGLT2i,[9,19,20] and ≥30 ml/min/1.73 m^2 for ARNi and MRA.[16,17] Large RCTs in HFrEF detected no statistical interaction between treatment benefits and the presence of CKD.[16,17,19,20,65–67] Therefore, patients with HFrEF and CKD, if eGFR is above the aforementioned thresholds, should be considered to gain equal relative risk reductions from HFrEF GDMT as patients without CKD.

Second, it is important to recognize that, although RASi/ARNi, MRA and SGLT2i may lead to an initial drop in renal function upon initiation, this early decline is frequently self-limiting, rarely reflects kidney damage, is associated with long-term kidney benefits, and should not routinely prompt therapy de-escalation. In large RCTs, SGLT2i (as compared with placebo) and ARNi (as compared with ACEi) have been demonstrated to reduce the slope of eGFR decline and the risk of renal events in patients with HFrEF.[18,19,63] Such effects have not been observed for RASi in HF RCTs,[68] although they have established nephroprotective roles in CKD. MRA use leads to acute declines in eGFR but does not modify long-term kidney disease trajectories in HFrEF.[69] In the EMPHASIS-HF, patients with eGFR 30–49 ml/min/1.73 m^2 were started on 25 mg eplerenone on alternate days and then up-titrated to 25 mg daily.[16] In RCTs the non-steroidal MRA finerenone showed improved renal outcomes and reduced HF hospitalizations in patients with diabetes and CKD, although patients with HFrEF were excluded.[70–73]

In patients with severe CKD, evidence is mostly limited to small trials and observational data. In the STOP-ACEi trial, discontinuation of ACEi in patients progressing to severe CKD was not associated with any renal benefit.[74] Although patients

with severe CKD were not included in HFrEF trials, observational data might suggest better outcome with sacubitril/valsartan also in patients with severe and end-stage kidney disease.[75,76] Treatment with beta-blockers does not lead to acute effects on eGFR, is generally well-tolerated in patients with CKD, with reduced morbidity/mortality found in an RCT on patients with HFrEF undergoing dialysis.[77] In SwedeHF, MRA use appeared safe in terms of mortality/renal outcomes regardless of eGFR, leading to question the need for MRA discontinuation in patients with severe CKD if strict laboratory surveillance is feasible.[78] Vericiguat is approved in patients with worsening HF and eGFR 15–30 ml/min/1.73 m^2, being a potential therapeutic option when RASi or ARNi are contraindicated.[79]

A well-structured biochemical monitoring (creatinine and potassium levels) in patients initiating/on treatment with ACEi/ARB/ARNi/MRA, in particular those with significant CKD, is key to avoid missed initiation/unnecessary discontinuation due to fear for potential safety issues. Among several toolkits which might facilitate physicians in their daily decision-making, one on the optimization of RASi/ARNi/MRA in the setting of CKD has previously been developed in joint collaboration between the HFA, the International Society of Nephrology, the Renal Physicians Association, and the Kidney Disease: Improving Global Outcomes.[80] According to this toolkit, RASi/ARNi/MRA should be initiated and up-titrated to maximum tolerated doses, advising that an early creatinine increase <30% may be considered as an appropriate haemodynamic change in response to treatment initiation, and that kidney function and electrolytes should be frequently monitored until they are in safe ranges. Additionally, no changes in RASi/ARNi/MRA are needed if kidney function stabilizes after an increase in creatinine <50% (as long as eGFR remains >20 ml/min/1.73 m^2) following treatment initiation/up-titration.

Hyperkalaemia

Hyperkalaemia is prevalent in patients with HFrEF and is associated with increased mortality,[81] although possibly as a risk marker rather than a risk factor.[82] Within 1 year, up to ~25% of HFrEF patients experience a hyperkalaemic event (K >5.0 mmol/L) and ~10% a moderate/severe event (K >5.5 mmol/L).[83] Among GDMTs, RASi/ARNi and MRA have the greatest impact on potassium homeostasis. In EMPHASIS-HF, eplerenone led to an increased risk of K >5.5 mmoL/L but not of K >6.0 mmoL/L and of hospitalization for hyperkalaemia or discontinuations due to adverse events, and the treatment effect, as well as the safety, was consistent across the potassium spectrum regardless of renal function.[64] In PARADIGM-HF the risk of any and moderate/severe hyperkalaemia was lower with sacubitril/valsartan as compared with enalapril, and sacubitril/valsartan treatment effect was consistent across the investigated potassium spectrum.[84] However, trials exclude patients with severe CKD and apply a strict follow-up, implying that the observed occurrence of hyperkalaemia might not be representative in the real-world setting.

The publication of RALES and the subsequent implementation of spironolactone use was followed by reports highlighting increased hyperkalaemia-associated morbidity and mortality in the real-world setting.[85] These observations have not been replicated elsewhere, and they might have been partially explained by early mis-use and/or inadequate monitoring, leading to a call for closer laboratory monitoring in real-world care.[86,87] Although MRA-related hyperkalaemia represents a factor which might limit MRA implementation,[88] the disproportion between the actual risk of hyperkalaemia and the observed underuse of MRA might indicate that fear of hyperkalaemic events is itself a major barrier to implementation.[25] Notably, part of the increased mortality observed in patients experiencing a hyperkalaemic event under treatment with MRA might be mediated by the withdrawal of MRA rather than the risk of hyperkalaemia itself. Patients with hyperkalaemia have lower mortality when treated with spironolactone as compared with patients on placebo with similar potassium levels.[89] It has been observed that stopping an MRA after an episode of hyperkalaemia was associated with reduced risk of recurrent hyperkalaemia, but a higher risk of death and CV events in patients with an indication.[90]

Stable potassium levels <5.5 mmol/L are acceptable in HFrEF patients on treatment with GDMT. Beyond this cut-off, the 2021 ESC guidelines on HF recommend renin–angiotensin–aldosterone system inhibitor (RAASi)/ARNi discontinuation whilst seeking specialist advice.[23] SGLT2i have been shown to be potential enablers for MRA use, which is likely mediated by a reduction in risk of hyperkalaemia.[91] Beyond providing careful instructions on the diet, current guidelines propose novel potassium binders as enablers for RAASi/ARNi initiation and dose optimization.[23,92] Novel potassium binders have been shown to maintain lower potassium levels under treatment with GDMT, reduce the risk of recurrent hyperkalaemia, and facilitate the optimized use of RAASi.[93–95] Optimizing lab monitoring could facilitate to fill the gap between the poor use of MRA observed in real world and the one observed in RCTs (~80% in the most contemporary trial).[96]

Residual congestion

Recent RCTs showed that irrespective of the type or intensity of the applied diuretic strategy, there was no association between decongestion and post-discharge mortality.[97–99] Additionally, enhanced decongestion therapy may delay and compromise GDMT implementation by inducing electrolyte abnormalities, creatinine increases and blood pressure decreases.[97,98] There is no evidence from RCTs supporting the approach of waiting for complete decongestion before initiating GDMT rather than starting GDMT earlier.[99] In the STRONG-HF, comprehensive neurohormonal blockade might have promoted decongestion by itself as patients in the high intensity care arm received a significantly lower dose of diuretics at day 90.[100] Consistently, SGLT2i use and up-titration of ARNi have been seen to be associated with better decongestion and less diuretic use.[101,102] These findings suggest that in HF patients without significant fluid overload, optimizing GDMT could lead to additional decongestion without requiring higher doses of diuretics. Appropriate monitoring of congestion through a properly planned follow-up, which in specific patients might be aided by implantable sensors,[96,103] remains the most judicious strategy to

select those patients in need of additional decongestion in order to improve tolerance to GDMT and prevent hospitalizations.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is highly prevalent in patients with HFrEF (up to ~20%) and is more frequent in HF as compared with the general population.[104] It has been repeatedly shown as a major factor associated with non-use and missed dose optimization of beta-blockers in real-world populations.[26,105,106] Beyond the well-demonstrated efficacy as HFrEF GDMT, beta-blockers have been suggested to have non-cardiac targets and were associated with lower risk of COPD exacerbations in patients with CV disease in a meta-analysis of observational studies.[107] Nevertheless, the recent BLOCK COPD RCT, which enrolled 532 patients with moderate–severe COPD and no established indications to beta-blockers, was terminated after the second interim analysis due to futility and safety concerns, as higher risk of exacerbation leading to hospitalization was observed in the metoprolol arm.[108] However, BLOCK COPD should not be interpreted as discouraging the use of cardioselective beta-blockers in patients with COPD and HFrEF. Although randomized evidence on beta-blocker use in patients with HFrEF and concomitant COPD is scarce (in MERIT-HF, 5.3% of patients had COPD),[109] beta-blockers have well-established benefits in HFrEF overall, and were safe in patients with concomitant COPD in observational studies.[106] There is no guideline recommendation specific to the treatment of patients with HFrEF and concomitant COPD.[23] Asthma also does not constitute an absolute contraindication to cardioselective beta-blockers, but starting with low doses combined with closer monitoring for signs of obstruction should be encouraged.[23] Cardioselective beta-blockers such as bisoprolol, metoprolol or nebivolol should be the substances of choice when initiating beta-blocker therapy in patients with HFrEF and concomitant obstructive pulmonary diseases. If beta-blocker up-titration is poorly tolerated, initiation of ivabradine may facilitate the achievement of target heart rate.[59]

Frailty and ageing

Frailty is defined as a multidimensional condition that increases the patient's vulnerability to endogenous and exogenous stressors; it affects up to 45% of the HF population regardless of age, and leads to poor outcome.[110–114] The assessment of frailty is based on four domains: clinical (including comorbidities, falls and weight loss), functional (mobility, physical impairment), psycho-cognitive (cognitive impairment, dementia and depression) and social (living alone, no social support).[110] Frailty, a severe health burden, is linked with the need of polypharmacy, impairs patients' compliance, tolerability to treatments, and increases the risk of side effects, leading to sometimes necessary treatment discontinuation but also to unnecessary missed initiation. The presence of frailty and/or ageing may limit access to treatments and interventions, thus leading to frailtyism and ageism, defined as a stereotyping, prejudice and discrimination against people only based on the presence of frailty (frailtyism) and/or ageing (ageism).[115,116]

In a post-hoc analysis of patients with HFrEF enrolled in the GUIDE-IT trial, participants with high frailty burden had a significantly lower likelihood of achieving optimal GDMT (17.7% vs. 28.4%).[117] In a sub-analysis of the FLAGSHIP study, the severity of physical frailty was independently associated with the non-use of GDMT, which in turn was linked with worse prognosis.[118–120] This highlights the need to minimize the unnecessary discontinuation/non-initiation of GDMT in all patients, including the more vulnerable ones.

Similar considerations can be applied to older patients, who represent a substantial portion of the HFrEF population (e.g. 35% ≥80 years in SwedeHF and 34% >75 years in the ESC-HF-LT registry), but are more poorly treated compared with younger patients.[26,41,121] They might be more prone to tolerability issues and side effects with GDMT due to higher risk of symptomatic hypotension, bradycardia, renal impairment, hyperkalaemia, and polypharmacy to address the multi-comorbid status. However, after adjustment for these and many other variables linked with potential limited tolerability, in SwedeHF older age was independently associated with lower use of GDMT, suggesting clinical inertia as a likely cause.[26] One argument which has been proposed as a potential reason behind the underuse of GDMT in older (as well as in frail) patients is their limited representation in RCTs, in particular of those >80 years.[122] However, as for frailty,[120] no signal for decreasing GDMT efficacy has been detected with older age in subgroup analyses of trials,[123–128] and observational studies suggest similar benefit in terms of outcome as in younger populations, with no increased risk of hospitalization for syncope, adopted as a surrogate of hypotensive or bradyarrhythmic events.[129,130]

Initiation and optimization of GDMT in older and frail patients should be always attempted under strict monitoring for potential tolerability issues and side effects. Advances in technology with for example, telemonitoring, might support the optimization of follow-up in this specific subgroup of patients.[131] Better access to primary care and nurse-led clinics, home-based education and support by nurses and physicians may be useful in all patients with HFrEF,[132] but especially important in frail and elderly patients. In these patients hospital admissions are frequent, and when they occur (for CV or non-CV reasons), the in-hospital setting can provide an opportunity for a safe optimization of HFrEF treatments once haemodynamic stability is achieved.[23]

Polypharmacy

Polypharmacy reduces patients' adherence but also increases the risk of adverse drug reactions and drug–drug interactions, leading to under-prescription and under-dosing of the full list of GDMT, especially in elderly and frail patients.[133,134] The implementation of alerts in the electronic journal systems might aid the detection of inappropriate prescribing and potentially unrecognized drug interaction, thereby potentially facilitating safer GDMT initiation in the setting of polypharmacy. The ESC has previously provided a document highlighting potentially inappropriate prescriptions in patients with HFrEF.[134] Implementation of GDMT could be deprioritized due to other non-HF/non-CV conditions which require immediate attention. A careful analysis of the patient's

treatments list should be performed to identify and deprescribe those treatments which are no longer required or to identify newly emerged potentialities of GDMT implementation due to the change of patient's clinical status.

Socioeconomic factors

Socioeconomic status has an important impact on the incidence of HF as well as on its prognosis.[135–137] A lower socioeconomic status, defined according to income, educational level and living arrangement has been linked with less access to follow-up in specialty care or nurse-led HF clinics, lower use of HF medical therapies and devices, and higher risk of morbidity/mortality.[25,138–140] These associations may be partially mediated by costs and patient preferences related to the socioeconomic environment. Living far from tertiary care centres, living alone, and lack of referral to specialists have also been associated with less likely referral for HF device implantation (implantable cardioverter-defibrillator [ICD] and cardiac resynchronization therapy [CRT]).[140–142] While highlighting the urgent need for greater and more equal access to care, telemedicine could contribute to improve healthcare accessibility and overcome geographic and social inequalities.[143] It should also be acknowledged that how GDMT is reimbursed within different healthcare systems can also affect the impact of socioeconomic status on GDMT implementation.

Approaches to foster guideline-directed medical therapy implementation and prevent clinical inertia (*Figure 2*)

Personalized drug layering according to patient profiles

Until recently, European and American HF guidelines recommended a sequential approach to initiation and up-titration to target doses of HFrEF medications that broadly reflected the order in which they had been tested in landmark trials.[144,145] This approach lacked a biological rationale, and further caused delays in GDMT initiation, since the goal of target doses is rarely achieved in clinical practice.[24,146] Current international HF guidelines recommend the simultaneous or near-simultaneous initiation of the 'four pillars' of HFrEF pharmacotherapy, that is, RASi/ARNi, beta-blockers, MRA, and SGLT2i, which should be attempted in all patients and might lead to fewer delays and less missed initiation.[22,23] Key patient characteristics impacting treatment initiation/optimization and therefore defining different patient profiles suitable for different treatment implementation approaches in clinical practice are renal function, blood pressure, heart rate/rhythm, and potassium levels.[147–149] Starting all the four treatments at once might be challenging in clinical practice due to limited 'spending function' of these four parameters,[150] and in this setting patient profiling should guide treatment prioritization.[149] Since the number of initiated GDMT classes has been suggested to outweigh target dose achievement for mortality/morbidity reduction, treatment initiation should be prioritized over treatment dose optimization.[21,31] When all the tolerated foundational treatments are initiated, dose optimization for drugs in need of up-titration should be performed according to patient profiles. Evidence on potential sequential approaches to guide GDMT initiation which might be needed in case of unfeasible simultaneous initiation of the four foundational therapies is limited. In an analysis of five RCTs, an accelerated sequence of SGLT2i plus MRA, followed by an ARNi and then beta-blocker was the most effective in reducing the risk of CV death or HF hospitalization.[151] Indeed, starting with an SGLT2i and MRA might allow to take advantage of the potential for SGLT2i to reduce the risk of hyperkalaemia when initiating an MRA,[91] and might only limitedly affect blood pressure,[46–48] while the up-front initiation and up-titration of RASi/ARNi and beta-blockers might be less well-tolerated, in particular in terms of blood pressure spending function. Similar tailoring considerations can be made for patients with residual congestion, which might not be the optimal setting for beta-blocker initiation/up-titration, but might benefit from the small diuretic effect achieved with SGLT2i.

Personalized HFrEF therapy also involves careful consideration of comorbidities and therefore of non-HF medications, as well as screening for indications for HFrEF therapies beyond the mandatory four pillars of HFrEF GDMT (e.g. device therapy, ivabradine, vericiguat, and intravenous iron). Although patients with multiple non-cardiac comorbidities are traditionally perceived as riskier candidates for rapid intensification of GDMTs, the results of a secondary analysis of the STRONG-HF trial showed feasibility and outcome benefit of GDMT optimization regardless of number of comorbidities.[152]

Overall pharmacological treatment of HFrEF patients should also be regularly checked for medications that might exacerbate HF or decrease tolerability to HFrEF pharmacotherapy, such as non-steroidal anti-inflammatory drugs, and non-HF treatments with hypotensive or negative chronotropic effects.[134]

Structured heart failure follow-up

According to the 2021 ESC HF guidelines, all patients with HFrEF should receive structured follow-up at a maximum interval of 6 months, and even more frequently after hospital discharge or during the process of optimizing HFrEF treatment.[23]

A large proportion of patients with HF might receive follow-up in the primary care setting, as often secondary care clinicians need to prioritize the most symptomatic patients. This has been suggested to be feasible and safe in patients who are stable and already on OMT,[153] but supporting data are sparse and clear referral pathways should be in place in case of a clinical change that might motivate evaluation for advanced therapies, triggering a rapid referral back to specialty care. In patients who are not yet on full GDMT, the stringent follow-up needed for a rapid up-titration of HFrEF pharmacotherapy might be unfeasible in most primary care settings.[154] Consistently, observational data have shown that HF follow-up in specialty versus primary care was associated with higher use of GDMT and lower mortality.[140] Awareness of changes

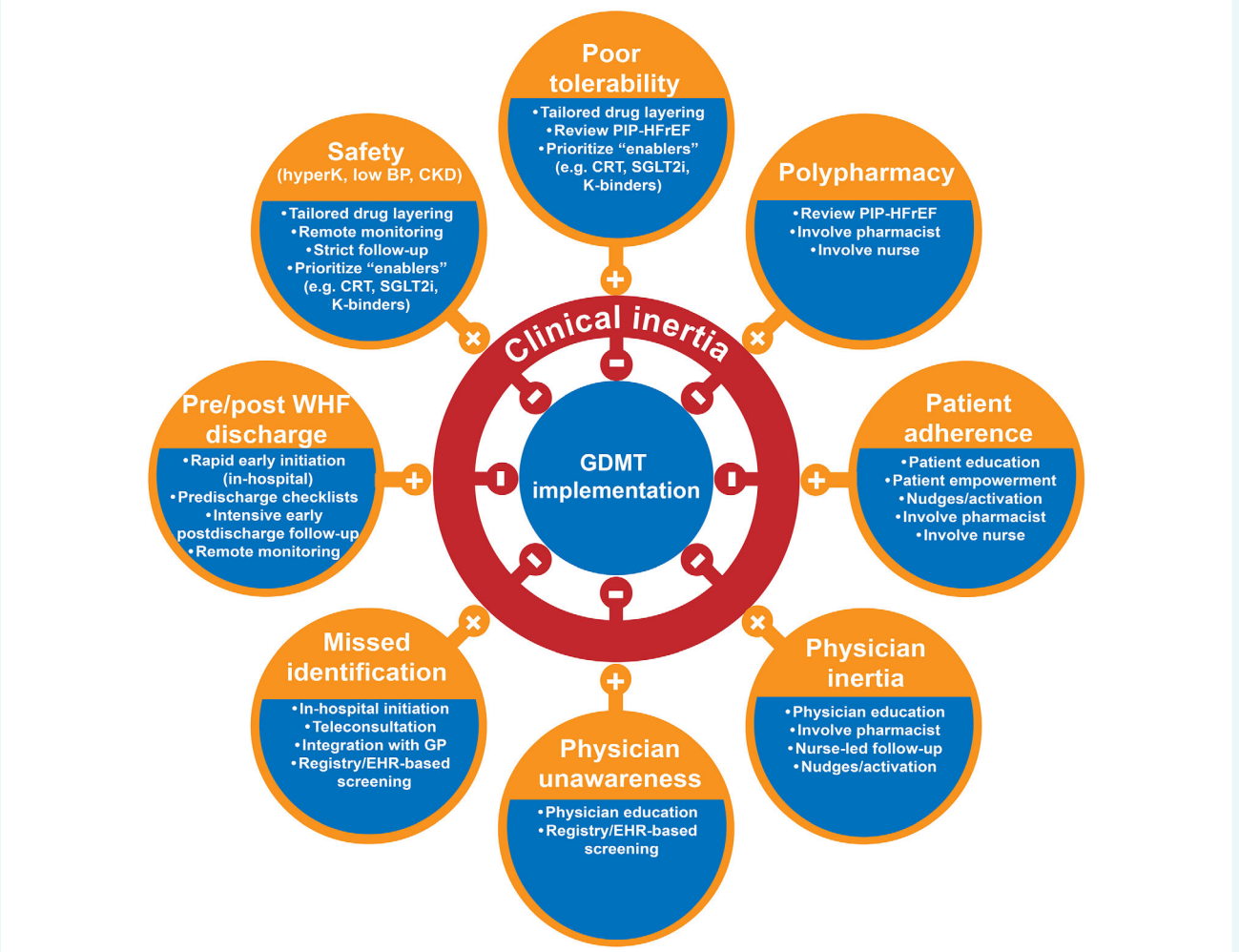


Figure 2 Strategies to overcome key contributors to clinical inertia. BP, blood pressure; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; EHR, electronic health record; GDMT, guideline-directed medical therapy; GP, general practitioner; PIP-HFrEF, potentially inappropriate prescriptions in heart failure with reduced ejection fraction[134]; SGLT2i, sodium–glucose cotransporter 2 inhibitor; WHF, worsening heart failure.

in HF guidelines and availability of novel HF therapies are also likely to be delayed in primary care,[23] highlighting the importance of initiatives aiming to disseminate knowledge on updates in best HF practice and better interaction between primary and secondary care.

Specialized HF nurses might have a key role in providing strict monitoring of clinical status and laboratory tests, and therefore triggering treatment optimization.[155] Referral to a nurse-led HF clinic has been associated with a lower risk of morbidity and mortality or HF hospitalization together with better use of HF medications.[139,155,156] The implementation of a multidisciplinary HF management programme involving specialized HF nurses and cardiologists in a Swedish regional healthcare system was linked with improved GDMT implementation and lower HF hospitalizations and mortality.[157] In a post-hoc analysis of the Interdisciplinary Network HF study, the nurse-coordinated arm achieved greater prescription rates/dosages of RASi and beta-blockers.[158] Nurse-led HF clinics are, however, not ubiquitously available[159]; improved utilization of such services should be sought to facilitate implementation of GDMT.

As for nurses, pharmacist's participation to care of HF patients might favour medication reconciliation, treatment optimization, patient education and promotion of medication adherence.[160] In a cluster RCT, HFrEF patients seen in the primary care clinics allocated to GDMT implementation led by a pharmacist were >2-fold more likely to intensify beta-blocker and/or RASi therapy.[161] In the PHARM-CHF trial, pharmacy-based follow-up and medication review improved adherence to HF GDMT.[162] A meta-analysis reported that pharmacist-led interventions in outpatient HF care could improve adherence to GDMT and quality of life, but with uncertain effects on morbidity/mortality.[163]

Pre- and post-discharge transitional care after a heart failure hospitalization

The 2021 ESC guidelines on HF included a recommendation for the pre-discharge initiation of evidence-based medical treatment and for an early follow-up visit at 1–2 weeks after discharge to assess signs of congestion, drug tolerance and start and/or up-titrate evidence-based therapy.[23] The attempt behind these recommendations is to start GDMT as soon as possible to avoid delays, and lead to consider a hospitalization as an opportunity for therapy optimization.[24,164] Since then, two large RCTs have demonstrated benefits of transitional care strategies consisting of high-intensity treatment up-titration and follow-up during and following acute HF.[100,165]

The COACH trial was a cluster RCT assessing a risk-stratified management intervention using a validated point-of-care tool. Low risk patients were recommended for early discharge (<3 days) followed by 30 days standardized outpatient follow-up staffed by a nurse supervised by a cardiologist, whereas intermediate-high risk patients were admitted to hospital.[165] The intervention reduced the primary outcome of all-cause death/CV hospitalization, suggesting a beneficial effect of such post-discharge care approach.[165] STRONG-HF was an open-label RCT assessing the effectiveness and safety of a rapid up-titration of ACEi, beta-blocker, and MRA, starting 2 days prior to the estimated discharge and aiming to reach 100% of target doses within 2 weeks of discharge.[100] Patients in the intervention arm further received intensive follow-up at 1, 2, 3, and 6 weeks post-randomization, with close monitoring of clinical status and laboratory measurements. The high-intensity care arm showed a lower risk of the primary outcome (HF readmission or all-cause death), improvement in symptoms and quality of life, and a higher proportion of patients reaching target dose of RASi (55% vs. 2%), beta-blockers (49% vs. 4%), and MRA (84% vs. 46%). Previous prospective trials assessing intensive follow-up transitional care strategies have largely failed to improve outcomes when not involving a clear strategy of initiation/up-titration of GDMT.[166–169] Based on the newly available evidence, the 2023 update of the 2021 ESC HF guidelines recommends a rapid initiation and up-titration of GDMT accompanied by frequent follow-up during the first 6 weeks after discharge.[57,170]

Hospital admissions for non-HF causes also represent an opportunity to boost GDMT implementation by utilizing the multidisciplinary resources that are typically available in hospital but less accessible in an outpatient setting. The utilization of a virtual team of cardiologists and pharmacists performing GDMT prescriptions in HFrEF patients hospitalized for non-CV reasons was associated with greater GDMT intensification versus usual care.[171] Two recent RCTs reported that virtual peer-to-peer consultations in HFrEF patients hospitalized in non-cardiology wards increased GDMT initiation and intensification.[172,173] A hospitalization (for any cause) should be considered an opportunity to initiate and improve HFrEF GDMT, discontinue inappropriate medications, facilitate continuity of HF care, and identify the need for intensified post-discharge follow-up. Protocols for transitionary care should be in place to ensure optimal medical care at the discharge and close monitoring in the vulnerable period after a HF hospitalization in order to enable rapid up-titration of HFrEF GDMT.[100,165]

Educational efforts increasing physicians' and patients' awareness

Caregivers' understanding of the importance of and the strategies for achieving OMT in HFrEF is central and represents a likely target to improve GDMT implementation. The association between the enrolment in a HF registry and improved HF care is likely explained by greater attention to HF management in registry-participating sites which are typically secondary/tertiary hospitals.[36,174] However, RCTs testing quality-improvement interventions targeting caregivers' awareness have reported mixed results, and their success is likely sensitive to methodology, mode of delivery, and the setting in which the intervention is implemented.[166,167,175,176] Multifaceted quality-improvement interventions including coaching, audit, and site-level feedback did not improve GDMT implementation in previous trials.[167,176]

Educational interventions have been more successful to implement GDMT use when performed in close conjunction to a clinical encounter.[177–180] The BETTER CARE-HF trial randomized 180 cardiologists to usual care or one of two interventions aiming at improving MRA initiation: an electronic health record (EHR) alert regarding a single patient at the time of visit, or a message regarding multiple patients between visits.[179] Although the between-visits message increased MRA use versus usual care (16% vs. 12% MRA initiation), the alert in conjunction with the clinical encounter was superior to both (30% MRA initiation).[179] In the EPIC-HF trial, including 290 HFrEF patients planned for a near-term cardiologist visit, patients were randomly assigned to receive an electronically delivered text/video-based tool encouraging patients to work collaboratively with their physician to optimize their HFrEF therapy.[177] The intervention arm more frequently experienced initiation/intensification of GDMT versus usual care (49% vs. 30%).[177] The PROMPT-HF trial randomized 100 care providers to receive an EHR-based alert notifying of individualized GDMT recommendations for their patients versus usual care.[178] The proportion of patients experiencing an increase in the number of GDMT classes was higher in the alert arm (26% vs. 17%).[178] A similar alert strategy did not improve implementation in an inpatient setting in the following PROMPT-AHF trial, highlighting that the setting can impact the effectiveness of nudges/alerts.[181] 'Alert fatigue',[182] likely amplified by a partially unmonitored adoption of EHR alerts, might have contributed to the neutral findings.[181] This underscores that EHR alerts should be scrutinized in trials prior to broad implementation, in order to prevent dilution of evidence-based and high-priority alerts.[182] Further studies exploring the role of positive 'nudges', as exemplified in the PROMPT-HF, should be encouraged to identify strategies to overcome clinical inertia.[183]

A list of selected randomized trials testing strategies aiming at GDMT implementation in HFrEF is provided in *Table 1*.

Table 1 Selected randomized trials testing strategies aiming at the implementation of guideline-directed medical therapy use in heart failure with reduced ejection fraction

Trial	Setting	Design	Sample size	Intervention	Primary outcome and findings on implementation
Transitional care and follow-up strategies					
Mebazaa *et al.*, 2022 (STRONG-HF)[100]	Haemodynamically stable inpatients admitted to hospital for acute HF <72 h prior, within 2 days before anticipated hospital discharge, tolerant to but not yet receiving optimal doses of RASi/beta-blockers.	Randomized controlled trial, 2 arms	1085 patients	Start of GDMT initiation/up-titration towards optimal doses immediately upon inclusion; goal to reach target doses of RASi, beta-blockers, and MRA within 2 weeks; follow-up visits at 1, 2, 3, and 6 weeks	• All-cause death/HF readmission within 180 days (primary outcome) was lower in the intervention arm (adjusted RR 0.66, $p = 0.0021$) • By 90 days, full doses were more often achieved in the intervention arm vs. usual care for the three assessed GDMT classes: RASi (55% vs. 2%), beta-blockers (49% vs. 4%), and MRA (84% vs. 46%). [Comment: The trial was terminated early by the safety monitoring board due to efficacy of the intervention.]
Van Spall *et al.*, 2019 (PACT-HF)[166]	Patients hospitalized for HF in Ontario, Canada	Cluster randomized trial (hospital level), 2 arms	10 hospitals (2494 patients)	A multifactorial intervention consisting of nurse-led self-care patient education, a GP follow-up <1 week after discharge, and, for high-risk patients, nurse home visits and HF clinic care	• The 3-month composite of all-cause readmission, emergency department visit, or all-cause death (primary outcome) did not differ across arms • There were no differences between the intervention vs. usual care arms in filled post-discharge prescriptions for RASi, beta-blockers, MRA, or diuretics at 7 days (82.5% vs. 79.8%, $p = 0.11$) or 30 days (92.8% vs. 92.7%, $p = 0.95$)
Rao and Walsh, 2007[154]	Outpatients with suspected HF, based GP open access echocardiography request card, and confirmed left ventricular systolic dysfunction	Randomized controlled trial, 2 arms	112 patients	Specialist care arm: follow-up in a dedicated HF clinic comprising a cardiology registrar and a HF nurse General care arm: primary care follow-up	• 84.7% were prescribed RASi and 50.8% beta-blockers in the specialist care arm, vs. 64.3% RASi and 1.9% beta-blockers in the general care arm ($p = 0.012$ for RASi and $p < 0.001$ for beta-blockers)
Alerts/nudges					
Mukhopadhyay *et al.*, 2023 (BETTER-CARE HF)[179]	Outpatients with HFrEF, with no active MRA use, in cardiology follow-up, no current contraindication to MRA	Cluster randomized (cardiologist level), 3 arms	180 cardiologists (encountering 2211 eligible HFrEF patients)	Alert arm: EHR alert regarding a single patient at the time of visit. Message arm: message regarding multiple patients between visits	• New MRA initiation (primary outcome) occurred in 30% of patients in the alert arm vs. 16% in the message arm vs. 12% in the usual care arm (alert vs. usual care: RR 2.53, $p < 0.0001$; alert vs. message: RR 1.67, $p = 0.002$; message vs. usual care: RR 1.52, $p = 0.029$)
Ghazi *et al.*, 2023 (PROMPT-AHF)[181]	Inpatients with HFrEF, not on all four GDMT drug classes, enrolled within 48 h of a hospital admission where they received intravenous diuretic	Randomized controlled trial, 2 arms	1012 patients	An EHR alert displaying relevant clinical data and highlighting HFrEF GDMT discrepancies upon engaging with the patient's EHR	• An increase in number of GDMT prescriptions (primary outcome) occurred in a similar proportion (34%) of patients in both arms (RR 0.95, $p = 0.99$)
Ghazi *et al.*, 2022 (PROMPT-HF)[178]	Outpatients with HFrEF encountered by HFrEF care providers in New Haven, CT (nurse practitioners, physician assistants, and physicians)	Cluster randomized (provider level), 2 arms	100 providers (encountering 1310 HFrEF patients)	An EHR alert displaying relevant clinical data and highlighting HFrEF GDMT discrepancies upon engaging with the patient's EHR	• Increase in number of HFrEF GDMT classes (primary outcome) occurred in 26% of patients in the alert arm vs. 19% in the usual care arm (adjusted RR 1.41, $p = 0.03$)
Ahmad *et al.*, 2022 (REVEAL-HF)[175]	Patients hospitalized for HF receiving intravenous diuretics within first 24 h of admission	Randomized controlled trial, 2 arms	3124 patients	EHR alert presenting 1-year mortality risk calculated using an algorithm that was derived and validated on historic patients in the same EHR system	• The composite of 30-day hospital readmission and all-cause death (primary outcome) was similar across arms (alert: 38.9%, usual care: 39.3%, $p = 0.89$) • There were no significant differences between the alert vs. usual care arms in discharge prescriptions of RASi/ARNi (48.18% vs. 48.11%), beta-blockers (82.2% vs. 82.4%), MRA (23.65% vs. 25.1%), SGLT2i (8.68% vs. 8.74%), or implantable cardioverter-defibrillator (1.19% vs. 1.37%).

Table 1 (Continued)

Trial	Setting	Design	Sample size	Intervention	Primary outcome and findings on implementation
Allen *et al.*, 2021 (EPIC-HF)[177]	Outpatients with HFrEF, with follow-up by cardiology clinicians in Colorado	Randomized controlled trial, 2 arms	306 patients (of whom 290 attended clinic visit during the study period)	Electronically delivered text/video-based tool encouraging patients to work collaboratively with their physician to optimize their HFrEF therapy, deployed 1 week, 3 days, and 24 h prior to the next cardiology clinic visit	• Initiation/up-titration of GDMT (primary outcome) occurred in 49.0% of patients in the intervention arm vs. 29.7% in the control arm ($p = 0.001$)
McKie *et al.*, 2020[180]	Primary care teams within the Mayo Clinic Health system in Olmsted County, MN.	Cluster randomized (primary care team level), 2 arms	20 primary care teams (totalling 109 clinicians, encountering 16 310 patients of whom 604 had HFrEF)	EHR-integrated clinical decision support tool that alerted clinicians of discrepancies in GDMT for HF, hyperlipidaemia, and atrial fibrillation, at the day of an outpatient visit	• The primary outcome was resolved GDMT discrepancies: 12% of HFrEF GDMT discrepancies resolved in the alert arm vs. 1.9% in the usual care arm (OR 7.57, $p = 0.03$), but there was no significant effect on GDMT discrepancies in atrial fibrillation or hyperlipidaemia
Pharmacist involvement					
Schulz *et al.*, 2019 (PHARM-CHF)[162]	Patients with chronic HF, ≥60 years, with diuretic treatment, hospitalized for HF past 12 months	Randomized controlled trial, 2 arms	285 patients	Medication review in the community pharmacy at baseline followed by dosing aid and bi-weekly pharmacy visits	• The primary outcome of adherence (mean proportion of days covered) for RASi, beta-blockers, and MRA during the first 365 days was 91.2% in the pharmacy arm and 85.5% in the usual care arm (mean difference 5.7%, $p = 0.007$).
Lowrie et al, 2012 (HOOPS)[161]	Outpatients with left ventricular systolic dysfunction receiving follow-up in the primary care in the UK. Symptoms or signs of HF were not mandatory for inclusion	Cluster randomized trial (primary care centre level), 2 arms	174 primary care practices (2164 patients)	A 30-min pharmacist appointment and medical review aimed at optimizing treatment for left ventricular systolic dysfunction, followed by subsequent pharmacist consultations to implement treatment modifications upon agreement with patient and GP	• The composite of HF hospitalization and all-cause death (primary outcome) was similar across the arms • Patients in the pharmacist intervention arm vs. usual care were more likely to initiate/up-titrate RASi (33.1% vs. 18.5%; OR 2.26, $p < 0.001$) and beta-blockers (17.9% vs. 11.1%; OR 1.76, $p < 0.001$)
Virtual teams					
Bhatt *et al.*, 2023 (IMPLEMENT-HF)[173]	Patients with HFrEF hospitalized for any cause to medical or surgical wards	Quasi-randomized trial (intervention allocated by birth month), 2 arms	252 patient encounters (198 unique patients)	Virtual team consisting of a centralized physician, study staff, and a local pharmacist delivering up to once daily instructions to the primary hospital team responsible for the care of the patient, according to a protocol aiming to optimize HFrEF GDMT	• The in-hospital change in GDMT optimization score (primary outcome) was improved in the intervention arm vs. usual care (adjusted difference +1.2, $p < 0.001$) • New initiations of GDMT occurred in 44% in the intervention arm vs. 23% in usual care ($p = 0.001$)
Rao *et al.*, 2023[172]	Patients with HFrEF admitted to non-cardiology wards for any cause	Cluster randomized trial (medical team level), 2 arms	20 medical teams (91 patients with HFrEF)	Virtual communication between HF-led specialty team and rounding non-cardiology team, including recommendations on HFrEF GDMT based on clinical characteristics	• The co-primary outcomes of GDMT initiation/continuation and OMT scores at discharge were both greater with the intervention arm vs. usual care. Initiation/continuation for RASi/ARNi was 71% vs. 49% ($p = 0.04$), beta-blocker 78% vs. 77% ($p = 0.90$), MRA 40% vs. 21% ($p = 0.05$), and SGLT2i 26% vs. 14% ($p = 0.19$) • The change in OMT score from admission to discharge was 0.44 in the intervention arm and −0.31 in usual care (adjusted between-group change: 0.86, $p = 0.041$)

Table 1 (Continued)

Trial	Setting	Design	Sample size	Intervention	Primary outcome and findings on implementation
Education, audit, and feedback					
DeVore *et al.*, 2021 (CONNECT-HF)[167]	Patients hospitalized for HFrEF at included US hospitals caring for at least 50 HF patients annually	Cluster randomized trial (hospital level), 2 arms	161 hospitals (5647 patients with HFrEF)	Intervention arm: regular education of clinicians by a trained group of HF and quality improvement experts and audit and feedback on for example use of HFrEF GDMT, and outcomes Usual care arm: access to a generalized HF education website	• There was no difference in the composite of HF rehospitalization or all-cause death (primary outcome) between the two arms • There were no significant differences between the intervention arm and the usual care arm in effects on use of RASi, beta-blocker, or MRA
DeVore *et al.*, 2015[176]	Hospitals participating in GWTG-HF	Cluster randomized trial (hospital level), 2 arms	147 hospitals (71 829 patients)	Personalized site-level feedback on adherence to metrics related to the quality of HF care	• The improvement in site composite quality of care score (primary outcome) was similar across the intervention and the control arms • There were no differences across arms in the change of RASi, beta-blocker, or MRA prescriptions at discharge
Potassium binders					
Butler *et al.*, 2022 (DIAMOND)[94]	Patients with HFrEF and current or history of RAASi-related hyperkalaemia	Randomized controlled trial, 2 arms	878 patients	The potassium-sparing agent patiromer	• The adjusted mean change in serum potassium (primary outcome) was +0.03 mmol/L in the patiromer arm vs. +0.13 mmol/L in the placebo arm (between-group difference −0.10 mmol/L, $p < 0.001$) • 13.9% of patients in the patiromer arm experienced a reduction in MRA vs. 18.9% in the placebo arm (HR 0.62, $p = 0.006$)

ARNi, angiotensin receptor–neprilysin inhibitor; BETTER CARE-HF, Building Electronic Tools to Enhance and Reinforce CArdiovascular REcommendations for Heart Failure; CONNECT-HF, Care Optimization Through Patient and Hospital Engagement For HF; DIAMOND, Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure; EHR, electronic health record; EPIC-HF, Electronically Delivered, Patient-Activation Tool for Intensification of Medications for Chronic Heart Failure with Reduced Ejection Fraction; GDMT, guideline-directed medical therapy; GP, general practitioner; GWTG-HF, Get With The Guidelines–Heart Failure; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HOOPS, Heart Failure Optimal Outcomes from Pharmacy Study; HR, hazard ratio; IMPLEMENT-HF, Implementation of Medical Therapy in Hospitalized Patients With Heart Failure With Reduced Ejection Fraction; MRA, mineralocorticoid receptor antagonist; OMT, optimal medical therapy; OR, odds ratio; PACT-HF, Patient-Centered Care Transitions in Heart Failure; PHARM-CHF, PHARMacy-based interdisciplinary program for patients with Chronic Heart Failure; PROMPT-AHF, Pragmatic Trial of Messaging to Providers About Treatment of Acute Heart Failure; PROMPT-HF, PRagmatic trial Of Messaging to Providers about Treatment of Heart Failure; RAASi, renin–angiotensin–aldosterone system inhibitor; RASi, renin–angiotensin system inhibitor; REVEAL-HF, Risk Evaluation and its Impact on Clinical Decision-Making and Outcomes in Heart Failure; RR, risk ratio; SGLT2i, sodium–glucose cotransporter 2 inhibitor; STRONG-HF, Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies.

Real-world data and quality registries

Real-world data and quality registries can be instrumental in addressing clinical inertia. Enrolment in registries may contribute to a more thorough review of patients' treatments, and has been reported to be associated with improved implementation of GDMT and quality of HF care.[36,174] Real-world studies are also key to raising the awareness of need of implementation, and in identifying potentially addressable barriers to implementation.[24–27,29,33,62,184–186]

Women and specific subpopulations (such as frail, older, multi-comorbid patients) are poorly represented in RCTs but commonly encountered in daily clinical practice.[187] Poor generalizability of RCTs might contribute to the perception that trial evidence is poorly applicable to the real-world setting, thus fostering clinical inertia.[187–189] While observational studies do not replace RCTs for efficacy assessment due to bias and residual confounding, they allow to explore long-term effectiveness and safety in subgroups of patients who are underrepresented in RCTs and where evidence is missing. Registries can also inform on the design of more generalizable RCTs by highlighting gaps of representation.[188–193] Real-world data can also contribute to structure accurate healthcare plans and improve resource allocation.[157]

Registries and EHR can also be used as a screening tool to identify need of and guide treatment implementation. In UK, EHRs were screened using a stepwise approach leveraging diagnosis codes and primary care medical records to identify potential missed cases of HFrEF, confirmed by a following cardiologist consultation. The intervention helped to identify a 'missed cohort' of HFrEF patients treated in the primary care setting, increasing the diagnoses of HF by 47%, and led to an increase of GDMT use from 49% to 85%, and 62% of the screened patients were identified as potentially suitable for advanced device therapy.[194]

There is currently an encouraging increase in efforts to collect data and build national and multinational registries, as also supported by international and national scientific associations, such as the HFA and the ESC. Implementation of local policies promoting data collection and creation of disease-specific registries should be sought to embrace the potential of registries to improve implementation at a systemic level.

Telehealth and digital tools

Telehealth offers several opportunities to improve GDMT implementation in HFrEF, for example, by improved personalization of HF care by frequent collection/transmission of clinical data (*remote monitoring*), by enabling distance care delivery (*telemedicine*), and by improved continuity of care and expertise-exchange between caregivers along the patient journey (*teleconsultation*).[195] Integrating these different aspects of telehealth in the healthcare system might also enable more efficient resource use, thereby contributing to filling the gap between available HF resources and need for HF care. Several meta-analyses have reported that, overall, telehealth interventions can improve hard outcomes in HF, including hospitalizations and mortality.[196–200] However, there has been great heterogeneity across the numerous available RCTs in terms of patient populations, setting, mode of intervention, and success.

Remote monitoring can allow early recognition of changes in a patient's clinical status which may necessitate therapeutic adaptations. Remote monitoring of ICD/CRT devices represents an established use-case of detecting device malfunction, atrial and ventricular arrhythmias and appropriate or inappropriate device shocks.[201] Modern devices can also transmit other parameters, such as respiratory rate, heart tone intensity, and surrogates of volume status, with the aim of predicting the occurrence of clinical HF events.[202] Underpinning this aim is the concept that HF decompensations follow a gradual worsening in clinical and volume status,[203] and therefore early detection and intervention might prevent these events.[204] Wireless haemodynamic monitoring using implantable pulmonary artery sensors (CardioMEMS) has been shown to improve quality of life and reduce HF hospitalizations in the CHAMPION trial,[103] in the pre-COVID-19 analysis of the GUIDE-HF trial,[205] and in the recent open-label RCT MONITOR-HF.[96] In a meta-analysis including six RCTs and 4869 patients, different systems of implant-based remote monitoring (e.g. intrathoracic impedance, tachyarrhythmias, and patient activity) significantly reduced all-cause death and HF hospitalizations.[206] In addition, remote monitoring can have a substantial role in empowering HF patients in improving their own health outcomes.[207]

Telemedicine (i.e. delivery of care at a distance) has seen increased importance during the COVID-19 pandemic, also supported by new technologies for virtual care and improved digital literacy in the community.[208] Despite clear practical and reasonable usefulness, remote patient consultations alone, without aspects of remote monitoring, have not overall convincingly improved hard outcomes.[209,210] Although remote patient consultations should therefore not replace in-person outpatient visits, they can act as a complement and facilitate delivery of care to patients and the achievement of OMT. Digital therapeutics, that is, the use of evidence-based software-driven interventions, often targeting patient behaviours, might also be studied in the realm of HF, particularly for enhancing cardiac rehabilitation.[211]

Telehealth interventions that have most successfully improved hard outcomes in RCTs were multifactorial, combining multiple aspects including remote monitoring, telemedicine, and teleintervention.[196,209,212–214] The physician-led telehealth intervention in the TIM-HF2 trial, which considered a multifactorial remote monitoring approach (electrocardiogram, blood pressure, weight, symptoms, and saturation) while allowing for a direct collaboration between the patient, telehealth staff, cardiologist and primary care, led to a 20% reduction in days lost due to unplanned CV hospitalizations or mortality.[212] In contrast, the BEAT-HF and the OSICAT trials showed no effect on hard outcomes of multifactorial remote monitoring interventions that did not involve any interaction with the physician in charge of the patient care.[215,216] These results highlight the importance of integrating telehealth solutions in the wider HF care. Ultimately, telehealth, and teleconsultation (i.e. telehealth involving clinician–clinician interaction) can improve the communication between centres of expertise with and community care, enabling a 'hub-and-spoke' model for HF care.[217]

Application to different regions and healthcare systems

The current document highlights several barriers to GDMT implementation and related strategies to mitigate clinical inertia. However, none of these strategies represents a universal solution, and their applicability may differ across healthcare systems depending on legislation, organizational set-up, resources, and care pathways. The applicability of these strategies may also be influenced by how treatments and interventions are subsidized, how care is incentivized (e.g. pay-for-service vs. pay-for-performance), and by the payment system (e.g. multiple vs. single-payer systems). Therefore, the outlined implementation strategies represent elements of a toolbox that might be refined in local implementation trials and applied according to local contexts.

Conclusions

In an ideal clinical setting, contemporary GDMT may lead to a greater than 60% reduction in the risk of CV mortality or HF hospitalization in patients with HFrEF, however GDMT remains underused. Limited implementation is not always justified by clinically-motivated reasons, but rather by clinical inertia, that is, the failure of the healthcare system to provide optimal medical treatment. Potential strategies to improve implementation are diverse, and include patient-tailored medical management, better structured follow-up and transitional care protocols, telehealth solutions, and physician/patient awareness or alerts. The diverse set of patient-related and organizational factors that predispose to clinical inertia are unlikely to be overcome by a universal solution, but rather require a targeted multifactorial approach tailored to each specific healthcare system.

Supplementary Information

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

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