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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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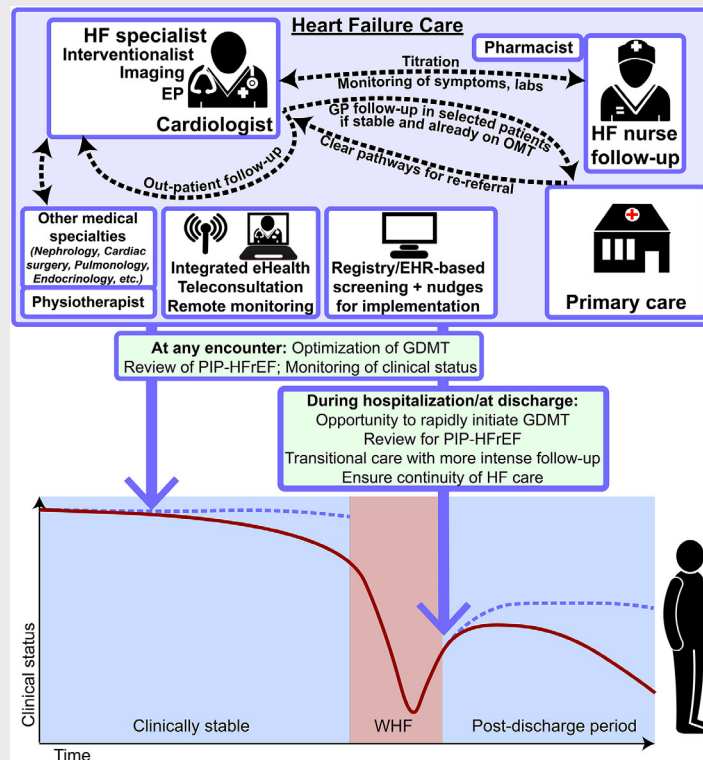
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Guideline-directed medical therapy (GDMT) in patients with heart failure and reduced ejection fraction (HFrEF) reduces morbidity and mortality, but its implementation is often poor in daily clinical practice. Barriers to implementation include clinical 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.

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

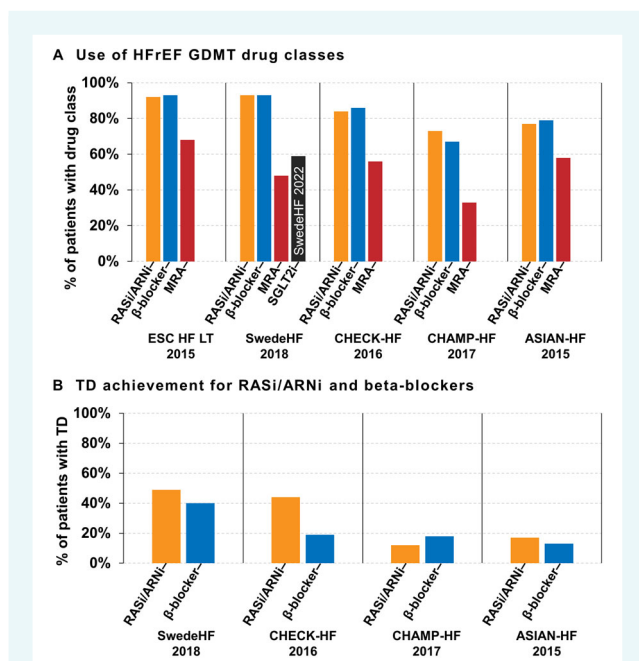


Figure 1 State of guideline-directed medical therapy (GDMT) implementation in heart failure with reduced ejection fraction (HFrEF) (A) and achievement of target dose (TD) (B) – data from large registries. ARNi, angiotensin receptor–neprilysin inhibitor; ASIAN-HF, Asian Sudden Cardiac Death in Heart Failure; 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.

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 m², and of ARNi when eGFR <30 ml/min/1.73 m².²³ However, real-world data show that even lesser degrees of impaired eGFR (30–60 ml/min/1.73 m²) 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 m² for ACEi/ARB and SGLT2i,^{9,19,20} and ≥ 30 ml/min/1.73 m² 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 m² 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 m², 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 m²) 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 frailtism and ageism, defined as a stereotyping, prejudice and discrimination against people only based on the presence of frailty (frailtism) 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

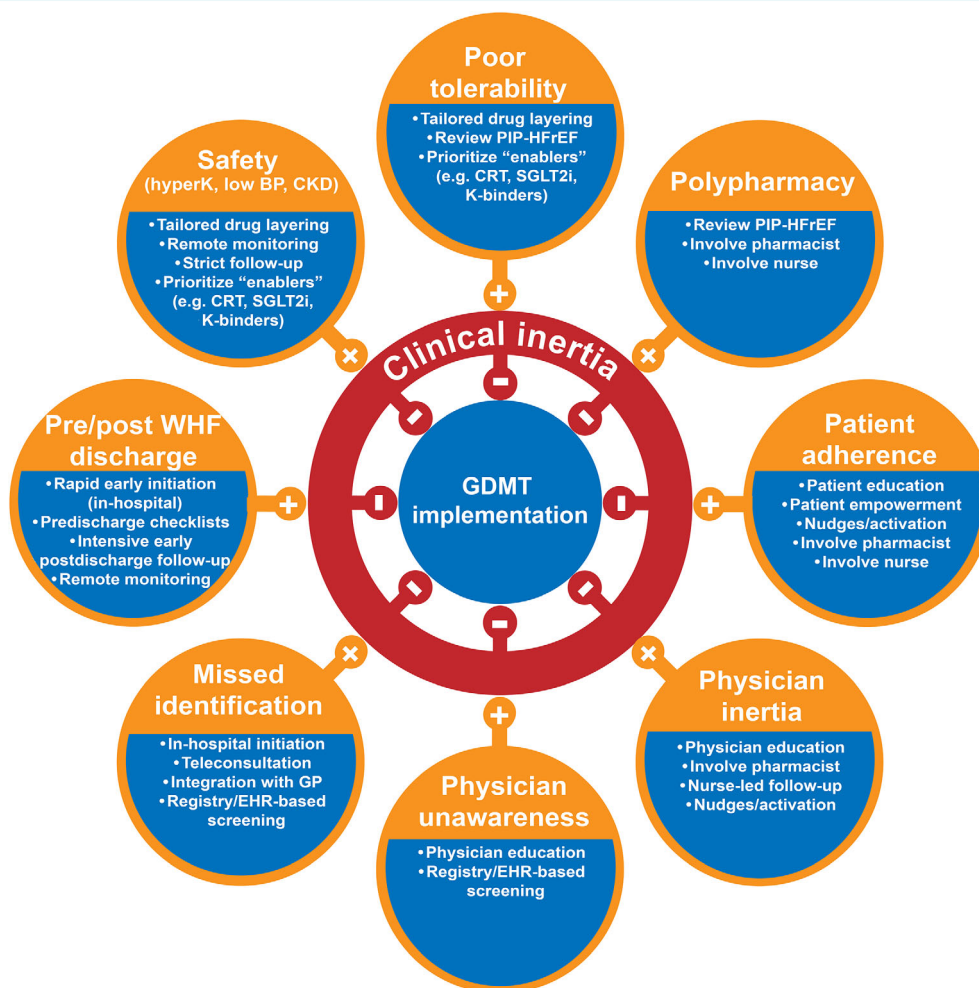


Figure 2 Strategies to overcome key contributors to clinical inertia. BP, blood pressure; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; EHR, electronic health record; GDMT, guideline-directed medical therapy; GP, general practitioner; PIP-HFrEF, potentially inappropriate prescriptions in heart failure with reduced ejection fraction¹³⁴; 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 available¹⁵⁹; 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 multi-disciplinary 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 transitional 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	<ul style="list-style-type: none"> 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%). <p>[Comment: The trial was terminated early by the safety monitoring board due to efficacy of the intervention.]</p> <ul style="list-style-type: none"> 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%, $p = 0.95$) 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)
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	
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	
Alerts/nudges Mukhopadhyay et al., 2023 (BETTER-CARE HF) ¹⁷⁹	Outpatients with HF+EF; 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 HF+EF patients)	Alert arm: EHR alert regarding a single patient at the time of visit. Message arm: message regarding multiple patients between visits	<ul style="list-style-type: none"> 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, $p = 0.029$) 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., 2023 (PROMPT-AHF) ¹⁸¹	Inpatients with HF+EF; 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 HF+EF GDMT discrepancies upon engaging with the patient's EHR	<ul style="list-style-type: none"> Increase in number of HF+EF GDMT classes (primary outcome) occurred in 26% of patients in the alert arm vs. 19% in the usual care arm (adjusted RR 1.41, $p = 0.03$)
Ghazi et al., 2022 (PROMPT-HF) ¹⁷⁸	Outpatients with HF+EF encountered by HF+EF care providers in New Haven, CT (nurse practitioners, physician assistants, and physicians)	Cluster randomized (provider level), 2 arms	100 providers (encountering 1310 HF+EF patients)	An EHR alert displaying relevant clinical data and highlighting HF+EF GDMT discrepancies upon engaging with the patient's EHR	
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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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) ⁷³	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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 HF+EF at included US hospitals caring for at least 50 HF patients annually	Cluster randomized trial (hospital level), 2 arms	161 hospitals (5647 patients with HF+EF)	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 HF+EF GDMT, and outcomes Usual care arm: access to a generalized HF education website	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 HF+EF and current or history of RASi-related hyperkalaemia	Randomized controlled trial, 2 arms	878 patients	The potassium-sparing agent patiromer	<ul style="list-style-type: none"> 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 Hyperkalaemia in Subjects Receiving RASi Medications for the Treatment of Heart Failure; EHR, electronic health record; EPIC-HF, Electronicly 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; HF+EF, 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 HF_{rEF}, confirmed by a following cardiologist consultation. The intervention helped to identify a 'missed cohort' of HF_{rEF} 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 HF_{rEF}, 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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References

- Johansson I, Joseph P, Balasubramanian K, McMurray JVV, Lund LH, Ezekowitz JA, et al.; G-CHF Investigators. Health-related quality of life and mortality in heart failure: The Global Congestive Heart Failure study of 23 000 patients from 40 countries. *Circulation* 2021;**143**:2129–2142. <https://doi.org/10.1161/CIRCULATIONAHA.120.050850>
- Shahim B, Kapelios CJ, Savarese G, Lund LH. Global public health burden of heart failure: An updated review. *Card Fail Rev* 2023;**9**:e11. <https://doi.org/10.15420/cfr.2023.05>
- Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, et al.; Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016;**18**:613–625. <https://doi.org/10.1002/ehf.566>
- Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med* 2015;**175**:996–1004. <https://doi.org/10.1001/jamainternmed.2015.0924>
- Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. *Eur J Heart Fail* 2017;**19**:1624–1634. <https://doi.org/10.1002/ehf.945>
- Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: A comprehensive and updated review of epidemiology. *Cardiovasc Res* 2023;**118**:3272–3287. <https://doi.org/10.1093/cvr/cvac013>
- Metra M, Tomasoni D, Adamo M, Bayes-Genis A, Filippatos G, Abdelhamid M, et al. Worsening of chronic heart failure: Definition, epidemiology, management and prevention. A clinical consensus statement by the Heart Failure Association

- of the European Society of Cardiology. *Eur J Heart Fail* 2023;**25**:776–791. <https://doi.org/10.1002/ehf.2874>
8. Azad N, Lemay G. Management of chronic heart failure in the older population. *J Geriatr Cardiol* 2014;**11**:329–337. <https://doi.org/10.11909/j.issn.1671-5411.2014.04.008>
 9. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;**316**:1429–1435. <https://doi.org/10.1056/NEJM198706043162301>
 10. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN; SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302. <https://doi.org/10.1056/NEJM199108013250501>
 11. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–2007. [https://doi.org/10.1016/S0140-6736\(99\)04440-2](https://doi.org/10.1016/S0140-6736(99)04440-2)
 12. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;**334**:1349–1355. <https://doi.org/10.1056/NEJM199605233342101>
 13. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. *Lancet* 1999;**353**:9–13. [https://doi.org/10.1016/S0140-6736\(98\)11181-9](https://doi.org/10.1016/S0140-6736(98)11181-9)
 14. Packer M, Fowler MB, Roecker EB, Coats AJS, Katus HA, Krum H, et al.; Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. *Circulation* 2002;**106**:2194–2199. <https://doi.org/10.1161/01.cir.0000035653.72855.bf>
 15. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–717. <https://doi.org/10.1056/NEJM199909023411001>
 16. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al.; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21. <https://doi.org/10.1056/NEJMoa1009492>
 17. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al.; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004. <https://doi.org/10.1056/NEJMoa1409077>
 18. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al.; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008. <https://doi.org/10.1056/NEJMoa1911303>
 19. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al.; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424. <https://doi.org/10.1056/NEJMoa2022190>
 20. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al.; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: The CHARM-Alternative trial. *Lancet* 2003;**362**:772–776. [https://doi.org/10.1016/S0140-6736\(03\)14284-5](https://doi.org/10.1016/S0140-6736(03)14284-5)
 21. Tromp J, Ouwerkerk W, van Veldhuisen DJ, Hillege HL, Richards AM, van der Meer P, et al. A systematic review and network meta-analysis of pharmacological treatment of heart failure with reduced ejection fraction. *JACC Heart Fail* 2022;**10**:73–84. <https://doi.org/10.1016/j.jchf.2021.09.004>
 22. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;**145**:e895–e1032. <https://doi.org/10.1161/CIR.0000000000001063>
 23. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. <https://doi.org/10.1002/ehf.2333>
 24. Savarese G, Kishi T, Vardeny O, Adamsson Eryd S, Bodegård J, Lund LH, et al. Heart failure drug treatment-inertia, titration, and discontinuation: A multinational observational study (EVOLUTION HF). *JACC Heart Fail* 2023;**11**:1–14. <https://doi.org/10.1016/j.jchf.2022.08.009>
 25. Savarese G, Carrero JJ, Pitt B, Anker SD, Rosano GMC, Dahlström U, et al. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: An analysis of 11 215 patients from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2018;**20**:1326–1334. <https://doi.org/10.1002/ehf.1182>
 26. Stolfo D, Lund LH, Becher PM, Orsini N, Thorvaldsen T, Benson L, et al. Use of evidence-based therapy in heart failure with reduced ejection fraction across age strata. *Eur J Heart Fail* 2022;**24**:1047–1062. <https://doi.org/10.1002/ehf.2483>
 27. Greene SJ, Tan X, Yeh YC, Bernauer M, Zaidi O, Yang M, et al. Factors associated with non-use and sub-target dosing of medical therapy for heart failure with reduced ejection fraction. *Heart Fail Rev* 2022;**27**:741–753. <https://doi.org/10.1007/s10741-021-10077-x>
 28. Tomasoni D, Pagnesi M, Colombo G, Chiarito M, Stolfo D, Baldetti L, et al. Guideline-directed medical therapy in severe heart failure with reduced ejection fraction: An analysis from the HELP-HF registry. *Eur J Heart Fail* 2024;**26**:327–337. <https://doi.org/10.1002/ehf.3081>
 29. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2013;**15**:1173–1184. <https://doi.org/10.1093/eurjhf/hft134>
 30. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: An analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1574–1585. <https://doi.org/10.1002/ehf.813>
 31. D'Amario D, Rodolico D, Rosano GMC, Dahlström U, Crea F, Lund LH, et al. Association between dosing and combination use of medications and outcomes in heart failure with reduced ejection fraction: Data from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2022;**24**:871–884. <https://doi.org/10.1002/ehf.2477>
 32. Brunner-La Rocca HP, Linssen GC, Smeele FJ, van Drimmelen AA, Schaafsma HJ, et al.; CHECK-HF Investigators. Contemporary drug treatment of chronic heart failure with reduced ejection fraction: The CHECK-HF registry. *JACC Heart Fail* 2019;**7**:13–21. <https://doi.org/10.1016/j.jchf.2018.10.010>
 33. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry. *J Am Coll Cardiol* 2018;**72**:351–366. <https://doi.org/10.1016/j.jacc.2018.04.070>
 34. Teng TK, Tromp J, Tay WT, Anand I, Ouwerkerk W, Chopra V, et al.; ASIAN-HF Investigators. Prescribing patterns of evidence-based heart failure pharmacotherapy and outcomes in the ASIAN-HF registry: A cohort study. *Lancet Glob Health* 2018;**6**:e1008–e1018. [https://doi.org/10.1016/S2214-109X\(18\)30306-1](https://doi.org/10.1016/S2214-109X(18)30306-1)
 35. Stolfo D, Lund LH, Benson L, Lindberg F, Ferrannini G, Dahlström U, et al. Real-world use of sodium-glucose cotransporter 2 inhibitors in patients with heart failure and reduced ejection fraction: Data from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2023;**25**:1648–1658. <https://doi.org/10.1002/ehf.2971>
 36. Lund LH, Carrero JJ, Farahmand B, Henriksson KM, Jonsson Å, Jernberg T, et al. Association between enrolment in a heart failure quality registry and subsequent mortality – a nationwide cohort study. *Eur J Heart Fail* 2017;**19**:1107–1116. <https://doi.org/10.1002/ehf.762>
 37. Verhestraeten C, Heggermont WA, Maris M. Clinical inertia in the treatment of heart failure: A major issue to tackle. *Heart Fail Rev* 2021;**26**:1359–1370. <https://doi.org/10.1007/s10741-020-09979-z>
 38. Girerd N, Von Hunolstein JJ, Pellicori P, Bayés-Genis A, Jaarsma T, Lund LH, et al. Therapeutic inertia in the pharmacological management of heart failure with reduced ejection fraction. *ESC Heart Fail* 2022;**9**:2063–2069. <https://doi.org/10.1002/ehf2.13929>
 39. Seferović PM, Polovina M, Adbrecht C, Bělohávek J, Chioncel O, Gonçalvesová E, et al. Navigating between Scylla and Charybdis: Challenges and strategies for implementing guideline-directed medical therapy in heart failure with reduced ejection fraction. *Eur J Heart Fail* 2021;**23**:1999–2007. <https://doi.org/10.1002/ehf.2378>
 40. Gheorghide M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, et al.; OPTIMIZE-HF Investigators and Coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA* 2006;**296**:2217–2226. <https://doi.org/10.1001/jama.296.18.2217>
 41. Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, et al.; ESC Heart Failure Long-Term Registry Investigators. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: The ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1242–1254. <https://doi.org/10.1002/ehf.890>
 42. Arundel C, Lam PH, Gill GS, Patel S, Panjraht G, Faselis C, et al. Systolic blood pressure and outcomes in patients with heart failure with reduced ejection

- fraction. *J Am Coll Cardiol* 2019;**73**:3054–3063. <https://doi.org/10.1016/j.jacc.2019.04.022>
43. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, et al.; Meta-Analysis Global Group in Chronic Heart Failure. Predicting survival in heart failure: A risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013;**34**:1404–1413. <https://doi.org/10.1093/eurheartj/ehs337>
 44. Greene SJ, Fonarow GC, DeVore AD, Sharma PP, Vaduganathan M, Albert NM, et al. Titration of medical therapy for heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2019;**73**:2365–2383. <https://doi.org/10.1016/j.jacc.2019.02.015>
 45. Kittleson M, Hurwitz S, Shah MR, Nohria A, Lewis E, Givertz M, et al. Development of circulatory-renal limitations to angiotensin-converting enzyme inhibitors identifies patients with severe heart failure and early mortality. *J Am Coll Cardiol* 2003;**41**:2029–2035. [https://doi.org/10.1016/s0735-1097\(03\)00417-0](https://doi.org/10.1016/s0735-1097(03)00417-0)
 46. Böhm M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al.; EMPEROR-Reduced Trial Committees and Investigators. Empagliflozin improves cardiovascular and renal outcomes in heart failure irrespective of systolic blood pressure. *J Am Coll Cardiol* 2021;**78**:1337–1348. <https://doi.org/10.1016/j.jacc.2021.07.049>
 47. Serenelli M, Böhm M, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Effect of dapagliflozin according to baseline systolic blood pressure in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF). *Eur Heart J* 2020;**41**:3402–3418. <https://doi.org/10.1093/eurheartj/ehaa496>
 48. Serenelli M, Jackson A, Dewan P, Jhund PS, Petrie MC, Rossignol P, et al. Mineralocorticoid receptor antagonists, blood pressure, and outcomes in heart failure with reduced ejection fraction. *JACC Heart Fail* 2020;**8**:188–198. <https://doi.org/10.1016/j.jchf.2019.09.011>
 49. Böhm M, Young R, Jhund PS, Solomon SD, Gong J, Lefkowitz MP, et al. Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: Results from PARADIGM-HF. *Eur Heart J* 2017;**38**:1132–1143. <https://doi.org/10.1093/eurheartj/ehw570>
 50. Rouleau JL, Roecker EB, Tendera M, Mohacs P, Krum H, Katus HA, et al.; Carvedilol Prospective Randomized Cumulative Survival Study Group. Influence of pretreatment systolic blood pressure on the effect of carvedilol in patients with severe chronic heart failure: The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. *J Am Coll Cardiol* 2004;**43**:1423–1429. <https://doi.org/10.1016/j.jacc.2003.11.037>
 51. Anand IS, Rector TS, Kuskowski M, Thomas S, Holwerda NJ, Cohn JN. Effect of baseline and changes in systolic blood pressure over time on the effectiveness of valsartan in the Valsartan Heart Failure Trial. *Circ Heart Fail* 2008;**1**:34–42. <https://doi.org/10.1161/CIRCHEARTFAILURE.107.736975>
 52. Giererd N, Coiro S, Benson L, Savarese G, Dahlström U, Rossignol P, et al. Hypotension in heart failure is less harmful if associated with high or increasing doses of heart failure medication: Insights from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2024;**26**:359–369. <https://doi.org/10.1002/ehfj.3066>
 53. Cautela J, Tartiere JM, Cohen-Solal A, Bellemain-Appaix A, Theron A, Tibi T, et al. Management of low blood pressure in ambulatory heart failure with reduced ejection fraction patients. *Eur J Heart Fail* 2020;**22**:1357–1365. <https://doi.org/10.1002/ehfj.1835>
 54. Witt CT, Kronborg MB, Nohr EA, Mortensen PT, Gerdes C, Nielsen JC. Optimization of heart failure medication after cardiac resynchronization therapy and the impact on long-term survival. *Eur Heart J Cardiovasc Pharmacother* 2015;**1**:182–188. <https://doi.org/10.1093/ehjcvp/pvv016>
 55. Salimian S, Deyell MW, Andrade JG, Chakrabarti S, Bennett MT, Krahn AD, et al. Heart failure treatment in patients with cardiac implantable electronic devices: Opportunity for improvement. *Heart Rhythm O2* 2021;**2**:698–709. <https://doi.org/10.1016/j.hroo.2021.09.010>
 56. Adamo M, Tomasoni D, Stolz L, Stocker TJ, Pancaldi E, Koell B, et al. Impact of transcatheter edge-to-edge mitral valve repair on guideline-directed medical therapy uptitration. *JACC Cardiovasc Interv* 2023;**16**:896–905. <https://doi.org/10.1016/j.jcin.2023.01.362>
 57. Metra M, Adamo M, Tomasoni D, Mebazaa A, Bayes-Genis A, Abdelhamid M, et al. Pre-discharge and early post-discharge management of patients hospitalized for acute heart failure: A scientific statement by the Heart Failure Association of the ESC. *Eur J Heart Fail* 2023;**25**:1115–1131. <https://doi.org/10.1002/ehfj.2888>
 58. Lam CSP, Mulder H, Lopatin Y, Vazquez-Tanus JB, Siu D, Ezekowitz J, et al.; VICTORIA Study Group. Blood pressure and safety events with vericiguat in the VICTORIA trial. *J Am Heart Assoc* 2021;**10**:e021094. <https://doi.org/10.1161/JAHA.121.021094>
 59. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al.; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. *Lancet* 2010;**376**:875–885. [https://doi.org/10.1016/s0140-6736\(10\)61198-1](https://doi.org/10.1016/s0140-6736(10)61198-1)
 60. Metra M, Torp-Pedersen C, Swedberg K, Cleland JGF, di Lenarda A, Komajda M, et al. Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: Results from the COMET trial. *Eur Heart J* 2005;**26**:2259–2268. <https://doi.org/10.1093/eurheartj/ehi386>
 61. Savarese G, Settergren C, Schrage B, Thorvaldsen T, Löfman I, Sartipy U, et al. Comorbidities and cause-specific outcomes in heart failure across the ejection fraction spectrum: A blueprint for clinical trial design. *Int J Cardiol* 2020;**313**:76–82. <https://doi.org/10.1016/j.ijcard.2020.04.068>
 62. Janse RJ, Fu EL, Dahlstrom U, Benson L, Lindholm B, van Diepen M, et al. Use of guideline-recommended medical therapy in patients with heart failure and chronic kidney disease: From physician's prescriptions to patient's dispensations, medication adherence and persistence. *Eur J Heart Fail* 2022;**24**:2185–2195. <https://doi.org/10.1002/ehfj.2620>
 63. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, et al. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. *JACC Heart Fail* 2018;**6**:489–498. <https://doi.org/10.1016/j.jchf.2018.02.004>
 64. Eschaliér R, McMurray JJ, Swedberg K, van Veldhuisen DJ, Krum H, et al.; EMPHASIS-HF Investigators. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: Analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure). *J Am Coll Cardiol* 2013;**62**:1585–1593. <https://doi.org/10.1016/j.jacc.2013.04.086>
 65. Bowling CB, Sanders PW, Allman RM, Rogers WJ, Patel K, Aban IB, et al. Effects of enalapril in systolic heart failure patients with and without chronic kidney disease: Insights from the SOLVD Treatment trial. *Int J Cardiol* 2013;**167**:151–156. <https://doi.org/10.1016/j.ijcard.2011.12.056>
 66. Vardeny O, Wu DH, Desai A, Rossignol P, Zannad F, Pitt B, et al.; RALES Investigators. Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: Insights from RALES (Randomized Aldactone Evaluation Study). *J Am Coll Cardiol* 2012;**60**:2082–2089. <https://doi.org/10.1016/j.jacc.2012.07.048>
 67. Ghali JK, Wikstrand J, Van Veldhuisen DJ, Fagerberg B, Goldstein S, Hjalmarsson A, et al.; MERIT-HF Study Group. The influence of renal function on clinical outcome and response to beta-blockade in systolic heart failure: Insights from Metoprolol CR/XL Randomized Intervention Trial in Chronic HF (MERIT-HF). *J Card Fail* 2009;**15**:310–318. <https://doi.org/10.1016/j.cardfail.2008.11.003>
 68. McCallum W, Tighiouart H, Ku E, Salem D, Sarnak MJ. Trends in kidney function outcomes following RAAS inhibition in patients with heart failure with reduced ejection fraction. *Am J Kidney Dis* 2020;**75**:21–29. <https://doi.org/10.1053/j.ajkd.2019.05.010>
 69. Vaduganathan M, Ferreira JP, Rossignol P, Neuen BL, Claggett BL, Pfeffer MA, et al. Effects of steroidal mineralocorticoid receptor antagonists on acute and chronic estimated glomerular filtration rate slopes in patients with chronic heart failure. *Eur J Heart Fail* 2022;**24**:1586–1590. <https://doi.org/10.1002/ehfj.2635>
 70. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al.; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020;**383**:2219–2229. <https://doi.org/10.1056/NEJMoa2025845>
 71. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, et al.; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021;**385**:2252–2263. <https://doi.org/10.1056/NEJMoa2110956>
 72. Filippatos G, Anker SD, Agarwal R, Ruilope LM, Rossing P, Bakris GL, et al.; FIGARO-DKD Investigators. Finerenone reduces risk of incident heart failure in patients with chronic kidney disease and type 2 diabetes: Analyses from the FIGARO-DKD trial. *Circulation* 2022;**145**:437–447. <https://doi.org/10.1161/CIRCULATIONAHA.121.057983>
 73. Filippatos G, Pitt B, Agarwal R, Farmakis D, Ruilope LM, Rossing P, et al.; FIDELIO-DKD Investigators. Finerenone in patients with chronic kidney disease and type 2 diabetes with and without heart failure: A prespecified subgroup analysis of the FIDELIO-DKD trial. *Eur J Heart Fail* 2022;**24**:996–1005. <https://doi.org/10.1002/ehfj.2469>
 74. Bhandari S, Mehta S, Khwaja A, Cleland JGF, Ives N, Brettell E, et al.; STOP ACEI Trial Investigators. Renin-angiotensin system inhibition in advanced chronic kidney disease. *N Engl J Med* 2022;**387**:2021–2032. <https://doi.org/10.1056/NEJMoa2210639>
 75. Niu CY, Yang SF, Ou SM, Wu CH, Huang PH, Hung CL, et al. Sacubitril/valsartan in patients with heart failure and concomitant end-stage kidney disease. *J Am Heart Assoc* 2022;**11**:e026407. <https://doi.org/10.1161/JAHA.122.026407>
 76. Edner M, Benson L, Dahlstrom U, Lund LH. Association between renin-angiotensin system antagonist use and mortality in heart failure

- with severe renal insufficiency: A prospective propensity score-matched cohort study. *Eur Heart J* 2015;**36**:2318–2326. <https://doi.org/10.1093/eurheartj/ehv268>
77. Cice G, Ferrara L, D'Andrea A, D'Isa S, Di Benedetto A, Cittadini A, et al. Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: A prospective, placebo-controlled trial. *J Am Coll Cardiol* 2003;**41**:1438–1444. [https://doi.org/10.1016/s0735-1097\(03\)00241-9](https://doi.org/10.1016/s0735-1097(03)00241-9)
 78. Guidetti F, Lund LH, Benson L, Hage C, Musella F, Stolfo D, et al. Safety of continuing mineralocorticoid receptor antagonist treatment in patients with heart failure with reduced ejection fraction and severe kidney disease: Data from Swedish Heart Failure Registry. *Eur J Heart Fail* 2023;**25**:2164–2173. <https://doi.org/10.1002/ehf.3049>
 79. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al.; VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2020;**382**:1883–1893. <https://doi.org/10.1056/NEJMoa1915928>
 80. International Society of Nephrology. Optimization of RAASI Therapy Toolkit. <https://www.theisn.org/initiatives/toolkits/raasi-toolkit/> (15 January 2024)
 81. Cooper LB, Benson L, Mentz RJ, Savarese G, DeVore AD, Carrero JJ, et al. Association between potassium level and outcomes in heart failure with reduced ejection fraction: A cohort study from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2020;**22**:1390–1398. <https://doi.org/10.1002/ehf.1757>
 82. Lund LH, Pitt B. Is hyperkalemia in heart failure a risk factor or a risk marker? Implications for renin-angiotensin-aldosterone system inhibitor use. *Eur J Heart Fail* 2018;**20**:931–932. <https://doi.org/10.1002/ehf.1175>
 83. Savarese G, Xu H, Trevisan M, Dahlström U, Rossignol P, Pitt B, et al. Incidence, predictors, and outcome associations of dyskalemia in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Heart Fail* 2019;**7**:65–76. <https://doi.org/10.1016/j.jchf.2018.10.003>
 84. Ferreira JP, Mogensen UM, Jhund PS, Desai AS, Rouleau JL, Zile MR, et al. Serum potassium in the PARADIGM-HF trial. *Eur J Heart Fail* 2020;**22**:2056–2064. <https://doi.org/10.1002/ehf.1987>
 85. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004;**351**:543–551. <https://doi.org/10.1056/NEJMoa040135>
 86. Wei L, Struthers AD, Fahey T, Watson AD, Macdonald TM. Spironolactone use and renal toxicity: Population based longitudinal analysis. *BMJ* 2010;**340**:c1768. <https://doi.org/10.1136/bmj.c1768>
 87. Nilsson E, De Deco P, Trevisan M, Bellocco R, Lindholm B, Lund LH, et al. A real-world cohort study on the quality of potassium and creatinine monitoring during initiation of mineralocorticoid receptor antagonists in patients with heart failure. *Eur Heart J Qual Care Clin Outcomes* 2018;**4**:267–273. <https://doi.org/10.1093/ehjqcco/qcy019>
 88. Vukadinović D, Lavall D, Vukadinović AN, Pitt B, Wagenpfeil S, Böhm M. True rate of mineralocorticoid receptor antagonists-related hyperkalemia in placebo-controlled trials: A meta-analysis. *Am Heart J* 2017;**188**:99–108. <https://doi.org/10.1016/j.ahj.2017.03.011>
 89. Vardeny O, Claggett B, Anand I, Rossignol P, Desai AS, Zannad F, et al.; Randomized Aldactone Evaluation Study (RALES) Investigators. Incidence, predictors, and outcomes related to hypo- and hyperkalemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. *Circ Heart Fail* 2014;**7**:573–579. <https://doi.org/10.1161/CIRCHEARTFAILURE.114.001104>
 90. Trevisan M, Fu EL, Xu Y, Savarese G, Dekker FW, Lund LH, et al. Stopping mineralocorticoid receptor antagonists after hyperkalemia: Trial emulation in data from routine care. *Eur J Heart Fail* 2021;**23**:1698–1707. <https://doi.org/10.1002/ehf.2287>
 91. Ferreira JP, Zannad F, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. Interplay of mineralocorticoid receptor antagonists and empagliflozin in heart failure: EMPEROR-Reduced. *J Am Coll Cardiol* 2021;**77**:1397–1407. <https://doi.org/10.1016/j.jacc.2021.01.044>
 92. Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, et al. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: Coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J Cardiovasc Pharmacother* 2018;**4**:180–188. <https://doi.org/10.1093/ehjcvp/pyy015>
 93. Anker SD, Kosiborod M, Zannad F, Piña IL, McCullough PA, Filippatos G, et al. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: Results from a phase 3 randomized, double-blind, placebo-controlled trial. *Eur J Heart Fail* 2015;**17**:1050–1056. <https://doi.org/10.1002/ehf.300>
 94. Butler J, Anker SD, Lund LH, Coats AJS, Filippatos G, Siddiqi TJ, et al. Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: The DIAMOND trial. *Eur Heart J* 2022;**43**:4362–4373. <https://doi.org/10.1093/eurheartj/ehac401>
 95. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ; PEARL-HF Investigators. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J* 2011;**32**:820–828. <https://doi.org/10.1093/eurheartj/ehq502>
 96. Brugs J, Radhoe SP, Clephas PRD, Aydin D, van Gent MWF, Szymanski MK, et al.; MONITOR-HF Investigators. Remote haemodynamic monitoring of pulmonary artery pressures in patients with chronic heart failure (MONITOR-HF): A randomised clinical trial. *Lancet* 2023;**401**:2113–2123. [https://doi.org/10.1016/S0140-6736\(23\)00923-6](https://doi.org/10.1016/S0140-6736(23)00923-6)
 97. Ter Maaten JM, Mebazaa A, Davison B, Edwards C, Adamo M, Arrigo M, et al. Early changes in renal function during rapid up-titration of guideline-directed medical therapy following an admission for acute heart failure. *Eur J Heart Fail* 2023;**25**:2230–2242. <https://doi.org/10.1002/ehf.3074>
 98. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, et al.; ADVOR Study Group. Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med* 2022;**387**:1185–1195. <https://doi.org/10.1056/NEJMoa2203094>
 99. Trullàs JC, Morales-Rull JL, Casado J, Carrera-Izquierdo M, Sánchez-Martel M, Conde-Martel A, et al.; CLOROTIC Trial Investigators. Combining loop with thiazide diuretics for decompensated heart failure: The CLOROTIC trial. *Eur Heart J* 2023;**44**:411–421. <https://doi.org/10.1093/eurheartj/ehac689>
 100. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): A multinational, open-label, randomised, trial. *Lancet* 2022;**400**:1938–1952. [https://doi.org/10.1016/S0140-6736\(22\)02076-1](https://doi.org/10.1016/S0140-6736(22)02076-1)
 101. Böhm M, Assmus B, Anker SD, Asselbergs FW, Brachmann J, Brett ME, et al. Less loop diuretic use in patients on sacubitril/valsartan undergoing remote pulmonary artery pressure monitoring. *ESC Heart Fail* 2022;**9**:155–163. <https://doi.org/10.1002/ehf2.13665>
 102. Dhingra NK, Verma S, Butler J, Anker SD, Ferreira JP, Filippatos G, et al.; EMPEROR-Reduced Trial Committees and Investigators. Efficacy and safety of empagliflozin according to background diuretic use in HFrEF: Post-hoc analysis of EMPEROR-Reduced. *JACC Heart Fail* 2024;**12**:35–46. <https://doi.org/10.1016/j.jchf.2023.06.036>
 103. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al.; CHAMPION Trial Study Group. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: A randomised controlled trial. *Lancet* 2011;**377**:658–666. [https://doi.org/10.1016/S0140-6736\(11\)60101-3](https://doi.org/10.1016/S0140-6736(11)60101-3)
 104. Stolfo D, Lund LH, Benson L, Hage C, Sinagra G, Dahlström U, et al. Persistent high burden of heart failure across the ejection fraction spectrum in a nationwide setting. *J Am Heart Assoc* 2022;**11**:e026708. <https://doi.org/10.1161/jaha.122.026708>
 105. Canepa M, Straburzynska-Migaj E, Drozd J, Fernandez-Vivancos C, Pinilla JMG, Nyczasz N, et al.; ESC-HFA Heart Failure Long-Term Registry Investigators. Characteristics, treatments and 1-year prognosis of hospitalized and ambulatory heart failure patients with chronic obstructive pulmonary disease in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur J Heart Fail* 2018;**20**:100–110. <https://doi.org/10.1002/ehf.964>
 106. Mentz RJ, Fiuza M, Wojdyla DM, Chiswell K, Gheorghide M, Fonarow GC, et al. Clinical characteristics and outcomes of hospitalized heart failure patients with systolic dysfunction and chronic obstructive pulmonary disease: Findings from OPTIMIZE-HF. *Eur J Heart Fail* 2012;**14**:395–403. <https://doi.org/10.1093/eurjhf/hfs009>
 107. Du Q, Sun Y, Ding N, Lu L, Chen Y. Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: A meta-analysis of observational studies. *PLoS One* 2014;**9**:e113048. <https://doi.org/10.1371/journal.pone.0113048>
 108. Dransfield MT, Voelker H, Bhatt SP, Brenner K, Casaburi R, Come CE, et al.; BLOCK COPD Trial Group. Metoprolol for the prevention of acute exacerbations of COPD. *N Engl J Med* 2019;**381**:2304–2314. <https://doi.org/10.1056/NEJMoa1908142>
 109. Hawkins NM, Petrie MC, Macdonald MR, Jhund PS, Fabbri LM, Wikstrand J, et al. Heart failure and chronic obstructive pulmonary disease the quandary of beta-blockers and beta-agonists. *J Am Coll Cardiol* 2011;**57**:2127–2138. <https://doi.org/10.1016/j.jacc.2011.02.020>
 110. Vitale C, Jankowska E, Hill L, Piepoli M, Doehner W, Anker SD, et al. Heart Failure Association/European Society of Cardiology position paper on frailty in patients with heart failure. *Eur J Heart Fail* 2019;**21**:1299–1305. <https://doi.org/10.1002/ehf.1611>
 111. Uchmanowicz I, Lee CS, Vitale C, Manulik S, Denfeld QE, Uchmanowicz B, et al. Frailty and the risk of all-cause mortality and hospitalization in chronic

- heart failure: A meta-analysis. *ESC Heart Fail* 2020;**7**:3427–3437. <https://doi.org/10.1002/ehf2.12827>
112. McNallan SM, Singh M, Chamberlain AM, Kane RL, Dunlay SM, Redfield MM, et al. Frailty and healthcare utilization among patients with heart failure in the community. *JACC Heart Fail* 2013;**1**:135–141. <https://doi.org/10.1016/j.jchf.2013.01.002>
 113. Denfeld QE, Winters-Stone K, Mudd JO, Gelow JM, Kurdi S, Lee CS. The prevalence of frailty in heart failure: A systematic review and meta-analysis. *Int J Cardiol* 2017;**236**:283–289. <https://doi.org/10.1016/j.ijcard.2017.01.153>
 114. Leong DP, Joseph P, McMurray JJV, Rouleau J, Maggioni AP, Lanus F, et al. Frailty and outcomes in heart failure patients from high-, middle-, and low-income countries. *Eur Heart J* 2023;**44**:4435–4444. <https://doi.org/10.1093/eurheartj/ehad595>
 115. Vitale C, Hill L. Assess frailty but avoid frailtyism. *Eur Heart J Suppl* 2019;**21**:L17–L19. <https://doi.org/10.1093/eurheartj/suz239>
 116. Bowling A. Ageism in cardiology. *BMJ* 1999;**319**:1353–1355. <https://doi.org/10.1136/bmj.319.7221.1353>
 117. Khan MS, Segar MW, Usman MS, Singh S, Greene SJ, Fonarow GC, et al. Frailty, guideline-directed medical therapy, and outcomes in HFrEF: From the GUIDE-IT trial. *JACC Heart Fail* 2022;**10**:266–275. <https://doi.org/10.1016/j.jchf.2021.12.004>
 118. Kondo T, Adachi T, Kobayashi K, Okumura T, Izawa H, Murohara T, et al. Physical frailty and use of guideline-recommended drugs in patients with heart failure and reduced ejection fraction. *J Am Heart Assoc* 2023;**12**:e026844. <https://doi.org/10.1161/JAHA.122.026844>
 119. Abe T, Jujo K, Maeda D, Saito K, Ogasahara Y, Saito K, et al. The interaction between physical frailty and prognostic impact of heart failure medication in elderly patients. *ESC Heart Fail* 2023;**10**:1698–1705. <https://doi.org/10.1002/ehf2.14114>
 120. Butt JH, Dewani P, Merkely B, Belohlávek J, Drozdž J, Kitakaze M, et al. Efficacy and safety of dapagliflozin according to frailty in heart failure with reduced ejection fraction: A post hoc analysis of the DAPA-HF trial. *Ann Intern Med* 2022;**175**:820–830. <https://doi.org/10.7326/M21-4776>
 121. Veenis JF, Brunner-La Rocca HP, Linssen GC, Geerlings PR, Van Gent MW, Aksoy I, et al.; CHECK-HF Investigators. Age differences in contemporary treatment of patients with chronic heart failure and reduced ejection fraction. *Eur J Prev Cardiol* 2019;**26**:1399–1407. <https://doi.org/10.1177/2047487319835042>
 122. Stolfo D, Sinagra G, Savarese G. Evidence-based therapy in older patients with heart failure with reduced ejection fraction. *Card Fail Rev* 2022;**8**:e16. <https://doi.org/10.15420/cfr.2021.34>
 123. Martinez FA, Serenelli M, Nicolau JC, Petrie MC, Chiang CE, Tereshchenko S, et al. Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to age: Insights from DAPA-HF. *Circulation* 2020;**141**:100–111. <https://doi.org/10.1161/CIRCULATIONAHA.119.044133>
 124. Young JB, Dunlap ME, Pfeffer MA, Probstfield JL, Cohen-Solal A, Dietz R, et al.; Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators and Committees. Mortality and morbidity reduction with candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: Results of the CHARM low-left ventricular ejection fraction trials. *Circulation* 2004;**110**:2618–2626. <https://doi.org/10.1161/01.CIR.0000146819.43235.A9>
 125. Kotecha D, Manzano L, Krum H, Rosano G, Holmes J, Altman DG, et al.; Beta-Blockers in Heart Failure Collaborative Group. Effect of age and sex on efficacy and tolerability of β blockers in patients with heart failure with reduced ejection fraction: Individual patient data meta-analysis. *BMJ* 2016;**353**:i1855. <https://doi.org/10.1136/bmj.i1855>
 126. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667–1675. <https://doi.org/10.1056/NEJMoa010713>
 127. Jhund PS, Fu M, Bayram E, Chen CH, Negrusz-Kawecka M, Rosenthal A, et al.; PARADIGM-HF Investigators and Committees. Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: Insights from PARADIGM-HF. *Eur Heart J* 2015;**36**:2576–2584. <https://doi.org/10.1093/eurheartj/ehv330>
 128. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: A systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000;**355**:1575–1581. [https://doi.org/10.1016/S0140-6736\(00\)02212-1](https://doi.org/10.1016/S0140-6736(00)02212-1)
 129. Stolfo D, Uijl A, Benson L, Schrage B, Fudim M, Asselbergs FW, et al. Association between beta-blocker use and mortality/morbidity in older patients with heart failure with reduced ejection fraction. A propensity score-matched analysis from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2020;**22**:103–112. <https://doi.org/10.1002/ehfj.1615>
 130. Savarese G, Dahlström U, Vasko P, Pitt B, Lund LH. Association between renin-angiotensin system inhibitor use and mortality/morbidity in elderly patients with heart failure with reduced ejection fraction: A prospective propensity score-matched cohort study. *Eur Heart J* 2018;**39**:4257–4265. <https://doi.org/10.1093/eurheartj/ehy621>
 131. Scherrerberg M, Marinus N, Giallauria F, Falter M, Kemps H, Wilhelm M, et al. The need for long-term personalized management of frail CVD patients by rehabilitation and telemonitoring: A framework. *Trends Cardiovasc Med* 2023;**33**:283–297. <https://doi.org/10.1016/j.tcm.2022.01.015>
 132. Malik AH, Malik SS, Aronow VWS; MAGIC (Meta-analysis And oriGinal Investigation in Cardiology) investigators. Effect of home-based follow-up intervention on readmissions and mortality in heart failure patients: A meta-analysis. *Future Cardiol* 2019;**15**:377–386. <https://doi.org/10.2217/fca-2018-0061>
 133. Tamargo J, Kjeldsen KP, Delpont E, Semb AG, Cerbai E, Dobrev D, et al. Facing the challenge of polypharmacy when prescribing for older people with cardiovascular disease. A review by the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy. *Eur Heart J Cardiovasc Pharmacother* 2022;**8**:406–419. <https://doi.org/10.1093/ehjcvp/pvac005>
 134. El Hadidi S, Rosano G, Tamargo J, Agewall S, Drexler H, Kaski JC, et al. Potentially inappropriate prescriptions in heart failure with reduced ejection fraction: ESC position statement on heart failure with reduced ejection fraction-specific inappropriate prescribing. *Eur Heart J Cardiovasc Pharmacother* 2022;**8**:187–210. <https://doi.org/10.1093/ehjcvp/pvaa108>
 135. Potter EL, Hopper I, Sen J, Salim A, Marwick TH. Impact of socioeconomic status on incident heart failure and left ventricular dysfunction: Systematic review and meta-analysis. *Eur Heart J Qual Care Clin Outcomes* 2019;**5**:169–179. <https://doi.org/10.1093/ehjqcco/qcy047>
 136. Aggarwal M, Bozkurt B, Panjra G, Aggarwal B, Ostfeld RJ, Barnard ND, et al. Lifestyle modifications for preventing and treating heart failure. *J Am Coll Cardiol* 2018;**72**:2391–2405. <https://doi.org/10.1016/j.jacc.2018.08.2160>
 137. Bobrowski D, Dorovenis A, Abdel-Qadir H, McNaughton CD, Alonzo R, Fang J, et al. Association of neighbourhood-level material deprivation with adverse outcomes and processes of care among patients with heart failure in a single-payer healthcare system: A population-based cohort study. *Eur J Heart Fail* 2023;**25**:2274–2286. <https://doi.org/10.1002/ehfj.3090>
 138. Schrage B, Lund LH, Benson L, Stolfo D, Ohlsson A, Westerling R, et al. Lower socioeconomic status predicts higher mortality and morbidity in patients with heart failure. *Heart* 2021;**107**:229–236. <https://doi.org/10.1136/heartjnl-2020-317216>
 139. Savarese G, Lund LH, Dahlström U, Strömberg A. Nurse-led heart failure clinics are associated with reduced mortality but not heart failure hospitalization. *J Am Heart Assoc* 2019;**8**:e011737. <https://doi.org/10.1161/JAHA.118.011737>
 140. Lindberg F, Lund LH, Benson L, Schrage B, Edner M, Dahlström U, et al. Patient profile and outcomes associated with follow-up in specialty vs. primary care in heart failure. *ESC Heart Fail* 2022;**9**:822–833. <https://doi.org/10.1002/ehf2.13848>
 141. Lund LH, Braunschweig F, Benson L, Ståhlberg M, Dahlström U, Linde C. Association between demographic, organizational, clinical, and socio-economic characteristics and underutilization of cardiac resynchronization therapy: Results from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2017;**19**:1270–1279. <https://doi.org/10.1002/ehfj.781>
 142. Schrage B, Lund LH, Benson L, Dahlström U, Shadman R, Linde C, et al. Predictors of primary prevention implantable cardioverter-defibrillator use in heart failure with reduced ejection fraction: Impact of the predicted risk of sudden cardiac death and all-cause mortality. *Eur J Heart Fail* 2022;**24**:1212–1222. <https://doi.org/10.1002/ehfj.2530>
 143. Silva-Cardoso J, Juanatey JRG, Comin-Colet J, Sousa JM, Cavalheiro A, Moreira E. The future of telemedicine in the management of heart failure patients. *Card Fail Rev* 2021;**7**:e11. <https://doi.org/10.15420/cfr.2020.32>
 144. Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. *Eur J Heart Fail* 2021;**23**:882–894. <https://doi.org/10.1002/ehfj.2149>
 145. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al.; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200. <https://doi.org/10.1093/eurheartj/ehw128>
 146. Savarese G, Bodegard J, Norhammar A, Sartipy P, Thuresson M, Cowie MR, et al. Heart failure drug titration, discontinuation, mortality and heart failure hospitalization risk: A multinational observational study (US, UK and Sweden). *Eur J Heart Fail* 2021;**23**:1499–1511. <https://doi.org/10.1002/ehfj.2271>
 147. Musella F, Rosano GMC, Hage C, Benson L, Guidetti F, Moura B, et al. Patient profiles in heart failure with reduced ejection fraction: Prevalence, characteristics, treatments and outcomes in a real-world heart failure population. *Eur J Heart Fail* 2023;**25**:1246–1253. <https://doi.org/10.1002/ehfj.2892>

148. Rosano GMC, Allen LA, Abdin A, Lindenfeld J, O'Meara E, Lam CSP, et al. Drug layering in heart failure: Phenotype-guided initiation. *JACC Heart Fail* 2021;**9**:775–783. <https://doi.org/10.1016/j.jchf.2021.06.011>
149. Rosano GMC, Moura B, Metra M, Böhm M, Bauersachs J, Ben Gal T, et al. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2021;**23**:872–881. <https://doi.org/10.1002/ehjhf.2206>
150. Allen LA, Teerlink JR, Gottlieb SS, Ahmad T, Lam CSP, Psotka MA. Heart failure spending function: An investment framework for sequencing and intensification of guideline-directed medical therapies. *Circ Heart Fail* 2022;**15**:e008594. <https://doi.org/10.1161/CIRCHEARTFAILURE.121.008594>
151. Shen L, Jhund PS, Docherty KF, Vaduganathan M, Petrie MC, Desai AS, et al. Accelerated and personalized therapy for heart failure with reduced ejection fraction. *Eur Heart J* 2022;**43**:2573–2587. <https://doi.org/10.1093/eurheartj/ehac210>
152. Chioncel O, Davison B, Adamo M, Antohi LE, Arrigo M, Barros M, et al. Non-cardiac comorbidities and intensive up-titration of oral treatment in patients recently hospitalized for heart failure: Insights from the STRONG-HF trial. *Eur J Heart Fail* 2023;**25**:1994–2006. <https://doi.org/10.1002/ehjhf.3039>
153. Schou M, Gustafsson F, Videbaek L, Tuxen C, Keller N, Handberg J, et al.; NorthStar Investigators, all members of The Danish Heart Failure Clinics Network. Extended heart failure clinic follow-up in low-risk patients: A randomized clinical trial (NorthStar). *Eur Heart J* 2013;**34**:432–442. <https://doi.org/10.1093/eurheartj/ehs235>
154. Rao A, Walsh J. Impact of specialist care in patients with newly diagnosed heart failure: A randomised controlled study. *Int J Cardiol* 2007;**115**:196–202. <https://doi.org/10.1016/j.ijcard.2006.03.010>
155. Blue L, Lang E, McMurray JJ, Davie AP, TA MD, Murdoch DR, et al. Randomised controlled trial of specialist nurse intervention in heart failure. *BMJ* 2001;**323**:715–718. <https://doi.org/10.1136/bmj.323.7315.715>
156. He J, Balmain S, Kobulnik J, Schofield A, Mak S. The role of ambulatory heart failure clinics to avoid heart failure admissions. *CJC Open* 2020;**2**:15–21. <https://doi.org/10.1016/j.cjco.2019.11.007>
157. Matan D, Löfström U, Corovic Cabrera C, Eriksson B, Ekström M, Hage C, et al. Reorganization of heart failure management and improved outcome – the 4D HF project. *Scand Cardiovasc J* 2021;**55**:1–8. <https://doi.org/10.1080/14017431.2020.1820075>
158. Güder G, Störk S, Gelbrich G, Brenner S, Deubner N, Morbach C, et al. Nurse-coordinated collaborative disease management improves the quality of guideline-recommended heart failure therapy, patient-reported outcomes, and left ventricular remodelling. *Eur J Heart Fail* 2015;**17**:442–452. <https://doi.org/10.1002/ehjhf.252>
159. Fowokan A, Frankfurter C, Dobrow MJ, Abrahamyan L, McDonald M, Virani S, et al. Referral and access to heart function clinics: A realist review. *J Eval Clin Pract* 2021;**27**:949–964. <https://doi.org/10.1111/jep.13489>
160. Parajuli DR, Franzon J, McKinnon RA, Shakib S, Clark RA. Role of the pharmacist for improving self-care and outcomes in heart failure. *Curr Heart Fail Rep* 2017;**14**:78–86. <https://doi.org/10.1007/s11897-017-0323-2>
161. Lowrie R, Mair FS, Greenlaw N, Forsyth P, Jhund PS, McConnachie A, et al.; Heart Failure Optimal Outcomes from Pharmacy Study (HOOPS) Investigators. Pharmacist intervention in primary care to improve outcomes in patients with left ventricular systolic dysfunction. *Eur Heart J* 2012;**33**:314–324. <https://doi.org/10.1093/eurheartj/ehr433>
162. Schulz M, Griese-Mammen N, Anker SD, Koehler F, Ihle P, Ruckes C, et al.; PHARM-CHF Investigators. Pharmacy-based interdisciplinary intervention for patients with chronic heart failure: Results of the PHARM-CHF randomized controlled trial. *Eur J Heart Fail* 2019;**21**:1012–1021. <https://doi.org/10.1002/ehjhf.1503>
163. Schumacher PM, Becker N, Tsuyuki RT, Griese-Mammen N, Koshman SL, McDonald MA, et al. The evidence for pharmacist care in outpatients with heart failure: A systematic review and meta-analysis. *ESC Heart Fail* 2021;**8**:3566–3576. <https://doi.org/10.1002/ehf2.13508>
164. Schrage B, Lund LH, Benson L, Braunschweig F, Ferreira JP, Dahlström U, et al. Association between a hospitalization for heart failure and the initiation/discontinuation of guideline-recommended treatments: An analysis from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2023;**25**:1132–1144. <https://doi.org/10.1002/ehjhf.2928>
165. Lee DS, Straus SE, Farkouh ME, Austin PC, Taljaard M, Chong A, et al.; COACH Trial Investigators. Trial of an intervention to improve acute heart failure outcomes. *N Engl J Med* 2023;**388**:22–32. <https://doi.org/10.1056/NEJMoa2211680>
166. Van Spall HGC, Lee SF, Xie F, Oz UE, Perez R, Mitoff PR, et al. Effect of patient-centered transitional care services on clinical outcomes in patients hospitalized for heart failure: The PACT-HF randomized clinical trial. *JAMA* 2019;**321**:753–761. <https://doi.org/10.1001/jama.2019.0710>
167. DeVore AD, Granger BB, Fonarow GC, Al-Khalidi HR, Albert NM, Lewis EF, et al. Effect of a hospital and postdischarge quality improvement intervention on clinical outcomes and quality of care for patients with heart failure with reduced ejection fraction: The CONNECT-HF randomized clinical trial. *JAMA* 2021;**326**:314–323. <https://doi.org/10.1001/jama.2021.8844>
168. Logeart D, Berthelot E, Bihry N, Eschaliier R, Salvat M, Garçon P, et al. Early and short-term intensive management after discharge for patients hospitalized with acute heart failure: A randomized study (ECAD-HF). *Eur J Heart Fail* 2022;**24**:219–226. <https://doi.org/10.1002/ehjhf.2357>
169. Jaarsma T, van der Wal MH, Lesman-Leegte I, Luttkik ML, Hogenhuis J, Veeger NJ, et al. Effect of moderate or intensive disease management program on outcome in patients with heart failure: Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH). *Arch Intern Med* 2008;**168**:316–324. <https://doi.org/10.1001/archinternmed.2007.83>
170. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2024;**26**:5–17. <https://doi.org/10.1002/ehjhf.3024>
171. Bhatt AS, Varshney AS, Nekoui M, Moscone A, Cunningham JW, Jering KS, et al. Virtual optimization of guideline-directed medical therapy in hospitalized patients with heart failure with reduced ejection fraction: The IMPLEMENT-HF pilot study. *Eur J Heart Fail* 2021;**23**:1191–1201. <https://doi.org/10.1002/ehjhf.2163>
172. Rao VN, Shah A, McDermott J, Barnes SG, Murray EM, Kelsey MD, et al. In-hospital virtual peer-to-peer consultation to increase guideline-directed medical therapy for heart failure: A pilot randomized trial. *Circ Heart Fail* 2023;**16**:e010158. <https://doi.org/10.1161/CIRCHEARTFAILURE.122.010158>
173. Bhatt AS, Varshney AS, Moscone A, Claggett BL, Miao ZM, Chatur S, et al. Virtual care team guided management of patients with heart failure during hospitalization. *J Am Coll Cardiol* 2023;**81**:1680–1693. <https://doi.org/10.1016/j.jacc.2023.02.029>
174. Heidenreich PA, Hernandez AF, Yancy CW, Liang L, Peterson ED, Fonarow GC. Get With The Guidelines program participation, process of care, and outcome for Medicare patients hospitalized with heart failure. *Circ Cardiovasc Qual Outcomes* 2012;**5**:37–43. <https://doi.org/10.1161/CIRCOUTCOMES.110.959122>
175. Ahmad T, Desai NR, Yamamoto Y, Biswas A, Ghazi L, Martin M, et al. Alerting clinicians to 1-year mortality risk in patients hospitalized with heart failure: The REVEAL-HF randomized clinical trial. *JAMA Cardiol* 2022;**7**:905–912. <https://doi.org/10.1001/jamacardio.2022.2496>
176. DeVore AD, Cox M, Heidenreich PA, Fonarow GC, Yancy CW, Eapen ZJ, et al. Cluster-randomized trial of personalized site performance feedback in Get With The Guidelines-Heart Failure. *Circ Cardiovasc Qual Outcomes* 2015;**8**:421–427. <https://doi.org/10.1161/CIRCOUTCOMES.114.001333>
177. Allen LA, Venchuk G, McIlvennan CK, Page RL 2nd, Knoop CE, Helmkamp LJ, et al. An electronically delivered patient-activation tool for intensification of medications for chronic heart failure with reduced ejection fraction: The EPIC-HF trial. *Circulation* 2021;**143**:427–437. <https://doi.org/10.1161/CIRCULATIONAHA.120.051863>
178. Ghazi L, Yamamoto Y, Riello RJ, Coronel-Moreno C, Martin M, O'Connor KD, et al. Electronic alerts to improve heart failure therapy in outpatient practice: A cluster randomized trial. *J Am Coll Cardiol* 2022;**79**:2203–2213. <https://doi.org/10.1016/j.jacc.2022.03.338>
179. Mukhopadhyay A, Reynolds HR, Phillips LM, Nagler AR, King WC, Szerencsy A, et al. Cluster-randomized trial comparing ambulatory decision support tools to improve heart failure care. *J Am Coll Cardiol* 2023;**81**:1303–1316. <https://doi.org/10.1016/j.jacc.2023.02.005>
180. McKie PM, Kor DJ, Cook DA, Kessler ME, Carter RE, Wilson PM, et al. Computerized advisory decision support for cardiovascular diseases in primary care: A cluster randomized trial. *Am J Med* 2020;**133**:750–756.e2. <https://doi.org/10.1016/j.amjmed.2019.10.039>
181. Ghazi L, Yamamoto Y, Fuery M, O'Connor K, Sen S, Samsky M, et al. Electronic health record alerts for management of heart failure with reduced ejection fraction in hospitalized patients: The PROMPT-AHF trial. *Eur Heart J* 2023;**44**:4233–4242. <https://doi.org/10.1093/eurheartj/ehad512>
182. McGreevey JD, Mallozzi CP, Perkins RM, Shelov E, Schreiber R. Reducing alert burden in electronic health records: State of the art recommendations from four health systems. *Appl Clin Inform* 2020;**11**:1–12. <https://doi.org/10.1055/s-0039-3402715>
183. Ubel PA, Rosenthal MB. Beyond nudges – when improving health calls for greater assertiveness. *N Engl J Med* 2019;**380**:309–311. <https://doi.org/10.1056/NEJMp1806371>

184. Becher PM, Schrage B, Ferrannini G, Benson L, Butler J, Carrero JJ, et al. Use of sodium-glucose co-transporter 2 inhibitors in patients with heart failure and type 2 diabetes mellitus: Data from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2021;**23**:1012–1022. <https://doi.org/10.1002/ejhf.2131>
185. Lindberg F, Lund LH, Benson L, Linde C, Orsini N, Carrero JJ, et al. Iron deficiency in heart failure: Screening, prevalence, incidence and outcome data from the Swedish Heart Failure Registry and the Stockholm CREAinine Measurements collaborative project. *Eur J Heart Fail* 2023;**25**:1270–1280. <https://doi.org/10.1002/ejhf.2879>
186. Komajda M, Hanon O, Hochadel M, Lopez-Sendon JL, Follath F, Ponikowski P, et al. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. *Eur Heart J* 2009;**30**:478–486. <https://doi.org/10.1093/eurheartj/ehn539>
187. Filbey L, Zhu JW, D'Angelo F, Thabane L, Khan MS, Lewis E, et al. Improving representativeness in trials: A call to action from the Global Cardiovascular Clinical Trialists Forum. *Eur Heart J* 2023;**44**:921–930. <https://doi.org/10.1093/eurheartj/ehac810>
188. Nguyen NV, Lindberg F, Benson L, Ferrannini G, Imbalzano E, Mol PGM, et al. Eligibility for vericiguat in a real-world heart failure population according to trial, guideline and label criteria: Data from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2023;**25**:1418–1428. <https://doi.org/10.1002/ejhf.2939>
189. Thorvaldsen T, Ferrannini G, Mellbin L, Benson L, Cosentino F, JVV MM, et al. Eligibility for dapagliflozin and empagliflozin in a real-world heart failure population. *J Card Fail* 2022;**28**:1050–1062. <https://doi.org/10.1016/j.cardfail.2022.04.011>
190. Moghaddam N, Hawkins NM, McKelvie R, Poon S, Joncas SX, MacFadyen J, et al. Patient eligibility for established and novel guideline-directed medical therapies after acute heart failure hospitalization. *JACC Heart Fail* 2023;**11**:596–606. <https://doi.org/10.1016/j.jchf.2022.10.013>
191. Lim YMF, Molnar M, Vaartjes I, Savarese G, Eijkemans MJC, Uijl A, et al. Generalizability of randomized controlled trials in heart failure with reduced ejection fraction. *Eur Heart J Qual Care Clin Outcomes* 2022;**8**:761–769. <https://doi.org/10.1093/ehjqcco/qcab070>
192. Khan M, Xu H, Fonarow G, Lautsch D, Hilkert R, Allen LA, et al. Applicability of vericiguat to patients hospitalized for heart failure in the United States. *JACC Heart Fail* 2023;**11**:211–223. <https://doi.org/10.1016/j.jchf.2022.11.007>
193. Savarese G, Hage C, Benson L, Schrage B, Thorvaldsen T, Lundberg A, et al. Eligibility for sacubitril/valsartan in heart failure across the ejection fraction spectrum: Real-world data from the Swedish Heart Failure Registry. *J Intern Med* 2021;**289**:369–384. <https://doi.org/10.1111/joim.13165>
194. Kahn M, Grayson AD, Chaggar PS, Ng Kam Chuen MJ, Scott A, Hughes C, et al. Primary care heart failure service identifies a missed cohort of heart failure patients with reduced ejection fraction. *Eur Heart J* 2022;**43**:405–412. <https://doi.org/10.1093/eurheartj/ehab629>
195. Frederix I, Caiani EG, Dendale P, Anker S, Bax J, Böhm A, et al. ESC e-Cardiology Working Group Position Paper: Overcoming challenges in digital health implementation in cardiovascular medicine. *Eur J Prev Cardiol* 2019;**26**:1166–1177. <https://doi.org/10.1177/2047487319832394>
196. Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JG. Structured telephone support or non-invasive telemonitoring for patients with heart failure. *Cochrane Database Syst Rev* 2015;**2015**:CD007228. <https://doi.org/10.1002/14651858.CD007228.pub3>
197. Kitsiou S, Vatani H, Pare G, Gerber BS, Buchholz SW, Kansal MM, et al. Effectiveness of mobile health technology interventions for patients with heart failure: Systematic review and meta-analysis. *Can J Cardiol* 2021;**37**:1248–1259. <https://doi.org/10.1016/j.cjca.2021.02.015>
198. Ding H, Chen SH, Edwards I, Jayasena R, Doecke J, Layland J, et al. Effects of different telemonitoring strategies on chronic heart failure care: Systematic review and subgroup meta-analysis. *J Med Internet Res* 2020;**22**:e20032. <https://doi.org/10.2196/20032>
199. Yun JE, Park JE, Park HY, Lee HY, Park DA. Comparative effectiveness of telemonitoring versus usual care for heart failure: A systematic review and meta-analysis. *J Card Fail* 2018;**24**:19–28. <https://doi.org/10.1016/j.cardfail.2017.09.006>
200. Kotb A, Cameron C, Hsieh S, Wells G. Comparative effectiveness of different forms of telemedicine for individuals with heart failure (HF): A systematic review and network meta-analysis. *PLoS One* 2015;**10**:e0118681. <https://doi.org/10.1371/journal.pone.0118681>
201. Varma N, Braunschweig F, Burri H, Hindricks G, Linz D, Michowitz Y, et al. Remote monitoring of cardiac implantable electronic devices and disease management. *Europace* 2023;**25**:eua233. <https://doi.org/10.1093/eurpace/uead233>
202. Bekfani T, Fudim M, Cleland JGF, Jorbenadze A, von Haehling S, Lorber A, et al. A current and future outlook on upcoming technologies in remote monitoring of patients with heart failure. *Eur J Heart Fail* 2021;**23**:175–185. <https://doi.org/10.1002/ejhf.2033>
203. Vaduganathan M, Claggett BL, McMurray JVV, Solomon SD. Health status trajectories before and after hospitalization for heart failure. *Circulation* 2022;**145**:1872–1874. <https://doi.org/10.1161/CIRCULATIONAHA.122.059282>
204. Braunschweig F, Anker SD, Proff J, Varma N. Remote monitoring of implantable cardioverter-defibrillators and resynchronization devices to improve patient outcomes: Dead end or way ahead? *Europace* 2019;**21**:846–855. <https://doi.org/10.1093/eurpace/euz011>
205. Lindenfeld J, Zile MR, Desai AS, Bhatt K, Ducharme A, Horstmanshof D, et al. Haemodynamic-guided management of heart failure (GUIDE-HF): A randomised controlled trial. *Lancet* 2021;**398**:991–1001. [https://doi.org/10.1016/S0140-6736\(21\)01754-2](https://doi.org/10.1016/S0140-6736(21)01754-2)
206. Zito A, Restivo A, Ciliberti G, Laborante R, Princi G, Romiti GF, et al. Heart failure management guided by remote multiparameter monitoring: A meta-analysis. *Int J Cardiol* 2023;**388**:131163. <https://doi.org/10.1016/j.ijcard.2023.131163>
207. Stevenson LW, Ross HJ, Rathman LD, Boehmer JP. Remote monitoring for heart failure management at home. *J Am Coll Cardiol* 2023;**81**:2272–2291. <https://doi.org/10.1016/j.jacc.2023.04.010>
208. Gorodeski EZ, Goyal P, Cox ZL, Thibodeau JT, Reay RE, Rasmussen K, et al. Virtual visits for care of patients with heart failure in the era of COVID-19: A statement from the Heart Failure Society of America. *J Card Fail* 2020;**26**:448–456. <https://doi.org/10.1016/j.cardfail.2020.04.008>
209. Kuan PX, Chan WK, Fern Ying DK, Rahman MAA, Peariasamy KM, Lai NM, et al. Efficacy of telemedicine for the management of cardiovascular disease: A systematic review and meta-analysis. *Lancet Digit Health* 2022;**4**:e676–e691. [https://doi.org/10.1016/S2589-7500\(22\)00124-8](https://doi.org/10.1016/S2589-7500(22)00124-8)
210. Angermann CE, Sehner S, Faller H, Güder G, Morbach C, Frantz S, et al.; INH Study Group and of the Competence Network Heart Failure. Longer-term effects of remote patient management following hospital discharge after acute systolic heart failure: The randomized E-INH trial. *JACC Heart Fail* 2023;**11**:191–206. <https://doi.org/10.1016/j.jchf.2022.10.016>
211. Zhang X, Luo Z, Yang M, Huang W, Yu P. Efficacy and safety of digital therapeutics-based cardiac rehabilitation in heart failure patients: A systematic review. *ESC Heart Fail* 2022;**9**:3751–3760. <https://doi.org/10.1002/ehf2.14145>
212. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan BA, et al. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): A randomised, controlled, parallel-group, unmasked trial. *Lancet* 2018;**392**:1047–1057. [https://doi.org/10.1016/S0140-6736\(18\)31880-4](https://doi.org/10.1016/S0140-6736(18)31880-4)
213. Cleland JG, Louis AA, Rigby AS, Janssens U, Balk AH; TEN-HMS Investigators. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: The Trans-European Network-Home-Care Management System (TEN-HMS) study. *J Am Coll Cardiol* 2005;**45**:1654–1664. <https://doi.org/10.1016/j.jacc.2005.01.050>
214. Krzesiński P, Jankowska EA, Siebert J, Galas A, Piotrowicz K, Stańczyk A, et al. Effects of an outpatient intervention comprising nurse-led non-invasive assessments, telemedicine support and remote cardiologists' decisions in patients with heart failure (AMULET study): A randomised controlled trial. *Eur J Heart Fail* 2022;**24**:565–577. <https://doi.org/10.1002/ejhf.2358>
215. Galinier M, Roubille F, Berdague P, Briere G, Cantie P, Dary P, et al.; OSICAT Investigators. Telemonitoring versus standard care in heart failure: A randomised multicentre trial. *Eur J Heart Fail* 2020;**22**:985–994. <https://doi.org/10.1002/ejhf.1906>
216. Ong MK, Romano PS, Edgington S, Aronow HU, Auerbach AD, Black JT, et al.; Better Effectiveness After Transition–Heart Failure (BEAT-HF) Research Group. Effectiveness of remote patient monitoring after discharge of hospitalized patients with heart failure: The Better Effectiveness After Transition–Heart Failure (BEAT-HF) randomized clinical trial. *JAMA Intern Med* 2016;**176**:310–318. <https://doi.org/10.1001/jamainternmed.2015.7712>
217. Huitema AA, Harkness K, Heckman GA, McKelvie RS. The spoke-hub-and-node model of integrated heart failure care. *Can J Cardiol* 2018;**34**:863–870. <https://doi.org/10.1016/j.cjca.2018.04.029>