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POSITION PAPER

How to handle polypharmacy in heart failure. A clinical consensus statement of the Heart Failure Association of the ESC

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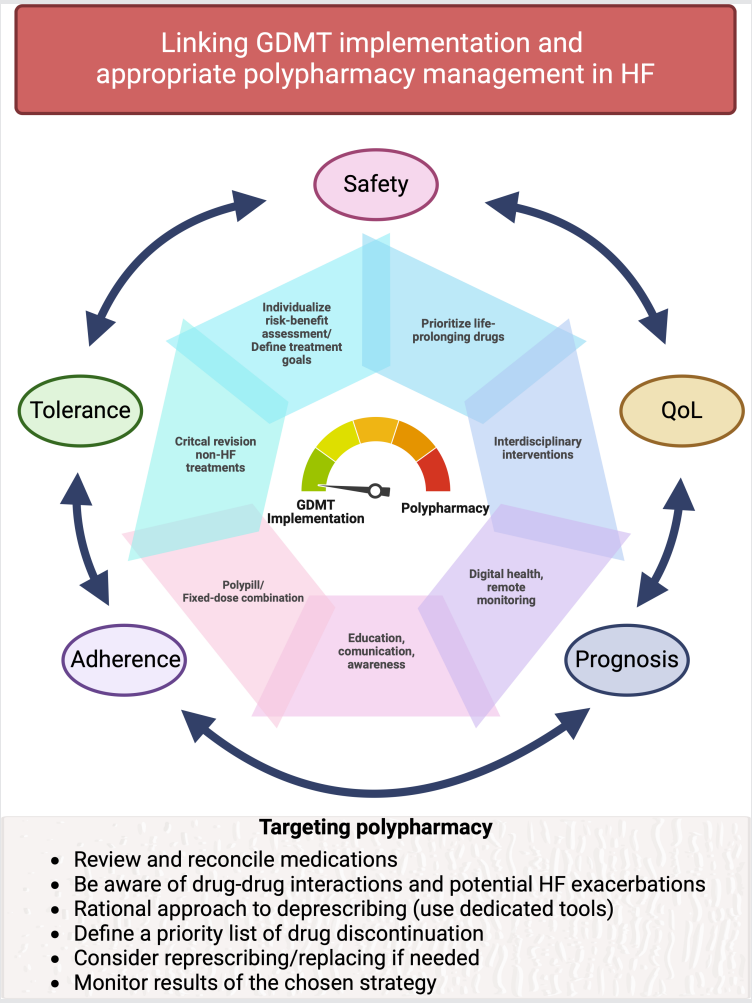
The multiplicity of coexisting comorbidities affecting patients with heart failure (HF), together with the availability of multiple treatments improving prognosis in HF with reduced ejection fraction, has led to an increase in the number of prescribed medications to each patient. Polypharmacy is defined as the regular use of multiple medications, and over the last years has become an emerging aspect of HF care, particularly in older and frailer patients who are more frequently on multiple treatments, and are therefore more likely exposed to tolerability issues, drug–drug interactions and practical difficulties in management. Polypharmacy negatively affects adherence to treatment, and is associated with a higher risk of adverse drug reactions, impaired quality of life, more hospitalizations and worse prognosis. It is important to adopt and implement strategies for the management of polypharmacy from other medical disciplines, including medication reconciliation, therapeutic revision and treatment prioritization. It is also essential to develop new HF-specific strategies, with the primary goal of avoiding the use of redundant treatments, minimizing adverse drug reactions and interactions, and finally improving adherence. This clinical consensus statement document from the Heart Failure Association of the European Society of Cardiology proposes a rationale, pragmatic and multidisciplinary approach to drug prescription in the current era of multimorbidity and 'multi-medication' in HF.

Graphical Abstract



Linking guideline-directed medical therapy (GDMT) implementation and appropriate polypharmacy management in heart failure (HF). Polypharmacy can represent a barrier to the proper implementation of life-prolonging GDMT for HF. A reasonable balance between the optimization of GDMT and avoiding inappropriate polypharmacy is mandatory in the contemporary care of patients with HF. Clinicians are encouraged to use individualized risk–benefit assessments, and patient-centred goals should be defined and pursued, which include outcomes such as prognosis and quality of life (QoL), or factors more related with treatments such as adherence, tolerance and safety. There are multiple aspects that can contribute to the success of the overall process: collaboration with other healthcare professionals and structured interdisciplinary interventions, implementation of digital technologies, use, when appropriate, of fixed-dose combinations for simplification of medication regimens. Life-prolonging medications should be regularly prioritized during the processes of medication revision and appropriateness of non-HF treatment medications critically reassessed. Targeting polypharmacy through a stepwise approach can contribute to facilitate GDMT implementation strategies, to preserve adherence and, finally, to better GDMT.

Keywords Adherence • Comorbidities • Heart failure • Polypharmacy

Introduction

Heart failure (HF) is a worldwide pandemic with growing prevalence and poor prognosis.[1–5] Older age, together with the presence of other comorbid chronic diseases, complicate its management.[6–9] Most patients with HF have ≥3 coexisting comorbidities, with the burden of cardiovascular (CV) and non-CV comorbidities rising over time.[10] This has direct consequences in terms of number of concomitant prescribed medications, and therefore polypharmacy (i.e. use ≥5 medications) is frequently encountered in contemporary HF care.[11–16] Notably, in patients with HF with reduced ejection fraction (HFrEF), the use of guideline-directed medical therapy (GDMT) consists of ≥4 drugs, which further contributes to the pill burden.[2]

This scientific statement document from the Heart Failure Association of the European Society of Cardiology (ESC) aims to provide advice on how to optimize the use of polypharmacy in the context of HF management, and to propose a rational, pragmatic and multidisciplinary approach to drug prescription in the current era of multimorbidity and 'multi-medication' in HF.

Polypharmacy in heart failure: definition and epidemiology

Polypharmacy is broadly defined as the regular use of multiple medications, and has been classified as the chronic use of ≥5 medications, while hyper-polypharmacy refers to the use of ≥10 medications.[17] However, in patients with HFrEF requiring four medications (plus eventual loop diuretics), which represents the foundational GDMT, polypharmacy is almost the rule if this standard definition is applied.[2] The proportion of HF patients taking ≥10 drugs ranges between 25% and 50%.[18,19] Therefore, the focus should be on the appropriateness of medications rather than simply the number of medications when defining polypharmacy in HF.[11]

Polypharmacy is associated with the underuse of GDMT in HF, and patients with HFrEF who are on multiple non-CV medications have lower odds of achieving optimal medical treatment for HF.[20] Polypharmacy increases the risk of non-adherence and adverse drug reactions (ADRs), which are enhanced by both drug–drug and drug–disease interaction, and also contribute to increased healthcare costs.[21]

Key points:

- Polypharmacy is classified as the daily use of ≥5 medications.
- Hyper-polypharmacy refers to ≥10 medications.
- The standard definition of polypharmacy (i.e. chronic use of ≥5 drugs) is almost the rule in patients with HFrEF on foundational quadruple therapy.
- In patients on polypharmacy, the focus of the management should be on the appropriateness of prescriptions rather than on an arbitrary number of drugs.

Strategies to manage polypharmacy and reduce burden pill

Prioritizing the treatment of comorbidities by using heart failure guideline-directed medical therapy

In the setting of specific comorbidities, use of treatments with multiple indications (including HF) can be prioritized to reduce burden pill.

In patients with HFrEF and atrial fibrillation, beta-blockers should be prioritized for rate control as already indicated for the treatment of HF,[2] whereas due to the increasing evidence supporting the prognostic benefit of catheter ablation in HF, interventional strategies could represent a valid option to be discussed within the multidisciplinary team and with the patient.[22,23]

Beta-blockers can be prioritized for the relief of angina in chronic coronary syndromes if HF coexists.[24]

Antihypertensive treatments with strong evidence for the treatment of HFrEF, but also with less strong evidence when the ejection fraction phenotype is preserved or mildly reduced, should be prioritized and optimized over other antihypertensive treatments.

In patients with type 2 diabetes mellitus and HF regardless the ejection fraction phenotype, sodium–glucose cotransporter 2 inhibitors (SGLT2i) should be prioritized over other

glucose-lowering agents, eventually using fixed-dose combinations (FDC) if treatment association is needed,[2,25] together with glucagon-like peptide-1 (GLP-1) receptor agonists and dual GLP-1/glucose-dependent insulinotropic polypeptide receptor agonists in patients with HF with preserved ejection fraction and obesity.[26–28]

Chronic kidney disease is a frequent real or perceived barrier to the optimization of HF GDMT, but GDMT has evidence of benefit and safety also in patients with chronic kidney disease up to stage 3b/4,[29] and therefore during the processes of therapeutic revision and reassessment of treatments appropriateness these drugs should be continued unless contraindicated.

Key points:

- Prioritize the use of treatments with multiple indications (including HF) to reduce burden pill, when multiple comorbidities coexist.
- Deprescribing/discontinuation of GDMT should be avoided in absence of clear contraindications.

Therapeutic competition and priority in polypharmacy

Therapeutic competition is defined as a clinical situation where a medication that treats one condition is harmful to another, introducing the complex issue of treatment prioritization. Competing health priorities complicate treatment optimization in patients with HF, especially in older adults, leading to the need of developing evidence-based patient-centred strategies for managing patients with polypharmacy.[30]

Drug prescribing usually follows a disease-specific approach based on guideline recommendations. By focusing on the direct relationship between a specific drug and a disease, without considering the patient's overall health, polypharmacy can be used inappropriately. This approach leads to fragmented care rather than promoting a holistic, person-centred treatment plan, which is particularly an issue in HF given the frequent coexistence of CV and non-CV comorbidities leading to likely polypharmacy.[11] Patient's characterization is key to achieve proper treatment prioritization. The presence, number and severity of comorbidities should be carefully evaluated, as well as their impact on life expectancy. For instance, HF and cancer are diseases strongly affecting patient's prognosis. Therefore, it becomes a primary goal to keep patients on these treatments, while eventually reconsidering those for other non-life-limiting conditions. This is even more valuable for younger patients with longer life expectancy.

Decisions on treatment selection should take into consideration that older patients with HF often contend with physical and functional limitations that span multiple domains: medical (HF-related), cognitive, physical and socio-economical.[31] Age alone should not be intended as a barrier to treatment initiation; however, if a patient presents overt deficits in one or more of these domains, the aim should be achieving the best balance between the need of GDMT optimization and potential safety, tolerability and adherence issues.[11]

Self-reported health status and quality of life are also important aspects to be discussed with patients, and the aim should be finding the optimal compromise between the implementation of evidence-based treatments, therapeutic adherence and quality of life.[11] The further step is the definition of therapeutic goals, which is influenced by the comorbidities that might affect life expectancy and, in the more advanced disease stages, by the presence of frailty or the need for palliative care. In older patients with HF, who may not have longer survival as the primary goal but rather quality of life, treatment should be redefined accordingly. However, given the unquestionable benefit in quality of life achieved with HF GDMT,[32] its implementation maintains a solid basis also in these patients. The entire process of prioritization should be therefore shared across all the specialists involved in the patient care.

Key points:

- Decisions on treatment prioritization should follow a patient-centred approach with main focus on the patient's overall health.
- This comprehensive patient-centred assessment should consider physical and functional limitations, the co-existence of comorbidities and related treatments, and the presence of socioeconomic barriers.
- The final goal is the identification of the best balance between GDMT optimization, safety, tolerance, adherence, and quality of life.

Revision of therapy: deprescribing

Drug–drug interactions as well drug–disease interactions, and other drug-related specific issues, are very common when patients are prescribed multiple treatments (*Table 1*). Inappropriate prescribing warrants careful consideration by specialists and requires timely review for each patient during every medical encounter. Several medications may cause or exacerbate HF, and should therefore represent the first-choice targets for deprescribing.[33] However, in daily clinical practice, such drugs are often not discontinued at discharge in patients hospitalized for HF.[34] The use of over-the-counter (OTC) products and the access to self-care medications are also extremely frequent in the HF population and contribute to polypharmacy.[35,36] Eighty-eight percent of HF patients use products not requiring any prescription,[37] and this is also often not reported by the patient to the treating physicians.[38]

The core principle of prescribing medications only when the potential benefits exceed the risks has recently been complemented by a paradigm shift towards proactive deprescribing when the harms outweigh the benefits.[11,39]

A comprehensive definition of deprescribing should include: (1) a structured process of medication withdrawal, especially of inappropriate and unnecessary medications, or dose reduction; (2) oversight of the deprescribing process by a member of the healthcare team; (3) the goal of improving one or more specific outcomes (e.g. mortality, morbidity, quality of life, disease relapse); and (4) consideration of the patient's overall physiological status, stage of life, and goals of care.[40]

Table 1 **Potential safety/tolerability issues related to the main cardiovascular and non-cardiovascular comorbidities treatments and potential solutions in patients with heart failure**

Comorbidity	Potential issues	Potential interactions	Potential solutions
AF	Anticoagulants may increase bleeding risk, hypokinetic arrhythmias secondary to rate/rhythm control treatments	Amiodarone and digoxin can cause hypokinetic arrhythmias in association with beta-blockers	Reduce amiodarone dose, monitor digoxin concentration, prefer non-pharmacological interventions
CAD	Antiplatelets may increase bleeding risk, antianginal treatments can induce bradycardia/hypotension	Long-acting nitrates may cause postural hypotension when associated with other vasodilators	Use the minimal effective dose, educate patients to avoid/control postural hypotension, use alternative drugs without action on blood pressure/heart rate (i.e. trimetazidine, ranolazine)
Cancer	Potential for drug interactions with chemotherapy agents	Some cancer treatments may adversely affect cardiac function and interact with medications	Collaborate with oncologist; monitor for cardiotoxicity during treatment
COPD	COPD exacerbation, potential for drug interactions with bronchodilators	Beta-blockers may exacerbate COPD symptoms; consider cardioselective agents	Patients with HFrEF and COPD benefit from beta-blockers; use cardioselective beta-blockers; monitor respiratory function and symptoms closely
CKD	Reduced renal function may impact drug clearance, potential for drug accumulation and toxicity	Adjust drug dosages based on renal function; avoid nephrotoxic agents	Regularly monitor renal function; consider alternative medications
Dementia/cognitive impairment	Difficulty managing complex medication regimens	Risk of adverse effects and drug interactions	Involve caregivers and specific professional figures in daily patient care (e.g. HF nurse); simplify the regimen and consider longer-acting formulations to reduce dosing frequency
Gender-specific pathologies	Drug interactions with treatment for ED, hypotension with alpha-blockers, worsening hypertension with oestrogen replacement therapy	Risk of adverse effects, hypotension, GDMT dose reduction or discontinuation	Avoid PDE5-i in association with nitrates or vericiguat, prefer 5-alpha reductase inhibitors for BPH, implement antihypertensive in women on oestrogen replacement therapy
Hypertension	Postural hypotension, worsening renal function	Hypotension, adverse effects, drug accumulation and interactions, GDMT de-escalation/withdrawal	Prioritize HFrEF GDMT as antihypertensive drugs, consider single-pill combination
Infections	Potential for drug interactions with antibiotics, especially fluoroquinolones and antivirals	Some antibiotics may interact with cardiac medications; monitor for side effects	Choose antibiotics with minimal cardiac adverse effects; monitor for interactions
Metabolic disorders	Potential for drug interactions with antidiabetic agents	Some metabolic medications may have CV effects; monitor glucose levels	Coordinate care between cardiologist and endocrinologist; adjust medications
Osteoarthritis	NSAIDs may exacerbate HF symptoms	NSAIDs can interact with diuretics and ACE inhibitors; Cox-2 inhibitor associated with higher rate of CV events; consider alternative pain management	Use acetaminophen or non-pharmacological pain management; monitor for fluid retention
Mental disorders	Potential for drug interactions with psychotropic and nootropic medications	Antidepressants may interact with beta-blockers; monitor for mood changes and sodium level	Collaborate with psychiatrist; consider non-interfering psychiatric medications; monitor ECG for QTc interval
Sleeping disorders	Potential for drug interactions with sedatives and hypnotics	Sedatives may exacerbate HF symptoms; monitor for respiratory depression	Non-pharmacological approaches for sleep; cautious use of sedatives
Thyroid disorders	Altered metabolism and potential for drug interactions	Thyroid hormones may impact CV function; monitor thyroid levels	Adjust cardiac medications based on thyroid function; regular monitoring

AF, atrial fibrillation; BPH, benign prostatic hyperplasia; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Cox-2, cyclooxygenase 2; CV, cardiovascular; ECG, electrocardiogram; ED, erectile dysfunction; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NSAID, non-steroidal anti-inflammatory drug; PDE5-i, phosphodiesterase-5 inhibitor.

Table 2 Most used tools (criteria) for deprescribing

	Characteristics	Advantages/disadvantages
Beers criteria[91]	List of: • Specific drug–drug interactions • Potential inappropriate medications • Medications to avoid in certain conditions • Medications to use with caution • Medications needing dose adjustment in renal dysfunction	• Multiple updates • Promoted by the American Geriatrics Society • Regularly updated
STOPP/START criteria[43]	Twelve reported sections (CV system, coagulation system, central nervous system, renal system, gastrointestinal system, respiratory system, musculoskeletal system, urogenital system, endocrine system, falls risk increasing drugs, analgesic drugs, vaccines) with criteria to start and stop medications	• Approved by NICE, Royal College of General Practitioners and British Geriatrics Society (UK) • Detailed criteria for stopping and starting medications • Regularly updated • STOPPFrail criteria for end-stage patients are also available[92]
Medication appropriateness index[93]	Ten questions to be addressed for potential drug-related problems associated with a specific medication (degree 1 to 3)	• Assessment of a range of issues relevant for a variety of medications
PRISCUS and PRISCUS 2.0 criteria[94,95]	List of potentially inappropriate medications for older patients, possible alternative drugs, and precautions if cannot be avoided.	• Based on a consensus panel (Delphi method) in Germany and focused on German pharmaceutical market
French consensus panel[96]	List of potentially inappropriate medications. List of criteria with reasons for concern and possible alternative drugs	• Based on expert consensus panel (Delphi method) • Designed for the French population aged >75 years
PIP-HFrEF[33]	List of medications to avoid as potentially harming HF patients Include an extensive list of CV and non-CV medications	• Based on ESC multidisciplinary and multinational expert consensus and systematic review • Designed for European adult and elderly populations

CV, cardiovascular; ESC, European Society of Cardiology; HF, heart failure; NICE, National Institute for Health and Care Excellence; PIP-HFrEF, potentially inappropriate prescribing in heart failure with reduced ejection fraction.

Disagreement in reported drug treatments across different healthcare providers (e.g. patients, specialists, general practitioners, etc.) can be frequent. The process of deprescribing starts with a careful revision of patient's therapies, including self-prescribed and OTC medications, in order to identify the most accurate list of all the ongoing treatments. This process is called medication reconciliation and consists in comparing the medical record to an external list of medications obtained from a patient, hospital, or other provider.[41] It should involve a collaborative decision-making between different healthcare providers, patients, and sometimes caregivers or family members. The aim is avoiding therapeutic mistakes such as omissions, duplicates, dosing errors, or drug interactions.[42]

Numerous tools have been developed to assist healthcare providers when deprescribing, particularly in the elderly population (*Table 2*), such as STOPP/START, Beers criteria and PIP-HFrEF, with the former two being the most widely utilized in practice and recently updated.[33,43–45] However, none of these tools has been specifically designed for HF, which must be carefully considered when they are applied to patients with HF, otherwise the potential risk is to deprescribe HF GDMT. Dedicated tools for the management of polypharmacy in HF are therefore strongly advocated.

Polypharmacy stewardship is a relatively novel concept aiming at integrating all the processes of medication revision and deprescribing, to promote the appropriate use of drugs and minimize medication-related harm. It is defined as a coordinated intervention designed to assess, monitor, improve, and measure the pharmacological treatment of multimorbidity, taking into account the use of potentially inappropriate medications, potential prescribing omissions, drug–drug and drug–disease interactions, and prescribing cascades (i.e. initiation of a new medicine to 'treat' an ADR associated with another medicine),[46] with the aim of aligning treatment regimens with the overall condition, prognosis, and preferences of the individual patient.[44] The medication steward is a skilled and experienced pharmacist who is expected to review medications in order to identify possible opportunities for deprescribing of non-essential drugs contributing to the high drug burden index score.

In this scientific statement document, we propose a deprescribing protocol including five steps (*Figure 1*):

1. To review and reconcile all drugs the patient is currently taking, the underlying indications and whether there is current or past history of non-adherence.

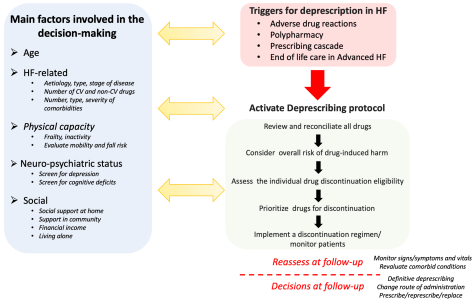


Figure 1 Multidomain approach for managing polypharmacy in heart failure (HF). Reconciliation of treatments and periodical assessment of therapeutic appropriateness follow multistep and multidisciplinary processes, which should consider patient and drug characteristics. Periodical review of these aspects is pivotal. When the possibility and need of deprescribing is ascertained, the deprescribing protocol represents a point-by-point guide that can support physicians' decisions. Alternatives to definitive deprescribing (i.e. represcribing/replacement, variation in the way of administration) should be always evaluated. CV, cardiovascular.

2. To consider the risk of drug-induced harm in individual patients: medication-related factors to consider include known ADRs, drug–drug or drug–disease interactions, and polypharmacy.
3. To assess each drug regarding its current or future expected benefit or harm, or the likelihood of being particularly burdensome (i.e. for instance big tablets difficult to swallow, treatments needing repetitive monitoring, etc.).
4. To prioritize for discontinuation drugs that have the lowest benefit–harm ratio, the lowest likelihood of adverse withdrawal reactions or disease rebound syndromes, and are easy to withdraw. Attention should be paid to patient preferences.
5. To implement a discontinuation regimen and closely monitor patients to early identify the results of the intervention. Slow tapering over time may be required for some agents associated with increased risk for an adverse drug withdrawal event. These events may include a relapse of symptoms as a result of the withdrawal, or a physiological withdrawal such as rebound tachycardia after discontinuation of beta-blockers or an increase in blood pressure after discontinuation of anti-hypertensive agents.[47] Practical application of these recommendations can be apparently difficult and not immediate in routine care.

Responsibility of therapy revision should not belong to one specific healthcare provider. Multidisciplinary discussion and mutual support in the decision-making and in the process of deprescribing are priorities. Together with the HF physician in charge, specialized HF nurses and pharmacists are of value in the management of every step of this process.

The rationale for drug discontinuation is inadequately addressed by randomized controlled trials (RCTs) and is not explored in the guidelines.[48] There are various barriers to deprescribing which can involve the healthcare system, physicians and patients.[49] There is no consensus nor solid evidence regarding the most appropriate approach to deprescribing in multimorbid HF patients. Patients may perceive deprescribing as a form of abandonment of care or a cost-saving measure. Both patients and physicians may hold beliefs in the continuation of treatment despite the lack of indication. Patients may be hesitant to discontinue a medication initiated by other physicians, and there is often a lack of proactive communication between healthcare professionals and patients regarding the rationale for deprescribing a specific treatment. Healthcare-related barriers to deprescribing may include the lack of dedicated time, lack of adequate staffing, lack of a consistent deprescribing workflow, and limited documentation in the medical records of patients.

Key points:

- Dedicated time to the careful revision of prescriptions at every medical encounter can contribute to avoid inappropriate prescribing.
- Deprescribing aims to reduce unnecessary or potentially harmful medication use in order to improve patient outcome.
- Several tools are available to address polypharmacy in the elderly population (*Table 2*).
- Deprescribing should follow a structured stepwise process (*Figure 1*).
- Multidisciplinary discussion is key to the practical process of deprescribing.

Fixed-dose combination in heart failure

Fixed-dose combination (or polypill) strategies, defined as FDC for multiple purposes,[50,51] consist of the association of ≥2 drugs in a single formulation and were first introduced in the early 2000s to substantially reduce CV disease in both primary and secondary prevention.[52–55] Such a strategy improves patient adherence, and can aid in mitigating the polypharmacy burden. In patients with systemic hypertension, FDC reduced the daily pills intake, has been found to increase patient adherence, and is currently recommended as initial strategy for most patients.[50,56,57] Exceptions are patients with moderate-to-severe frailty, symptomatic orthostatic hypotension, or older people (aged ≥85 years).[57]

Data from a meta-analysis confirmed the positive impact of FDC on CV outcomes in primary prevention.[58] In patients with recent myocardial infarction, a polypill including key medications (aspirin, angiotensin-converting enzyme inhibitor, statin) reduced CV events by 24% as compared with usual care, and European guidelines on hypertension support the use of FDC for primary and secondary prevention of CV outcomes.[57,59]

In HFrEF, the strong recommendation by ESC guidelines on HF supporting an early initiation of the four foundational classes of drugs with evidence-proved benefit on mortality/morbidity might encourage the development of a FDC in order to simplify the treatment schedule and to reinforce patient adherence.[2] Estimated eligibility for FDC and improved adherence in HFrEF are high.[60] However, no RCTs have specifically assessed the efficacy and more importantly the safety of FDC in HF. There are specific issues in the HFrEF treatment implementation that might represent an obstacle to FDC strategies: (1) three out of four HFrEF drugs require dose up-titration, (2) tolerated doses can be lower than the 100% target dose for one or more HFrEF drugs, (3) disease status (symptoms, blood pressure, heart rate, haemodynamic stability, etc.) is dynamic in HF and influences the maximally tolerated doses over time, and (4) in the case of ADRs or other tolerability issues, the identification of the implicated drug can be difficult. For all these reasons, FDC in HFrEF might be more appropriate for therapeutic maintenance rather than for the implementation phase. Once the patient has achieved the maximally tolerated dose and demonstrated disease stability, this approach could simplify medication self-management and reduce the daily pill burden. Two ongoing open-label RCTs are testing the FDC of GDMT therapies in patients with HFrEF (NCT04633005, NCT06029712).[61]

Key points:

- Single-pill combination of antihypertensive agents is recommended to reduce the daily pills burden.
- FDC can improve patient adherence and mitigate polypharmacy.

Digital health and remote monitoring

Digital systems might offer valuable solutions to optimize treatments and better manage polypharmacy. Over the last decades, with the aid of e-prescription, several computerized prescription support systems (CPSS) or computerized clinical decision support systems (CDSS) have been developed to reduce overdosing of drugs, medication errors, drug–drug interactions and the number of inappropriate prescriptions,[62,63] by assisting physicians in drug selection and dosing, flagging potential ADRs and drug allergies, and identifying duplication of therapy.[64,65] CPSS and CDSS can be differently applied to electronic health records at hospital institutions or in primary care. Alternatively, direct contact with patients through different virtual healthcare solutions can also represent valid strategies for therapeutic monitoring and implementation.[66,67]

In the in-hospital setting, virtual care-guided strategies of implementation were demonstrated to be safe and to improve GDMT in patients with HFrEF admitted for HF but also for non-HF causes.[68–70] The results available for CPSS supporting the prescription of pharmacological treatments are contradictory. There is a wide heterogeneity across the studies on the topic including differences in operative systems, modalities of integration of digital data in clinical records or the interaction with artificial intelligence technologies.[71] Moreover, remote patient monitoring with wearable devices can assist physicians and allow a prompt identification of potentially harmful situations linked with multiple drug administration (e.g. hypotension, low heart rate, etc.) along with early detection of worsening HF.[72] Telemedicine or more simply phone interviews can also support patients with managing their daily medication regimens, thus improving adherence. Alerts or reminders for timely drug intake, support in the recognition of ADRs, or FAQ pages can be particularly helpful for the correct adherence to treatments.[73–75]

Key points:

- Digital systems can support physicians in proper drug prescription, ADRs and drug–drug interactions monitoring, identification of inappropriate treatments and allergies, selection of better drugs and dosing.
- In-hospital virtual care-guided strategies of implementation are safe and can improve the implementation of GDMT.
- Remote patient monitoring can contribute to guide treatment implementation and to the early identification of harmful conditions linked with polypharmacy.

Linking implementation science with polypharmacy management

The uptake of life-prolonging GDMT for HF remains slow in clinical practice,[76] and the availability of additional evidence-based drugs for HFrEF may apparently contrast with the need of avoiding polypharmacy particularly in older people, which vice versa can affect GDMT optimization.[20] Clinicians are encouraged to use individualized risk–benefit assessments for therapeutic decisions. However, growing evidence suggests that alternative strategies and collaboration with other healthcare professionals can also effectively achieve optimal outcomes for patients. Although several studies have explored the effect of implementation strategies to improve the uptake of GDMT for HF,[36,69,77–80] the effects of interventions aiming at reducing the overall pill burden, for instance by critical review of the number and appropriateness of concomitant non-HF treatments, have not been investigated. The PHARM-CHF study assessed the effect of an interdisciplinary intervention involving the local pharmacy on medication adherence in patients with chronic HF. It consisted of a two-step approach: first, medication review and generation of a medication plan, and second, preparation of a weekly dosing aid. The pharmacy-care approach improved medication adherence, but no information was provided on impact of the medication review on the total number of medications.[36] Since it demonstrated to enhance the adherence to prescribed treatments with an improvement in quality of life, a dedicated study investigating the advantage obtained with this approach in terms of

overall pill burden and reduction in adverse effects might be a reasonable option to provide an evidence-based approach to polypharmacy.[81] An alternative strategy consisting of algorithm-based recommendations developed by a virtual care team (i.e. centralized physician, study staff, and local pharmacist) was also effective at improving treatment implementation, but still there was no specific focus on issues related with polypharmacy.[69] On the other hand, in the PAL-HF trial enrolling patients with advanced HF, palliative care failed to reduce medication counts in a setting where deprescribing unnecessary medications might significantly impact the quality of life in patients with end-stage HF.[82] In the more general setting of older adults with polypharmacy, deprescribing strategies are apparently safe. A review of 14 RCTs including patients aged 65 years or older in primary care or outpatient sites, community pharmacies, hospital or nursing home/long-term care facilities, tested several different types of interventions in terms of settings and preparation, use of different interdisciplinary teams, validated guidelines and tools, patient-centredness and implementation strategy. It confirmed the safety of deprescribing, the effectiveness in reducing the number of medications and suggested a potential positive effect on quality of life.[83] Few RCTs specifically focused on the safety of deprescribing CV medications in particular subsets of patients, apparently with positive results in terms of safety.[40,84] With the exception of the TRED-HF study, which was designed to address a different aim (i.e. evaluating the risk of relapsing dilated cardiomyopathy HF after withdrawal of GDMT in patients with recovered ejection fraction), no dedicated RCTs on polypharmacy management in patients with HF are currently available.[40,84]

Yet, such trials on therapeutic revision in the setting of HF, with specific attention to older and frail patients, are strongly needed to define the best strategy to achieve the combined goal of GDMT implementation and management of polypharmacy while ensuring patient adherence. As the burden of non-CV polypharmacy has demonstrated to negatively affect the likelihood of GDMT initiation and optimization,[85] appropriate deprescribing of redundant treatments might facilitate a better implementation of HF medications (*Graphical Abstract*).

Key points:

- Decision-making on therapeutic revision should follow an individualized risk–benefit assessment.
- Adherence to HF GDMT can be improved by implementation strategies; however, integrating critical and systematic review of the non-HF treatments might also contribute to reduce the burden pill, leading to better GDMT.
- Interdisciplinary interventions and multidisciplinary teams are strongly advised to simultaneously promote HF GDMT optimization and the management of polypharmacy in order to support patient adherence.

Polypharmacy from the patient perspective

For people living with HF, polypharmacy is associated with a reduction in quality of life, complicates adherence and contributes to altered disease perception.[86] Medicine management is the most performed self-care behaviour, but also carries negative psychological implications.[86,87] Patient participants of the TRED-HF trial explained that taking medication, obtaining repeat prescriptions, and managing comorbidities are all reminders of living with a chronic disease and contribute to a feeling of being defined by their disease.[87] They also described periods of non-adherence related to this perception, response to improvement of symptoms or a lack of understanding of why they were prescribed so many medications.[87] Lack of communication on the rationale for prescribing led to a perception that healthcare professionals were over-prescribing. Periods of non-adherence were strongly linked to increased risk of hospitalization and mortality.[88]

Healthcare professionals must ensure extensive communication with patients and caregivers to facilitate understanding of the rationale behind the use of medical therapies, assess the use of OTC medication, describe potential side effects and interactions, and how to report these and evaluate goals of care.[33,89] Empowering patients to be participants in care and not simply recipients provides opportunities to optimize outcomes in the presence of polypharmacy. Patient education, shared decision-making and self-care play a crucial role in the management of polypharmacy and may lead to improved medication adherence and health outcomes.[90] Patients should actively participate in a regular re-assessment of the appropriateness and necessity of their medication and be observant to potential side effects. Strategies to improve the organization of medication, for example, by using pill organizers, updated printed lists providing the medication schedule with track changes as well as established procedures for taking the prescribed drugs as part of daily routines are essential for promoting a safe and effective medication use.

Key points:

- Daily self-management of multiple treatments has strong psychological implications which, in turn, can contribute to non-adherence.
- Complete and clear communication with patients and caregivers on all the aspects related with prescribed treatment is mandatory and their complete understanding should be verified.
- Patient education and active involvement of patients in their care can contribute to improve adherence and reduce the issues related with polypharmacy.

Conclusions

The demographic changes in the HF population have introduced new important scenarios to consider when approaching the care of these patients. Polypharmacy, linked mainly with older age and multimorbidity, can negatively affect adherence to treatments, increase the risk of ADRs and drug–drug interactions, and therefore worsen patient outcomes. Although geriatricians have already integrated many strategies for the management of polypharmacy in the care of older patients in HF, and more generally in cardiology,

the awareness of this problem is still limited. Moreover, in the contemporary era of HFrEF treatment, based on the four foundational GDMTs with proven survival benefit and impact on risk of rehospitalization and quality of life, polypharmacy is also extremely frequent and therefore there is need of an HF-centred approach to its management allowing to preserve HF treatments, promote their optimization and avoid their discontinuation.

This entire process should incorporate a multifaceted approach balancing non-adherence and clinical inertia against a rational approach to polypharmacy, with prioritization of treatments with strong evidence of efficacy and safety, and therefore requires the involvement of different healthcare providers and specialties, the integration of regular care with technologies and with industries, and can be facilitated by educational programmes for patients, family specialists and general practitioners.

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