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POSITION PAPER

Adherence to guideline-directed medical treatments in heart failure. A scientific statement of the Heart Failure Association (HFA) of the ESC and the ESC Working Group on Cardiovascular Pharmacotherapy

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Heart failure (HF) affects over 60 million individuals globally. Contemporary guideline-directed medical therapies (GDMT) reduce cardiovascular mortality and HF hospitalizations. However, medication non-adherence represents a critical barrier limiting real-world efficacy of GDMT. This scientific statement aims to provide a comprehensive framework for understanding, measuring, and addressing medication non-adherence in HF management across diverse healthcare settings. Addressing medication non-adherence requires systematic, multifaceted approaches targeting individual patient barriers while implementing system-level interventions. Polypills, digital monitoring platforms, enhanced patient education and empowerment, and multidisciplinary care models represent promising strategies to optimize therapeutic adherence and improve clinical outcomes in HF management.

Keywords Heart failure • Adherence • Guidelines • Polypill • Fixed-dose combinations • Digital • Education • Multidisciplinary

Introduction

Heart failure (HF) is a global health challenge affecting over 60 million individuals worldwide, with an estimated prevalence of 1–3%.[1] The combined use of contemporary guideline-directed medical therapies (GDMT) for HF with reduced ejection fraction (HFrEF) has been demonstrated to reduce cardiovascular mortality and HF hospitalizations by 64%.[2] The evidence for the efficacy of comprehensive therapeutic approaches is now extended across the entire spectrum of left ventricular ejection fraction. Indeed, recent advances in HF pharmacotherapy, particularly sodium–glucose co-transporter 2 inhibitors (SGLT2i) and mineralocorticoid receptor antagonists (MRAs), support the use of these treatments across all ejection fraction phenotypes, including HF with preserved ejection fraction (HFpEF).[3–5]

The optimal clinical benefits of GDMT for HF can only be appreciated when these interventions are both appropriately prescribed, optimized/up-titrated, and subsequently adhered to by patients.[6–8] Consequently, therapeutic adherence has emerged as a fundamental determinant of both quality of life and prognostic improvement in patients with HF. The challenge of maintaining long-term medication adherence has been consistently documented across multiple chronic conditions, including HF.[8,9] Indeed, an international survey of physicians highlighted that 42% of respondents identified patient adherence as a principal clinical impediment to the successful implementation of GDMT in patients with HFrEF.[10] This persistent adherence challenge creates a significant discrepancy between the demonstrated efficacy of HF interventions in randomized controlled trials (RCT) and their real-world effectiveness when used in routine clinical practice. The efficacy–effectiveness gap represents a critical public health concern, as the potential benefits of evidence-based therapies are lost in a substantial proportion of patients. The magnitude of this gap necessitates systematic interventions at the level of healthcare providers, patients, and healthcare systems, in order to implement and sustain therapeutic adherence. Such efforts must encompass multifaceted strategies, including enhanced patient education programmes, simplified medication regimens, coordinated multidisciplinary care approaches, digital health technologies for monitoring and support, and addressing psychological-mental health and socioeconomic barriers that may impede access and adherence to medications. Furthermore, healthcare systems must evolve to incorporate routine adherence assessment as an integral component of HF management, alongside the development and implementation of targeted interventions designed to overcome identified barriers to adherence.

This scientific statement from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) in collaboration with the ESC Working Group on Cardiovascular Pharmacotherapy aims to provide a comprehensive overview of existing evidence on patient adherence in patients with HF, including the extent and consequences of non-adherence in real-world practice, contributing factors, ways of measuring and monitoring adherence, and current evidence for strategies to improve it. It also provides a comprehensive framework for understanding and addressing medication adherence in HF, including evidence-based strategies for measurement and intervention, with practical tools for implementation across diverse healthcare settings.

Conceptual framework for adherence in heart failure

Medication adherence in HF is influenced by multiple interconnected domains that collectively determine patients' ability to implement and maintain prescribed therapeutic regimens (*Figure 1*). These domains encompass factors which might be related to the patient, therapy, condition, healthcare system, mental health

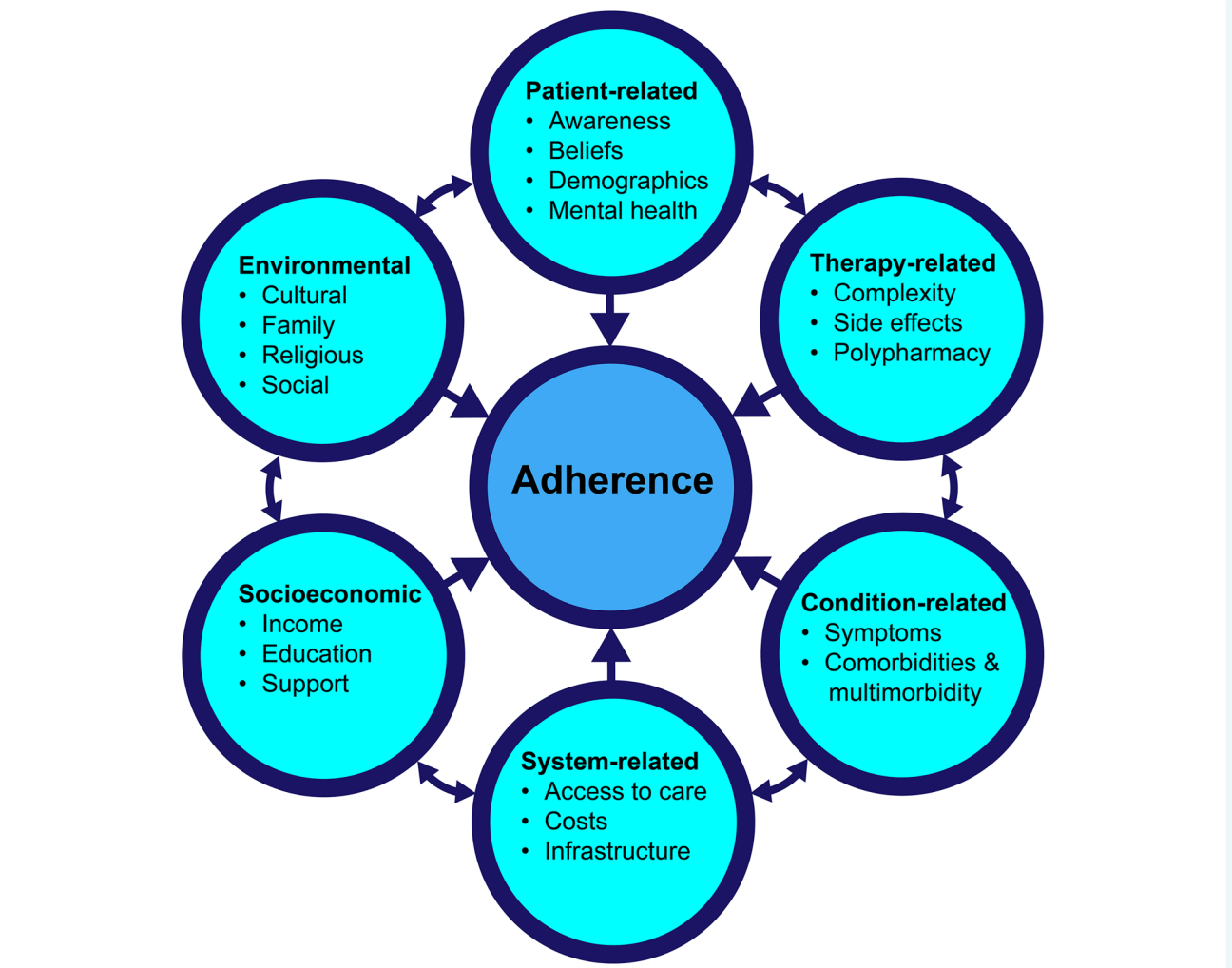

Figure 1 The heart failure adherence framework.

and socioeconomic and environmental settings. Understanding this multidimensional framework is essential for developing comprehensive, patient-centred interventions that address the complex interplay of determinants affecting adherence behaviour in HF management. Whilst we acknowledge that 'adherence' embraces a broad spectrum of behaviours at the patient, provider, and system level—including healthcare providers' adherence to guidelines or protocols, appointment adherence as a marker of engagement with scheduled care, and adherence to recommended health-monitoring schedules—the present statement purposefully restricts its scope to patients' medication adherence, recognizing that other equally important domains are outside the remit of this document and warrant dedicated treatment elsewhere.

Definition of adherence

The World Health Organization (WHO) defines adherence as 'the degree to which the person's behaviour corresponds with the agreed recommendations from a healthcare provider' and accurately follows the prescribed therapeutic regimens, in addition to lifestyle changes and healthy living advice.[11–18] Conversely, compliance refers only to the extent to which the patient follows the physician's instructions,[17,18] and is defined as 'the extent to which the patient's behaviour matches the prescriber's recommendations'.[11–16] The fundamental difference between these two apparently similar terms is subtle, but has an important implication: the benchmark to which 'adherence' should be measured is the regimen that is agreed-upon between the patient and the care provider (*Table 1*). This highlights that the therapeutic alliance between patients and healthcare professionals and enhanced patient empowerment is central to achieving adherence to medical therapy and self-care.[19]

Why measure adherence?

While adherence is often measured in RCTs, it is rarely assessed and measured in clinical practice. From the clinician's perspective, accurately evaluating adherence aids in the identification of

Table 1 Glossary of adherence terms

Term	Definition	Measurement method
Adherence	Degree to which behaviour corresponds with agreed recommendations	PDC, MPR, MEMS
Compliance	The extent to which the patient adheres to the doctor's instructions	PDC, MPR, MEMS
Initiation	Time from prescription until first dose	Pharmacy records
Persistence	Time from initiation until discontinuation	Pharmacy claims, EMR data
Implementation	How well patient executes dosing regimen	MEMS, self-report
Drug holiday	Gap in medication taking >3 consecutive days	MEMS, refill data

EMR, electronic medical record; MEMS, medication event monitoring system; MPR, medication possession ratio; PDC, proportion of days covered.

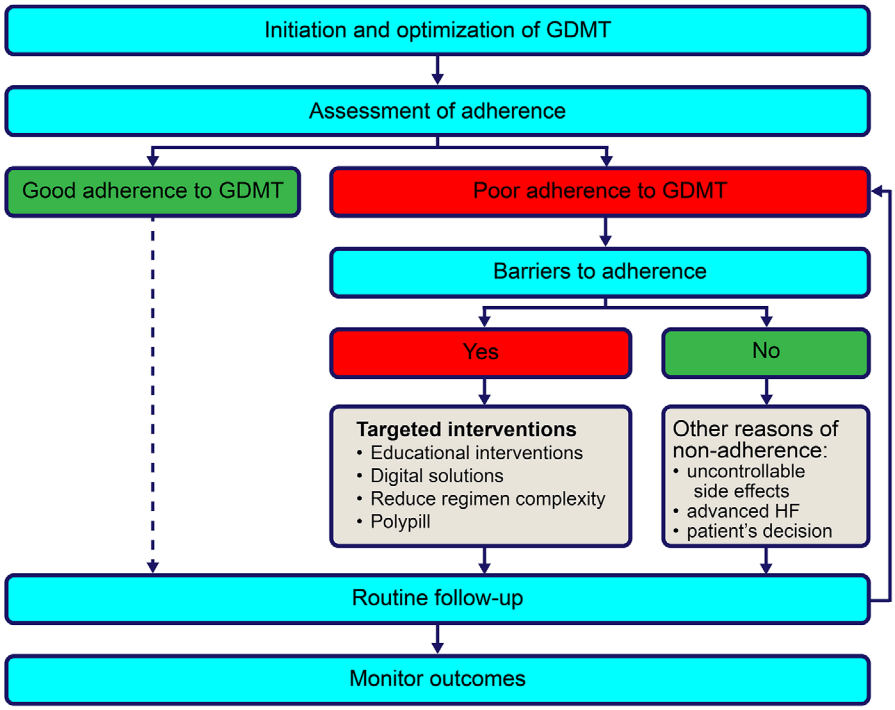

Figure 2 Implementation algorithm for assessment and adherence interventions. GDMT, guideline-directed medical therapy; HF, heart failure.

the causes for therapeutic limitations unattributable to disease progression or treatment inefficacy, hence potentially improving patient outcomes.[12,13,15,20–22] Failing to account for adherence might lead to the erroneous attribution of a change in outcomes (whether it be progression/improvement of HF or potential side effects) to the recommended regimen, and might therefore cause unnecessary or potentially harmful therapeutic adjustments and/or diagnostic work-up. From the patient's perspective, assessing adherence can provide insights into their health behaviours and can inform personalized, patient-centred interventions that promote better health outcomes (*Figure* 2).

How to measure adherence

Medication adherence can be evaluated using several conceptual measures: initiation (the interval between prescription and first dose taken), persistence (duration from initiation until discontinuation), and continuous metrics comparing prescribed versus actual medication usage patterns (such as proportion of prescribed medication taken, proportion of days covered [PDC], frequency of medication holidays, medication possession ratio [MPR], or maximum inter-dose intervals).[12] The relative significance of these measures varies according to clinical condition, therapeutic intervention, and healthcare context. In chronic HF management, straightforward metrics such as PDC or proportion of prescribed drug taken can provide valuable insight into the potential impact of non-adherence, and are associated with clinical outcomes.[23] Whilst a threshold of <80% commonly denotes significant non-adherence, observational evidence suggests that even adherence <88% could more accurately predict adverse outcomes in HF.[24] For clinical scenarios where health outcomes are particularly sensitive to medication timing, such as in left ventricular assist device recipients or heart

Table 2 Comparison of adherence measurement methods

Method	Advantages	Disadvantages	Cost	Ease of use	Setting
Self-report	Simple, low cost	Overestimates adherence	Low	High	All settings
Pharmacy refill	Objective, population-level	Does not confirm intake	Low	Medium	Health systems with EHR
MEMS	Detailed, accurate	Expensive, limited scalability	High	Medium	Research, high-risk patients
Blood/urine tests	Direct measure	Invasive, costly	High	Low	Research, special cases

EHR, electronic health record; MEMS, medication event monitoring system.

transplant patients, more granular adherence measurements may be required.[25]

There is no gold standard tool for measuring adherence (*Table 2*). Provider-assessed adherence alone demonstrates poor efficacy in identifying adherence across various settings: when pharmacy refill records indicated antihypertensive coverage for <80% of days, clinicians correctly identified significant non-adherence in only 37% of cases, performing worse than chance.[26] Numerous patient self-report questionnaires have been developed to estimate adherence in chronic diseases (e.g. the Morisky Medication Adherence Scale),[27–30] with some specifically adapted for HF (e.g. the European HF Self-care Behaviour Scale).[31,32] However, patient-reported adherence assessed by structured questionnaires also largely overestimates adherence in HF,[33,34] as in other chronic diseases.[28,35] Despite these limitations, patient self-reporting remains a simple, cost-effective approach: although it could be sometimes unreliable, it may identify non-adherence, assess non-pharmacological adherence, and provide valuable insights into behavioural and contextual factors influencing non-adherence when combined with more objective adherence measures.[36]

Pharmacy dispensation records can quantify remaining medication, indicating whether the dispensed quantity per time-period aligns with prescribed regimen. However, these data are not universally collected, cannot confirm actual consumption, and fail to detect certain non-adherence patterns (such as dosing delays or when drugs are retrieved without being consumed).

Caps that can be fitted on medication bottles and record the time the medication is accessed (medication event monitoring system [MEMS]) provide more direct and detailed information on adherence but are costly, precluding their widespread use in many clinical settings. They also do not ensure that medications have been actually consumed. MEMS can identify non-adherence missed by self-reported assessments. Indeed, in a study from the Netherlands, only 76% of 37 patients with HF and a self-reported adherence of 100% had MEMS-measured adherence ≥88%.[34] In a different HF cohort, MEMS-identified non-adherence, but not self-reported non-adherence, was associated with poor outcomes.[23]

Plasma and urine testing for drug metabolite concentrations represents another approach, though this strategy implies cost, uses additional healthcare resources, needs to account for patient factors that can influence these tests (e.g. diet, absorption, metabolism, comorbid conditions, and excretion), and requires patients' consent and collaboration. Indeed this approach has not been widely adopted in HF management but only reported in a few studies.[33,37–40] In a small study assessing adherence to digoxin in patients with HF, serum digoxin concentration revealed 20% non-adherence versus 5% by self-report.[33] Controversially, participants were not informed of the role of digoxin as an adherence monitoring tool in the study.[41]

Each adherence measurement method presents distinct challenges, and no perfect method exists. The lack of a gold standard is reflected in the wide range of measures used in HF studies. HF-specific standardized metrics are needed, balancing the requirements of clinical practice, ethical standards and research settings. Effective adherence measurement requires a combination of these approaches, tailored to individual patient contexts and clinical environments (Box 1).

Box 1 Practical tools for measuring adherence.

- Morisky Medication Adherence Scale (MMAS-8)
- European Heart Failure Self-care Behaviour Scale (EHFScB-9)
- Pharmacy refill data calculation tools
- Simple patient questions ('How many doses did you miss last week?')

Adherence in real-world and randomized controlled trial settings

The problem of maintaining patient adherence affects most chronic conditions requiring long-term therapy, including HF. Adherence may be further reduced in these patients because of poor tolerability of some medications such as neurohormonal modulators (hypotension, bradycardia, fatigue).[42] Estimates of adherence in the real-world HF population demonstrate considerable variability depending on the specific aspect of adherence being investigated, how it was measured, and in which healthcare system and context.[43]

Adherence in trial settings is generally higher than what is observed in real-world practice. In both the COMET and CHARM trials, ~89% of patients were considered adherent to the study

drug (defined as PDC >80% and ≥80%, respectively),[44,45] while in the PHARM-CHF trial, the mean PDC (considering beta-blockers, angiotensin-converting enzyme inhibitors [ACEi]/angiotensin receptor blockers [ARB], and MRA) during the 6 months preceding randomization was ∼68% (only ∼43% of patients having a mean PDC ≥80%), which increased up to ∼90% during the first year of the study.[46] In a prospective adherence study of patients enrolled in the STRONG-HF trial in Nigeria and Mozambique, enalaprilat and carvedilol were undetectable in the serum of ∼16% and 44% of patients, respectively, in the high-intensity arm at the 12-week visit.[47]

In the real-world setting, adherence (PDC or MPR >80% or ≥80%) for renin–angiotensin system inhibitors (RASi)/angiotensin receptor–neprilysin inhibitor (ARNi), beta-blockers, and MRAs, respectively, was 83%, 85%, and 85% in Sweden (estimated glomerular filtration rate ≥60 ml/min/1.73 m^2)[48]; 81–84%, 83%, and 61% in Norway[49]; and 35–59%, 61%, and 36% in the USA.[50,51] Adherence (PDC ≥80%) to triple anti-neurohormonal therapy was only 67% in Sweden and 5% in Norway.[48,49] The substantial heterogeneity of these numbers has likely several causes, including differences in time periods, healthcare system context (such as medication cost subsidies and healthcare access), and differing methods for measuring adherence. When adherence has been evaluated by MEMS, a patient took a mean of 89% of prescribed doses over 3 months, with the correct number of doses on 81% of days, and achieved timing adherence for 67% of doses.[52] Studies that assessed adherence to HF drugs by measuring their presence in serum or urine samples, reported absence of at least one prescribed HF drug in 25% of patients with HF in Portugal,[40] 18% of patients 4–6 weeks after HF hospitalization in Scotland,[37] 46% in BIOSTAT-CHF,[38] and 11% in ambulatory patients attending HF follow-up.[39]

Adherence and outcomes

Non-adherence to HF medications has been consistently shown to be independently associated with the risk of emergency department visits, hospital admissions, and death.[50,53] In the Get With the Guidelines-HF registry, a PDC ≥80% for ARNi in HFrEF was associated with a 31% and 47% lower risk of 1-year hospitalization and death, respectively.[54] In a large Danish registry-based study, non-persistence to RASi or beta-blockers was independently associated with 25–37% higher risk of all-cause mortality.[55] In BIOSTAT-CHF, non-adherence to RASi and beta-blockers, assessed by urinary analysis, was independently associated with 38% and 48% greater risk of all-cause death or HF hospitalization, respectively.[38] Although higher adherence is associated with a higher cost of medications, this is counterbalanced by the lower costs from prevented recurrent hospitalizations.[56]

Meta-analyses of RCTs found that interventions seeking to improve adherence in patients with HF led to 2–11% lower risk of death and 10–21% lower risk of hospital readmission.[57,58] In the CHARM programme, adherence to the allocated treatment was independently associated with ∼34–36% lower risk of death, regardless of whether the patient was assigned to candesartan or placebo.[45] This finding helps addressing a common limitation of real-world observational studies, where the apparent link between better adherence and improved outcomes may be confounded by disease severity: patients with more advanced illness may discontinue treatment due to poor tolerability, leading to worse outcomes. On the other hand, observing better outcome in patients adherent to placebo highlights that they might be also more adherent to other treatment and have overall better self-care behaviours. Non-adherence may thus reflect a broader at-risk profile, including factors such as greater disease severity (leading to intentional or unintentional treatment discontinuation), cognitive or psychological barriers (e.g. depression, denial of illness), or a general reluctance to engage with healthcare providers or accept help—each of which may independently contribute to poorer outcomes, beyond the effect of pharmacological treatment alone.

Factors influencing adherence

The WHO identifies five interacting dimensions that influence adherence: (1) patient-related factors; (2) socioeconomic factors; (3) condition-related factors; (4) therapy-related factors; (5) health system/healthcare team-related factors (*Figure 1*).[17] Furthermore, mental health issues also represent a key domain for adherence. All these factors are pertinent to adherence in the setting of HF,[59,60] and can be targeted through specific strategies.

Patient-related factors

Awareness, attitudes, beliefs and mental health

Patients' perception about the importance of the treated condition might influence adherence, and potentially explains why patients who had been hospitalized for HF in the past year are more likely to adhere to HF medications.[60] Patients with HF have been reported to overestimate their own prognosis, which might imply an underestimation of the importance of therapy.[61] Lack of belief in medications and patients' self-efficacy (i.e. their perception of their own ability to achieve a given objective) influence how patients attribute changes in health status to the medication, and increase the likelihood of withdrawal.[44,62] Furthermore, preconcepts, cultural and religious beliefs may influence the perspective on how patients perceive their illness, the importance of medical and device therapies, the acceptance of these interventions, and ultimately adherence.[63] Patients who perceive barriers to take medications, such as forgetfulness, cost, or belief that it is fine to skip medications, are also likely to have poorer adherence.[52] Lastly, mental health problems, such as mild to moderate levels of depression, are associated with a lower level of adherence to HF treatments.[64]

Sex and age

It is unclear whether adherence is influenced by sex or age among patients with HF.[65] In the CHARM programme, women had higher likelihood of non-adherence than men.[66] However, other studies have not confirmed these findings.[60] Women with HF may experience also additional barriers, such as greater susceptibility to drug adverse effects, competing caregiving responsibilities, and different symptom perception. Women often receive less comprehensive

counselling about medication and may prioritize family needs above their own health maintenance, are some examples of factors that may negatively affect adherence to prescribed medications.[67]

Elderly patients with HF often have multiple long-term conditions.[68] The presence of multiple comorbidities may influence adherence because of the impact of conditions like cognitive disorders, social isolation, higher propensity for side-effects, and also because of polypharmacy, which negatively affect adherence.[69] Furthermore, age and physician-perceived frailty may negatively influence the management of older patients with HF through ageism and frailtyism that are a major determinant of under-prescription and under-titration of medications.[70–73] The rate of discontinuation of medical therapy is similar in patients older or younger than 75 years, and age itself does not seem to be associated with non-adherence for HF therapies.[20,38,54,65,66,74] Impaired cognitive function in elderly patients with HF, in absence of a caregiver, is associated with poorer adherence.[75,76] thus underscoring the importance of family involvement or caregiver availability in maintaining medication adherence.

Socioeconomic factors

Poor socioeconomic status is associated with adverse outcomes in HF, is a known barrier of HF therapy implementation,[77] and may also impact adherence. Socioeconomic determinants warrant thorough consideration both in the assessment of therapeutic adherence and in the planning of interventions.[63,77,78] Financial constraints, especially in non-universal healthcare systems, may reduce adherence to medical treatment significantly impacting prognosis of HF patients. This phenomenon assumes particular relevance for the prescription of novel, non-genericized pharmaceutical agents. Evidence from the USA demonstrates that households with reduced pecuniary resources exhibited markedly lower propensity to adhere to ARNi prescriptions amongst the cohort of patients with HFrEF.[79] Furthermore, lower education levels, single living, and health insurance coverage constitute additional socioeconomic variables that influence suboptimal adherence amongst patients with HF.[80]

The demanding nature of HF self-care creates significant challenges for patients managing their condition independently, particularly for the elderly and in those with psycho-cognitive disorders. The presence of caregivers and familial support networks play a crucial role in augmenting therapeutic adherence. Their assistance may facilitate enhanced compliance with pharmaceutical regimens despite the complexity introduced by polypharmacy.[81]

From a financial point of view, reduced co-payment obligations may correlate with improved adherence rates in patients with diabetes mellitus and HF.[51] Notably, in the USA, each increment of 7.80 USD in co-payment obligation was associated with a corresponding 1.8% reduction in medication possession ratio.[82]

Health disparities and social determinants of therapeutic adherence

Social determinants of health, racial and ethnic disparities affect both the accessibility and adherence to pharmacological interventions for HF, with a majority of HF patients worldwide receiving limitedly implemented GDMT.[83] These discrepancies are underpinned by multifactorial inequities within healthcare systems but persist even in socialized healthcare. Health literacy represents a critical determinant of therapeutic adherence, as comprehension of complex medication regimens necessitates understanding of the rationale for polypharmacy. Inadequate health literacy correlates strongly with suboptimal adherence behaviours, and doctor–patient communication is often a significant factors limiting patients' understanding of the need for medical therapy.[84,85]

Healthcare providers' ability to communicate to patients the required information about drugs' evidence-based benefits, potential side effects and mechanisms in lay terms while taking the necessary time might influence adherence, also by mitigating eventual nocebo effect, that is, the occurrence of a negative outcome due to patient's belief that a therapeutic intervention will cause harm. Individuals with limited health literacy, minimal formal education, or those from minoritized communities often encounter challenges in comprehending medical terminology, complex therapeutic regimens, interpreting pharmaceutical instructions, and recognizing the significance of consistent medication administration and less often ask for clarifications.[84] Similarly, language barriers may preclude efficacious patient–clinician communication, thereby affecting the elucidation of treatment protocols. Therefore, physicians must employ simplified communication techniques, eschewing medical jargon in favour of more accessible terminology whilst utilizing visual aids, and culturally congruent explanatory models.

Cultural and religious backgrounds may also be a limiting factor to patient adherence as conventional biomedical paradigms may conflict with alternative understanding of illness potentially causing reluctance to accept and engage with prescribed pharmacological interventions.[63,86]

The distribution of healthcare resources exacerbate disparities in treatment provisions and adherence, with pronounced rural-urban differences in both access to specialist cardiology services and pharmaceutical availability. Patients living in rural areas frequently encounter logistical impediments to medication procurement, specialist consultation, and therapeutic monitoring.[87]

A potentially relevant issue is the possible lack of appreciation on the side of doctors of what their patients actually consider most relevant with respect to the long-term consequences of their disease. A recent survey simultaneously assessing both patients and their physician at the time of a visit has shown a substantial divide on several outcome-related items.[88] With respect to HF, physicians were significantly more concerned about symptom worsening, while patients attributed greater importance to the risk of disability. This lack of appreciation of patients' feelings, and of sharing appropriate information, may contribute to not achieving adequate adherence to medications.

All these social determinants collectively contribute to adherence behaviours and necessitate nuanced, culturally sensitive interventional strategies.

Condition-related factors

Symptoms severity may affect adherence as they can increase the awareness of need for therapy and enhance motivation.[89] In

general, patients with impaired quality of life or severe functional limitations are more likely to strengthen their belief in medication adherence at follow-up.[44]

Comorbidities negatively affect prognosis in HF and are a well-recognized barrier to treatment adherence.[68,83] The majority of patients with HF have four or more comorbidities most of which require therapeutic interventions.[68] The presence of comorbidities leads to polypharmacy, and increases the risk of adverse drug reactions, negatively impacting treatment adherence. Some comorbidities such as cognitive impairment and dementia, depression and other mental health conditions directly impact treatment adherence.[3,90] Other co-existing pathologies, such as chronic kidney disease, hypotension,[42] and chronic obstructive pulmonary disease, diminish clinicians' propensity to implement comprehensive HF pharmacotherapy and may concomitantly reduce tolerability or engender patients' apprehension regarding adverse effects, thereby having a negative impact upon therapeutic adherence.[91–93] In the Swedish HF registry, the decline in renal function was paralleled by a decreased adherence and 1-year persistence to RASi/ARNi, MRA, and triple therapy in patients with HFrEF.[48]

Therapy-related factors

Patients may have varying adherence to different HF medications, with one study suggesting that adherence is lowest to loop diuretics and beta-blockers.[94] Specific therapy-related factors and side-effects of HF medications on heart rate and blood pressure can lead to orthostatic hypotension and fatigue, might negatively influence adherence. Also, complex dosing regimens, need for pill splitting, and real or perceived risk of side effects play a role towards non-adherence. Polypharmacy is common in patients with HF,[81,95,96] and may introduce complexity that acts as a barrier to adherence.[97] In non-socialized healthcare systems, polypharmacy contributes to the overall medical costs reducing adherence. The presence of multiple prescriptions also frequently leads to complex medication schedules, substantial pill burden, and 'information overload' that might increase risk for forgetting or avoiding medication doses.[69,96]

Healthcare systems

The healthcare systems determine many factors that can influence adherence.[8] Out-of-pocket spending for medications is influenced by non-universal/universal coverage, insurance coverage, and co-payment structures. Higher co-payment has been associated with lower adherence in patients with HF, whereas medications free of charge have been shown to improve adherence and specific surrogate health outcomes in randomized trials.[56,82,98–101] Constrained healthcare systems with impaired access to care/follow-up for patients affect adherence as the frequency of outpatient visits has been reported to be correlated with HF medication adherence.[102]

Strategies to improve adherence

Several strategies can be employed to improve adherence,[58,103] which in turn may improve long-term outcomes in patients with HF and being cost-effective (*Figure 2* and *Table 3*).[57,58] Lessons can be learnt from a range of interventions that have been found to improve adherence in other cardiovascular and non-cardiovascular diseases, such as coronary artery disease, arterial hypertension, and oncology.[8,9] Multifaceted interventions incorporating several of these strategies might better improve adherence.[104]

Identifying non-adherence

Measuring medication adherence is key to tackle non-adherence with its routine assessment providing the opportunity to proactively intervene. Each component of pharmacological adherence, that is, prescription, dispensation, and refilling of medications, can be assessed in electronic health records, registries and claims and administrative databases but their use is limited in most healthcare systems.[105] The MATCH trial reported that an electronic adherence measurement intervention improved patient satisfaction in patients treated for uncontrolled hypertension.[106] Studies in hypertension have demonstrated that 25% of apparently treatment-resistant patients were non-adherent when screened,[107] whilst another study demonstrated urinary adherence measures predicted blood pressure control.[108] Although costly, urinary assessments are useful tools to assess adherence.[109] In HF, adherence to SGLT2i can be easily assessed by the presence of glycosuria in the standard urinalysis. However, the measurement alone is insufficient to improve adherence unless coupled with other interventions.

Implementing healthcare teams

Healthcare professionals frequently overestimate adherence.[26] The involvement of a multidisciplinary team, including nurses, pharmacists, and other healthcare professionals, in the care and follow-up of patients with HF can positively impact treatment adherence.[46] Pharmacists and nurses can enhance adherence through HF

Table 3 Evidence-based interventions with cost-effectiveness data

Intervention	Effectiveness	Cost	Implementation requirements	Level of evidence
Educational programmes	+10–15% adherence	Low-medium	Staff training	High
Pharmacist integration	+15–20% adherence	Medium	Pharmacist availability	High
Digital reminders	+5–10% adherence	Low	Technology infrastructure	Moderate
Reduced copayments	+10–25% adherence	High	Policy change	High

and self-care education, treatment up-titration and prescription, monitoring of prescription refill rates, medication reviews and reconciliation, and increased healthcare–patient contacts, which has been shown to be associated with lower risk of morbidity and mortality.[110–112] A recent economic review found that pharmacy-based interventions to improve medication adherence were cost-effective with the healthcare costs averted exceeding the cost of the intervention.[113] The integration of other physician specialties (e.g. internists, geriatricians, nephrologists, and primary care physicians) can also facilitate comprehensive, coherent, and streamlined treatment plans and transitions of care.[114–117]

Educational interventions

Educational interventions improve patients' understanding of their condition, the importance of and how to use HF therapy, thereby potentially improving adherence. Patient education should also encompass the development of a trusting relationship. Physicians should actively identify patients' concerns and provide support in addressing them. A common example is the fear of committing to lifelong treatments. A meta-analysis of 18 randomized trials evaluating educational interventions in patients with hypertension, hyperlipidaemia or diabetes found that educational interventions increased adherence.[118] Interventions that were delivered at home or face-to-face and that included ≥3 sessions appeared to be particularly effective especially in patients discharged after a hospitalization for HF.[118–123]

Educational interventions do not necessarily need to be administered in person. A structured telephone support intervention alone or combined with pre-discharge education booklets or nurse-led pre-discharge self-management training have all been shown to improve medication adherence and reducing the risk of all-cause mortality or readmission.[119–121]

Extending educational interventions to patients' care partners, such as family, relatives, and close friends, has been shown to further enhance medication adherence in HF.[124] Additionally, caregiver involvement in self-care education leads to better self-care behaviours, reduced hospital readmissions, and increased confidence in managing HF.[125] These findings support the integration of caregivers and care partners into educational programmes to empower them to support patients' adherence and HF management more effectively.

Patient empowerment and self-care

While various tools can help identify patients with impaired adherence, taking daily medications ultimately depends on the patient's own actions. For this reason, patient empowerment is a key strategy for improving adherence.[126] Empowered patients possess the knowledge, skills, and confidence to participate actively in their care,[127] make informed decisions, and address barriers to adherence. HF patients who understand the rationale for their medications, are expected to feel comfortable asking questions during consultations, be able to weigh treatment options in collaboration with their clinicians and are likely to follow their treatment plan more consistently.

Building empowerment involves education, shared decision-making, and the development of self-care skills that foster a sense of ownership over treatment. By deepening patients' understanding of their condition, improving their ability to recognize and respond to symptoms and medication side effects, and supporting them in integrating treatment into daily life, empowerment may promote sustained medication use and timely communication with healthcare providers. This, in turn, may strengthen self-care behaviours, such as regular medication-taking, daily weight monitoring, dietary adherence, and appropriate physical activity, enabling patients to maintain better control over their health in everyday life. However, more systematic research is needed to determine the most effective ways to implement patient empowerment and self-care strategies and to clarify their impact on adherence and clinical outcomes in HF.

Digital solutions

Scientific and technological advancements have led to a digital revolution in the healthcare system.[128] Digital solutions have emerged as promising tools in monitoring and managing different types of patients, including patients with HF. The use of digital devices alone or associated with text or nurse-led interventions can increase patients' awareness of the disease, provide education on their condition and allow better monitoring of clinical status. Remote monitoring can enable timely interventions to prevent complications, allow to tailor treatments based on real-time patient data, thereby enhancing tolerability.[129–132]

Text message reminders combined with a post-discharge educational message have been shown to improve medication adherence in patients discharged after a HF hospitalization.[119] In a recent trial including outpatients with HF, daily text reminders tailored according to patients' medication regimen improved adherence versus usual care, but showed similar adherence as a pillbox organizer intervention.[133]

Digital health applications address medication non-adherence in HF through automated reminders, symptom tracking with algorithmic analysis, remote monitoring, and tailored education. These platforms enable early intervention through bidirectional communication, whilst behavioural economics principles maintain engagement.

Smart pharmaceutical dispensing systems with automated reminders can provide temporal medication prompts whilst simultaneously documenting administration patterns for clinical monitoring. Mobile health applications with electronic health record integration facilitate bidirectional data exchange, allowing therapeutic adjustments informed by patient-reported outcomes and medication consumption patterns. Remote health monitoring and non-pharmacological self-monitoring applications provide digital remote monitoring for HF patients by analysing patient-reported symptoms, vital parameters and medication adherence whilst enabling bidirectional clinical communication. The SUPPORT-HF2 trial showed that remote monitoring with applications is feasible.[134] The TIM-HF2 study showed a 20% reduction in the primary outcomes of days lost due to HF hospitalization or death of any cause, and a 30% relative decrease in

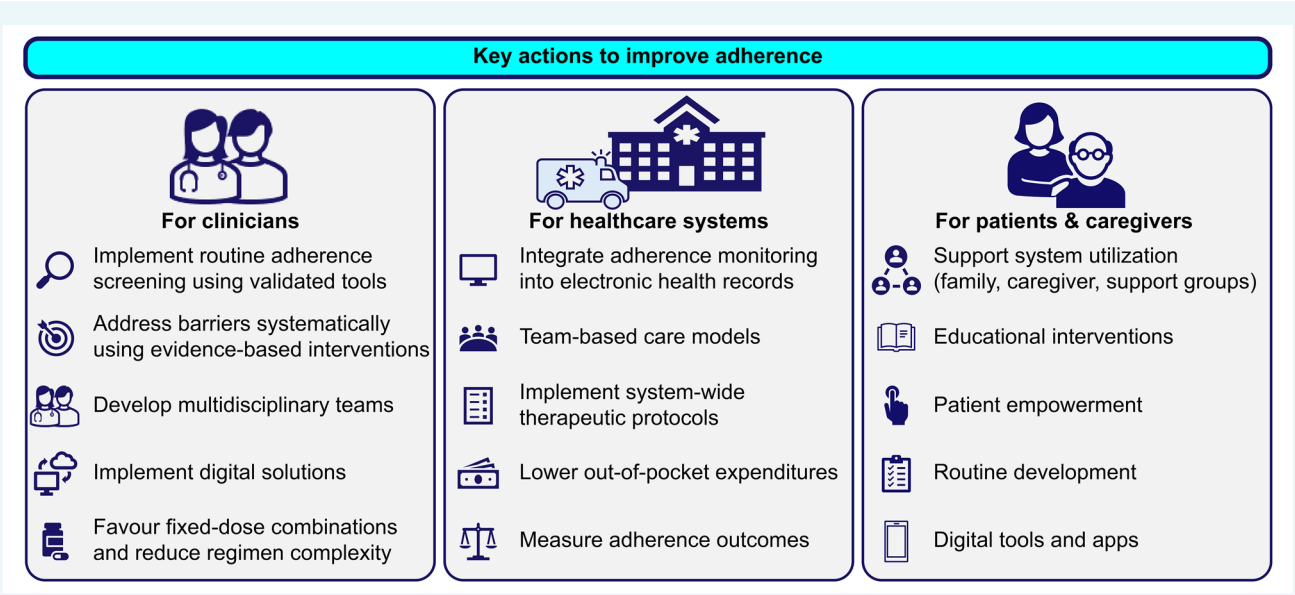

Figure 3 Key actions to improve adherence.

mortality.[135] The intervention showed particular efficacy amongst previously non-adherent patients, suggesting targeted implementation may optimize clinical outcomes. Health applications coupled with gamification might represent one further strategy to foster adherence in patients with HF.

This digital ecosystem represents a paradigm shift from the episodic assessment of adherence to continuous, personalized monitoring and interventions that address the medication-taking behaviours in HF.

Pharmacological strategies: reducing pill count and regimen complexity

Patients with HF are often prescribed with several pills often multiple times a day. Complexity of treatment regimens has been implicated as a contributor to non-adherence.[136] Some of this complexity can be addressed by de-prescribing and rationalization of therapies that are unnecessary or deemed of low priority for the patient.[83] In some cases, simplification of the treatment regimen can also be achieved by shifting to drugs with long half-lives or administering medications once daily.[137,138]

Single pill combinations—pills that contain ≥2 drug classes used to treat a single or multiple diseases—reduce pill count and patient's confusion regarding complex medication schedules, leading to improved adherence. Several trials have demonstrated that polypills can improve adherence and outcomes when implemented in cardiovascular and non-cardiovascular disease areas.[139] A meta-analysis including eight randomized trials examining polypill interventions on cardiovascular disease outcomes found that the use of polypills led to a 31% improved adherence and 10% lower risk of all-cause mortality.[140] From a health economics perspective, polypills may reduce costs through reduced dispensing fees and decreased healthcare utilization.[141]

As the HF therapeutic landscape evolves towards increasingly sophisticated polypharmacy regimens, polypills may represent a pragmatic strategy to enhance therapeutic adherence whilst simultaneously addressing several established barriers to optimal medication-taking behaviour. Although there is no specific supporting evidence in HF, there is no need, from a regulatory and scientific standpoint, of specific demonstration of benefit when used as substitution therapy (use in patients that are already receiving the free drugs). In HFrEF, where (1) three out of four HFrEF drugs require dose up-titration, (2) target doses might not be reached because of tolerability issues, (3) disease status (symptoms, blood pressure, heart rate, renal function, serum potassium) might change over time impacting the maximally tolerated doses, and (4) whether side effects or tolerability issues occur, the identification of the responsible drug could be challenging. Therefore, a polypill including more than two compounds could be more likely considered for therapeutic maintenance rather than for the initiation/implementation phase. When maximally tolerated dose of GDMT is achieved and stable, individual pills could be replaced with a polypill, leading to simplify medication self-management and a reduction in the daily pill burden.[81] Two RCTs are currently testing polypills in HFrEF (NCT04633005, NCT06029712). Using polypill also for initiating therapy might be simpler in patients with HFpEF where only two foundational therapies are available, with SGLT2i not being in need of up-titration and MRAs being available in limited dosages.

Reducing cost

Higher co-payment has been associated with lower adherence in patients with HF.[56,82,98] Medication-related costs for patients may be reduced by adopting polypills, lower co-payment, and patient assistance programmes. Such methods have been associated with improved adherence of treatments for a range of diseases.[99–101,142]

In cases where the prescribed medication is not affordable for the patient, a lower-cost alternative should be discussed, such as an ACEi/ARB instead of ARNi.

Gaps and future perspectives

The systematic implementation of patient-reported adherence measures would likely improve the identification of non-adherence in most settings. Ideally, this might be coupled with more objective measures of adherence, such as routine assessment of pharmacy refill data or adoption of MEMS in scenarios where outcomes might be highly sensitive to small deviations in adherence. These administrative data allow identification of gaps in prescription refills, flagging patients at risk for non-adherence. While indirect, such measures are increasingly used in large-scale adherence research and health system performance monitoring. However, their routine clinical use remains limited in many healthcare settings due to system fragmentation, data accessibility issues, or lack of integration with clinical workflows. Multidisciplinary involvement in HF care and follow-up is one tool to improve adherence, and there remain gaps in their implementation across Europe.

Future studies are needed to determine the appropriate cut-offs to define clinically meaningful non-adherence with these approaches. Beyond assessing adherence upon a clinical encounter, the increasing amounts of data available in electronic health records might enable systematic screening for non-adherence between encounters. Such approaches need to be rigorously evaluated in properly randomized strategy-based trials.[21,143,144]

With advancements in technology, digital solutions, including smartphone apps, telehealth platforms, and smart pillboxes, may support patients to improve adherence. However, future perspectives include integrating these digital tools into the healthcare system seamlessly and tailoring them to cater to diverse patient profiles. Ensuring accessibility and affordability of these digital solutions across different socioeconomic strata is a significant future goal. Additionally, the evolution of predictive analytics can help foresee non-adherence patterns, opening doors for preventive interventions.

Conclusions

Non-adherence to pharmacological medications is highly prevalent in HF and is associated with worse prognosis attenuating the benefits of evidence-based interventions. Recognizing non-adherence is key to addressing the problem and maximizing the clinical benefit observed in clinical trials to the general population of patients with HF.

Several interventional strategies are key when addressing and tackling non-adherence (*Figure 3*). Polypills substantially diminish regimen complexity whilst reducing polypharmacy, thereby addressing major determinants of non-adherence and, given their evidence in other cardiovascular settings, are strongly advocated also in the HF community. Structured educational programmes utilizing cognitive-behavioural principles and health literacy-appropriate methodologies may improve medication-taking behaviours. Multidisciplinary care paradigms, incorporating clinical pharmacists, specialist nurses and psychological support services that can provide comprehensive adherence support through monitoring, therapeutic adjustment and psychosocial intervention should be implemented wherever possible. Multifaceted interventions including educational programmes lead to improved adherence. Given the socioeconomic vulnerability characteristic of many HF patients, enhanced affordability through strategic formulary management, pharmaceutical assistance programmes and value-based insurance designs should be implemented to mitigate financial barriers to medication access in non-socialized healthcare system.

Key statements

- Non-adherence to HF medications is highly prevalent (20–80%) and independently associated with increased mortality and hospitalization risk.
- Monitoring of adherence should be integrated into routine clinical practice, and practical and effective methods for measuring non-adherence to treatments should be established.
- A comprehensive framework addressing patient, treatment, healthcare system, and social factors is required to improve adherence.
- Fixed-dose combinations of GDMT might improve adherence in stable patients with HF by reducing the pill burden.
- Digital tools, multidisciplinary care, multifaceted personalized interventions, and enhanced patient empowerment are useful for improving patients' adherence to medical treatment.

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