

Review Article

Open Access

Therapeutic Optimization in Elderly Patients with Heart Failure and Reduced Ejection Fraction: Real-World Evidence and the Importance of Timing

Gonzalo Martínez de las Cuevas^{1,2*}

¹Servicio de Medicina Interna, Hospital Universitario Marqués de Valdecilla, Santander, Cantabria, Spain

²Departamento de Medicina y Psiquiatría, Universidad de Cantabria, Spain

Article Info

Article Notes

Received: January 13th, 2026

Accepted: March 4th, 2026

*Correspondence:

Dr. Gonzalo Martínez de las Cuevas, Servicio de Medicina Interna, Hospital Universitario Marqués de Valdecilla, Santander, Cantabria, Spain; Departamento de Medicina y Psiquiatría, Universidad de Cantabria, Spain; Email: gomartinezdelascuevas@gmail.com.

© 2026 Martínez de las Cuevas G. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License.

Abstract

Heart failure with reduced ejection fraction (HFrEF) is highly prevalent among elderly patients, who frequently present with multimorbidity and frailty and are therefore at very high risk of hospitalization and mortality. Despite strong evidence supporting guideline-directed medical therapy (GDMT), therapeutic optimization remains suboptimal in this population, largely due to concerns regarding tolerability and comorbidities.

Emerging real-world data suggest that the early post-discharge period may represent a critical **“window of opportunity”** for therapeutic optimization in elderly patients with HFrEF. In this very high-risk population, early initiation and structured titration of disease-modifying therapies may confer substantial absolute benefits, potentially greater than those observed in lower-risk profiles, although this hypothesis requires further investigation.

This mini-review summarizes current evidence on GDMT implementation in elderly patients with HFrEF, with a focus on real-world experience, barriers to optimization, and the prognostic relevance of reducing heart failure hospitalizations. Unresolved controversies regarding patient selection, frailty, and outcome prioritization are discussed. Overall, available evidence suggests that age alone should not preclude therapeutic optimization and that structured, individualized approaches during this early phase may improve outcomes in elderly patients with HFrEF.

Heart Failure with Reduced Ejection Fraction in the Elderly Multimorbid Patient: An Unmet Clinical Need

Heart failure with reduced ejection fraction (HFrEF) remains a major cause of morbidity, hospitalization, and mortality worldwide, with a disproportionate burden among elderly patients. Population ageing has led to a growing number of patients with HFrEF characterized by advanced age, multimorbidity, and frailty, a profile associated with worse outcomes and increased healthcare utilization. Both European and American guidelines acknowledge that elderly patients represent the majority of heart failure admissions in routine practice, despite being underrepresented in pivotal randomized trials^{1,2}.

Current guidelines strongly recommend early initiation of guideline-directed medical therapy (GDMT), yet recognize the limited direct evidence in very old or complex patients^{1,2}. This gap contributes to uncertainty in clinical decision-making and often results in therapeutic conservatism. Comorbidities such as chronic kidney disease, diabetes, and anemia, together with polypharmacy

and functional impairment, are frequently perceived as barriers to treatment escalation.

However, the benefits of guideline-directed medical therapy in heart failure with reduced ejection fraction are supported by multiple large randomized clinical trials, which demonstrated consistent reductions in mortality and heart failure hospitalizations across broad patient populations³⁻⁷. Subgroup and post-hoc analyses from these trials further suggest that the relative benefits of guideline-directed medical therapy are largely preserved across age groups, even though absolute risks may be higher in older patients⁸⁻¹¹. Importantly, contemporary definitions of heart failure do not identify chronological age as a determinant of left ventricular ejection fraction recovery. This observation supports the concept that elderly patients may retain a meaningful potential for reverse remodeling when treated with optimized disease-modifying therapy¹².

This scenario raises a fundamental question for contemporary cardiology: are age and multimorbidity true biological limits to therapeutic optimization, or do they identify a subgroup of patients at very high risk in whom the potential absolute benefit of early intervention may be even greater? In elderly patients recently hospitalized for HFrEF, the immediate post-discharge period may represent a particularly vulnerable phase, but also a critical opportunity to modify the trajectory of the disease.

From Guidelines to Real-World Practice: Barriers to Therapeutic Optimization

Contemporary heart failure guidelines advocate the early use of multiple disease-modifying therapies, including renin-angiotensin system inhibition or angiotensin receptor-neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors^{1,2}. Landmark trials such as PARADIGM-HF, DAPA-HF, EMPEROR-Reduced, RALES, and MERIT-HF consistently demonstrated significant reductions in mortality and heart failure hospitalizations with these agents³⁻⁷.

Despite this robust evidence, real-world studies consistently show that the implementation of guideline-directed medical therapy remains suboptimal, particularly among elderly patients¹¹. Barriers include fragmented transitions of care after hospital discharge, the absence of structured titration pathways, and limited resources for close follow-up. In older patients, these system-level limitations are frequently compounded by concerns regarding hypotension, renal dysfunction, electrolyte disturbances, and clinically relevant pharmacological interactions.

Crucially, reluctance to intensify therapy is often driven by anticipated rather than observed adverse effects,

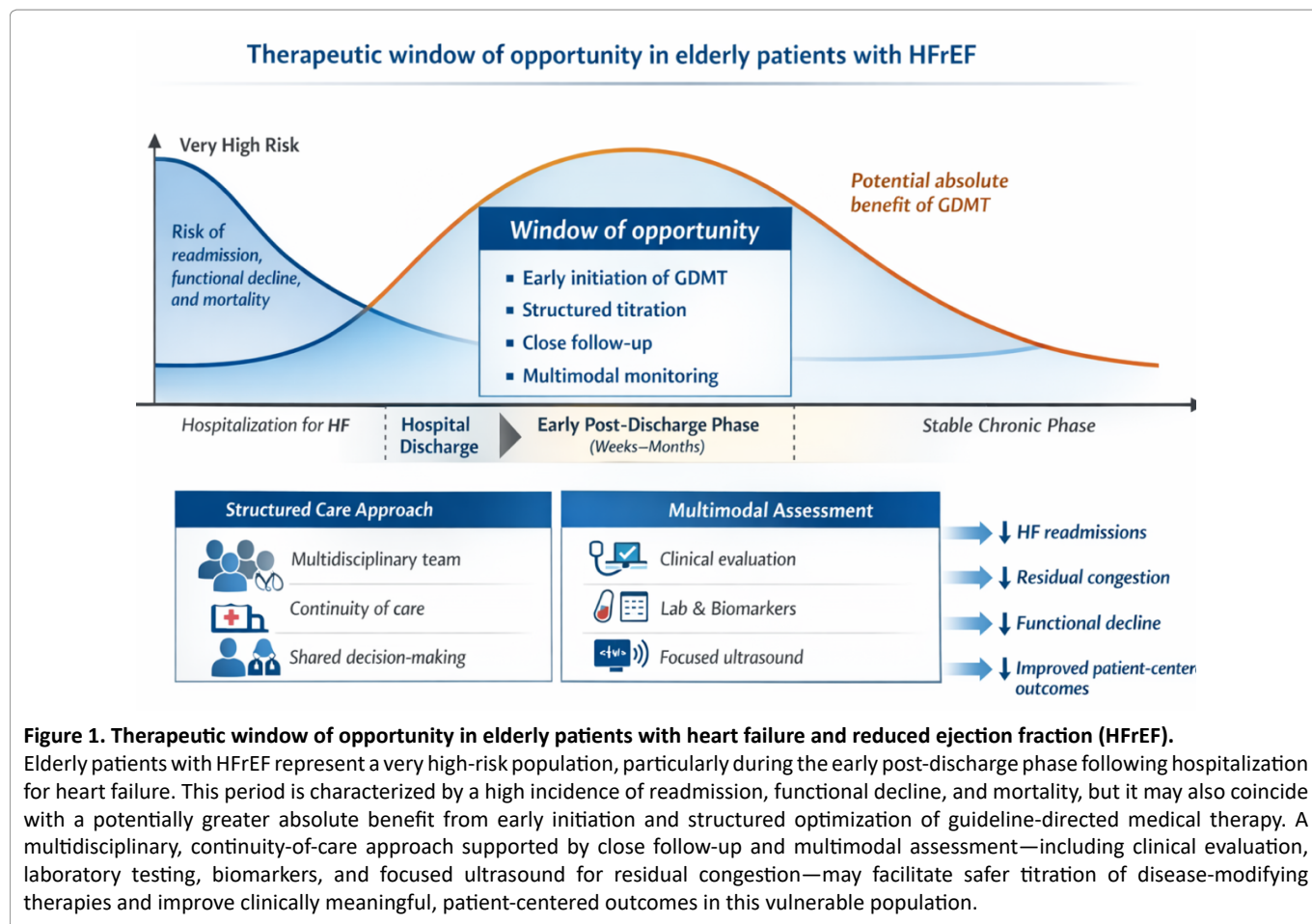
reflecting a degree of therapeutic nihilism in elderly and multimorbid patients. However, observational data suggest that many older patients tolerate guideline-directed medical therapy reasonably well when treatments are introduced gradually and monitored closely, even in the presence of comorbidities.^{8,9,13}

In this context, timing emerges as a central determinant of therapeutic success. The period following hospital discharge is characterized by a high incidence of early readmissions and adverse events, particularly in elderly and multimorbid patients. Although this phase is frequently perceived as clinically unstable, it may also represent a strategic opportunity to initiate and structure disease-modifying therapies under close supervision, potentially maximizing absolute benefit while minimizing treatment-related risk.¹³

Real-world Evidence: Feasibility, Timing and Clinical Meaning of Optimization

Evidence derived from registries and observational studies provides essential insight into the applicability of therapeutic optimization in elderly and multimorbid patients with HFrEF, a population traditionally underrepresented in randomized clinical trials¹¹. These data indicate that, within structured care settings, a substantial proportion of older patients can achieve meaningful exposure to disease-modifying therapies, although often without reaching the target doses used in pivotal trials. This observation challenges the notion that advanced age alone constitutes a major barrier to therapeutic optimization, particularly when frailty and functional status are taken into account.^{14,15}

A consistent finding across real-world studies is the importance of timing. Additional pragmatic and observational analyses further support the feasibility of early GDMT initiation and structured titration in high-risk patients under close follow-up.^{11,13} Unlike the controlled environment of clinical trials, optimization in routine practice is a dynamic process that typically unfolds over several weeks, with residual congestion control playing a central role.¹⁶ In this context, the immediate post-discharge period emerges as a critical phase. In elderly patients with HFrEF—a very high-risk population—this phase is associated with a high incidence of early readmissions and adverse events, but it may also represent the phase in which the potential impact of therapeutic optimization is greatest, provided that treatment is initiated early and in a structured manner under close monitoring¹³ (Figure 1). In this setting, the concept of a “window of opportunity” reflects not only a temporal phase after hospital discharge, but also the convergence of very high baseline risk and the potential to meaningfully modify the subsequent clinical trajectory.



From a clinical perspective, reducing heart failure hospitalizations has particular relevance in older patients. Beyond serving as a traditional endpoint, each hospitalization is associated with functional decline, loss of independence, and increased mid-term mortality¹⁷. In this vulnerable population, even modest relative risk reductions may translate into meaningful absolute benefits. Although this hypothesis requires confirmation in prospective pragmatic studies, available evidence suggests that early therapeutic optimization in real-world settings is not only feasible but may be pivotal in altering the clinical trajectory of elderly patients with HFReF.

Practical Implications for Clinical Cardiology

Optimizing therapy in elderly patients with HFReF requires moving beyond chronological age as the primary determinant of treatment decisions. Instead, clinicians should integrate comorbidity burden, frailty, renal function, functional status, and patient preferences into a comprehensive and individualized assessment.^{14,15}

Early post-discharge follow-up represents a critical window for initiating and adjusting guideline-directed medical therapy. Evidence indicates that proactive follow-up and close clinical monitoring facilitate safer titration

and higher rates of therapeutic optimization, particularly in elderly patients at very high risk.¹⁷ Introducing disease-modifying therapies at low doses and prioritizing agents with the strongest prognostic impact may help balance efficacy and tolerability in this population. In practical terms, this structured approach may include planned early follow-up within 1–2 weeks after discharge, nurse-led titration pathways, and telehealth-supported monitoring to facilitate safe adjustment of therapy.

Importantly, the occurrence of mild or manageable adverse effects should prompt careful adjustment rather than premature discontinuation of therapy. In this setting, continuity of care supported by a multidisciplinary team—including physicians and specialized nurses—and the use of multimodal assessment tools are key elements for successful titration. Specialized heart failure nurses play a pivotal role in this process, particularly in therapy titration, patient education, and early identification of intolerance or clinical deterioration. Nurse-led heart failure programs have been associated with improved adherence to guideline-directed medical therapy and favorable clinical outcomes in patients with HFReF¹⁸. The integration of clinical evaluation with laboratory testing, renal and electrolyte monitoring, biomarkers, and focused

ultrasound assessment of residual congestion allows a more precise evaluation of clinical stability and may help reduce the risk of recurrent hospitalization in this vulnerable population.^{13-15,17}

Grey Areas and Unresolved Controversies

Despite growing evidence, several uncertainties persist regarding therapeutic optimization in elderly patients with HFrEF. One key controversy concerns whether all elderly patients should be treated with full combination therapy or whether tailored approaches are preferable in selected cases. The marked heterogeneity of ageing—in terms of comorbidity burden, frailty, functional status, and life expectancy—suggests that a one-size-fits-all strategy may not be appropriate.

Future advances may rely on the development of more refined patient phenotyping strategies that move beyond an exclusive focus on left ventricular ejection fraction. While LVEF remains a cornerstone for therapeutic decision-making, an overly “LVEF-centric” approach may fail to capture the biological and clinical complexity of elderly patients with heart failure. Integrating clinical, functional, biomarker-based, and congestion-related parameters may allow more individualized and clinically meaningful treatment strategies.

Another unresolved issue relates to outcome prioritization. Although mortality and hospitalization remain important endpoints, patient-centered outcomes—such as quality of life, preservation of functional independence, and treatment burden—are likely to be of paramount importance in elderly and frail individuals.^{14,15} In this context, therapeutic success may need to be redefined according to goals that align more closely with patient preferences and daily functioning.

Frailty assessment is increasingly recognized as a powerful prognostic marker in heart failure; however, standardized tools to guide therapeutic decisions in routine cardiology practice are still lacking.¹⁴ As a result, clinical judgment continues to play a central role, inevitably contributing to variability in care. Importantly, therapeutic optimization should be contextualized within the broader trajectory of advanced heart failure. In patients with limited life expectancy or severe frailty, integration of palliative care principles may be appropriate, focusing on symptom control and quality of life rather than aggressive titration. Identifying the transition from optimization-focused to comfort-focused care remains a critical clinical judgment.¹⁹

Whether elderly patients with very high baseline risk derive greater absolute benefit from early therapeutic optimization compared with lower-risk profiles remains a hypothesis that warrants confirmation in pragmatic prospective studies.

Conclusions and Future Perspectives

Available evidence indicates that therapeutic optimization in elderly patients with HFrEF is feasible and clinically meaningful when implemented through structured, individualized approaches. Age alone should not preclude the use of disease-modifying therapies supported by strong evidence.^{1,2,8-11}

Future research should focus on pragmatic studies incorporating patient-centered outcomes and evaluating care models designed to facilitate optimization in real-world settings. Emphasizing early follow-up, flexible titration strategies, and shared decision-making may help bridge the gap between guidelines and everyday clinical practice.

Collaborative models involving cardiologists and internists may be particularly suited to address the needs of elderly patients with HFrEF and multimorbidity.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726. doi:10.1093/eurheartj/ehab368
2. 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. *Circulation*. 2022;145(18):e895-e1032. doi:10.1161/CIR.0000000000001063
3. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077
4. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995-2008. doi:10.1056/NEJMoa1911303
5. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413-1424. doi:10.1056/NEJMoa2022190
6. 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. *N Engl J Med*. 1999;341(10):709-717.
7. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjeksus J, et al. Effect of metoprolol CR/XL in chronic heart failure: the MERIT-HF trial. *Lancet*. 1999;353(9169):2001-2007. doi:10.1016/S0140-6736(99)04440-2
8. Jhund PS, Fu M, Bayram E, Chen CH, Negrusz-Kawecka M, Rosenthal A, et al. Efficacy and safety of LCZ696 according to age: insights from PARADIGM-HF. *Eur Heart J*. 2015;36(38):2576-2584. doi:10.1093/eurheartj/ehv330
9. Martinez FA, Serenelli M, Nicolau JC, Petrie MC, Chiang CE, Tereshchenko S, et al. Efficacy and safety of dapagliflozin according to age in heart failure with reduced ejection fraction: insights from DAPA-HF. *Circulation*. 2020;141(2):100-111. doi:10.1161/CIRCULATIONAHA.119.044133
10. Butrous H, Hummel SL. Heart failure in older adults. *Can J Cardiol*. 2016;32(9):1140-1147. doi:10.1016/j.cjca.2016.05.005

11. 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(4):351-366. doi:10.1016/j.jacc.2018.04.070
12. Perea-Armijo J, López-Aguilera J, Sánchez-Prats R, Castillo-Domínguez JC, González-Manzanares R, Ruiz-Ortiz M, et al. Improvement of left ventricular ejection fraction in patients with heart failure and reduced ejection fraction: predictors and clinical impact. *Med Clin (Barc)*. 2023;161(1):1-10. doi:10.1016/j.medcli.2023.02.009
13. Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure with reduced ejection fraction. *Eur J Heart Fail*. 2021;23(6):882-894. doi:10.1002/ejhf.2149
14. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, et al. Frailty assessment in cardiovascular care. *J Am Coll Cardiol*. 2014;63(8):747-762. doi:10.1016/j.jacc.2013.09.070
15. Pandey A, Kitzman DW, Reeves GR. Frailty and heart failure: mechanisms, prevalence, prognostic implications, and management. *JACC Heart Fail*. 2019;7(12):1001-1011. doi:10.1016/j.jchf.2019.10.005
16. Selvaraj S, Claggett B, Pozzi A, McMurray JJV, Jhund PS, Packer M, et al. Prognostic implications of congestion on physical examination among contemporary patients with heart failure and reduced ejection fraction: insights from PARADIGM-HF. *Circulation*. 2019;140(17):1369-1379. doi:10.1161/CIRCULATIONAHA.119.039920
17. Gheorghade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: problems and perspectives. *J Am Coll Cardiol*. 2013;61(4):391-403. doi:10.1016/j.jacc.2012.09.038
18. Lopez-Aguilera J, Perea-Armijo J, Muñoz-Villarreal AB, Castillo-Domínguez JC, González-Manzanares R, Ruiz-Ortiz M, et al. Nurse-specialized consultation in heart failure: impact on drug titration and cardiovascular events in patients with heart failure and reduced ejection fraction. *J Clin Med*. 2025;14(18):6681. doi:10.3390/jcm14186681
19. Campbell RT, Petrie MC, Jackson CE, Jhund PS, Wright A, Gardner RS, et al. Which patients with heart failure should receive specialist palliative care? *Eur J Heart Fail*. 2018;20(9):1338-1347. doi:10.1002/ejhf.1240