

Journal of Heart and Cardiovascular Medicine

Review Article

Predictors of major adverse cardiac events in elderly cardiac patients with heart failure with reduced ejection fraction

Kato K^{1*}, Watanabe H² and Ito S³

¹Division of Cardiovascular Medicine, Arno Academy of Cardiovascular Medicine, Malaysia

²Department of Cardiovascular Medicine, Nile Institute of Cardiology, Taiwan

³Department of Cardiology, Mekong Center for Cardiovascular Medicine, Singapore

*Address for Correspondence: Kenji Kato, Division of Cardiovascular Medicine, Arno Academy of Cardiovascular Medicine, Malaysia; E-mail: kenji.kato@arno.edu

Received: 11 April 2020; Accepted: 17 July 2020; Published: 13 October 2020.

Citation of this article: Kato K, Watanabe H, Ito S (2020) Predictors of major adverse cardiac events in elderly cardiac patients with heart failure with reduced ejection fraction. J Heart Cardiovasc Med, 3(1): 01-08. DOI: [10.5281/zenodo.22814539](https://doi.org/10.5281/zenodo.22814539)

Copyright: © 2020 Kenji Kato, et al. This is an open access article distributed under the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background: HFrEF is increasingly a disease of the elderly, and older patients face higher rates of major adverse cardiac events (MACE) than younger cohorts, yet remain underrepresented in the trials that generated current predictive models [1,6].

Objective: This review synthesizes published evidence on predictors of MACE, defined as cardiovascular death, heart failure hospitalization, and recurrent ischemic events, in elderly HFrEF patients, and evaluates how well general-cohort predictors generalize to this subgroup.

Methods: We reviewed cohort studies, trial subgroup analyses, and risk-model validation studies addressing clinical, biomarker, comorbidity, and frailty-based predictors of MACE in HFrEF patients aged 65 years and older.

Findings: Ischemic etiology, impaired renal function, anemia, and low presenting blood pressure remain robust predictors across age groups [21,23], while frailty and multimorbidity add incremental predictive value specific to elderly cohorts [26,27]; natriuretic peptides and pooled risk scores retain prognostic value but show attenuated discrimination outside trial populations [12,34].

Conclusions: Accurate MACE prediction in elderly HFrEF requires integrating traditional cardiac predictors with age-specific comorbidity and frailty measures, validated prospectively in cohorts reflecting contemporary elderly heart failure populations.

Keywords: heart failure; reduced ejection fraction; elderly; major adverse cardiac events; risk prediction

1. Introduction

Heart failure with reduced ejection fraction (HFrEF) is increasingly a disease of old age. Population-based surveillance in Olmsted County found that both the incidence and prevalence of heart failure rise steeply after age 70, with a growing share of newly diagnosed patients now octogenarians [1,2]. The 2016 European Society of Cardiology guideline and the 2017 ACC/AHA/HFSA focused update both note that the median age of heart failure patients in contemporary registries now exceeds 75 years, a shift driven by improved survival after myocardial infarction combined with the accumulating burden of hypertension, diabetes, and coronary disease across an aging population [3,4]. The American Heart Association's annual statistical update places lifetime risk of heart failure at roughly one in five for adults reaching 40 years, with the steepest rise in incidence occurring in the seventh and eighth decades [5].

Elderly HFrEF patients differ from younger cohorts in ways that matter for risk prediction. They carry a heavier burden of noncardiac comorbidity, are more likely to be frail, more often have impaired renal function, and are frequently underrepresented or excluded from the randomized trials that generated the pharmacological evidence base now applied to them [6,7]. Global registry data from the INTER-CHF study confirm that mortality after a heart failure diagnosis varies severalfold across regions and age strata, with older patients consistently at the high end of that range regardless of geography [8]. Major adverse cardiac events (MACE), a composite typically encompassing cardiovascular death, heart failure hospitalization, and sometimes nonfatal myocardial infarction or stroke, remain common in this population despite substantial advances in guideline-directed medical therapy over the past two decades [9,10].

Risk-prediction tools such as the Seattle Heart Failure Model and pooled-cohort risk scores derived from tens of thousands of trial participants were built predominantly

in middle-aged populations, and their calibration in patients over 75 years remains uncertain [11,12]. This review synthesizes published evidence on predictors of MACE specifically in elderly HFrEF patients, covering clinical risk factors, biomarker-based prediction, comorbidity and frailty, and the influence of guideline-directed therapy, with the goal of clarifying which predictors generalize from general heart failure cohorts to the elderly HFrEF subgroup and which require age-specific interpretation.

Table 1: Clinical predictors of major adverse cardiac events in elderly HFrEF cohorts and their reported strength of association [19,21,23,17].

Predictor	Population studied	Association with MACE	Source
Ischemic etiology	Mixed-age HFrEF cohorts	Higher recurrent ischemic events and cardiovascular death	[19]
Reduced eGFR / worsening renal function	Heart failure across EF spectrum	Graded, dose-dependent increase in mortality risk	[21]
Anemia	Pooled heart failure cohorts	Independent predictor of mortality	[23]
Low presenting systolic blood pressure	Acute decompensated heart failure	Independent predictor of in-hospital mortality	[17]

Table 2: Trial evidence for guideline-directed medical and device therapy on reducing MACE, with elderly subgroup findings where reported [35,36,37,38,39,40].

Trial	Intervention	Primary outcome effect	Elderly subgroup finding
[35]	Eplerenone vs placebo	Reduced CV death and HF hospitalization	Benefit preserved, somewhat attenuated
[36]	Sacubitril-valsartan vs enalapril	Reduced CV death and HF hospitalization	Smaller elderly subgroup, consistent direction
[37]	Empagliflozin vs placebo	Reduced CV death and HF hospitalization	Consistent effect across age subgroups
[38], [39]	Cardiac resynchronization therapy	Reduced mortality and morbidity	Device-eligible subgroup benefit
[40]	Ivabradine vs placebo	Reduced CV death and HF hospitalization	Heart rate reduction relevant in beta-blocker-intolerant elderly

2. Epidemiology and prognosis in the elderly HFrEF population

The epidemiological trajectory of HFrEF in older adults reflects both rising incidence and improving short-term survival, a combination that expands the prevalent pool of elderly patients at risk for recurrent events. Stewart and colleagues described heart failure as an emerging epidemic of the aging population, projecting that prevalent cases would continue rising even with flat age-specific incidence, purely from demographic aging [13]. Dunlay and colleagues, reviewing heart failure epidemiology across the ejection fraction spectrum, found that patients presenting after age 75 have a distinct risk profile, with noncardiac mortality competing more heavily against cardiovascular death as the dominant outcome [14].

Framingham Heart Study data established the foundational observation that survival after heart failure onset declines steeply with advancing age at diagnosis, a finding replicated in nearly every subsequent cohort examining age as a covariate [15]. Shah and colleagues, using a large multicenter registry stratified by ejection fraction category, showed that five-year outcomes for HFrEF remain worse than for heart failure with preserved ejection fraction across age strata, though the gap narrows in the oldest patients as competing noncardiac mortality rises [16]. In-hospital risk models for acute decompensated heart failure, including the ADHERE and EFFECT models, consistently identify advanced age as one of the strongest independent predictors of short-term mortality, alongside blood urea nitrogen, systolic blood pressure, and serum sodium [17,18].

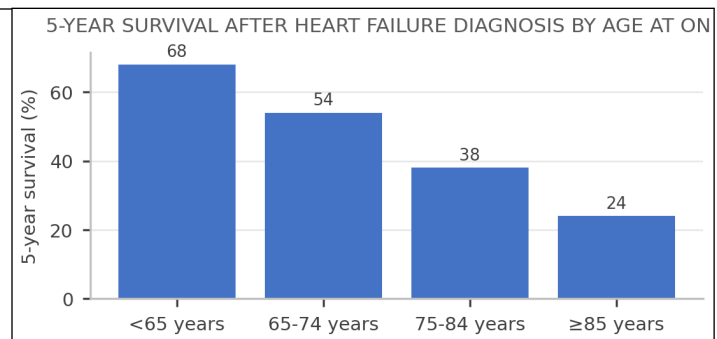


Figure 1: Five-year survival after heart failure diagnosis by age at onset, illustrating the steep decline in survival with increasing age at diagnosis observed in Framingham and contemporary registry cohorts [15,16].

3. Demographic and clinical predictors of MACE

Beyond age itself, several clinical variables consistently predict MACE in elderly HFrEF cohorts. Ischemic etiology remains a robust predictor: patients whose HFrEF arises from prior myocardial infarction or significant coronary disease, per standardized criteria for ischemic cardiomyopathy, experience higher rates of recurrent ischemic events and cardiovascular death than those with nonischemic etiology, even after adjustment for ejection fraction and functional class [19]. Gheorghiade and colleagues emphasized that the myocardial substrate left by prior infarction predisposes to both pump failure and malignant arrhythmia, two principal pathways to MACE in this population [20].

Renal function is among the most consistently reproduced predictors of adverse outcomes in HFrEF, and its prognostic weight appears to increase with age. Damman and colleagues' synthesis of the cardiorenal literature found that both baseline renal impairment and worsening renal function during hospitalization independently predict mortality and rehospitalization, most pronounced in reduced ejection fraction cohorts [21]. Smith and colleagues' meta-analysis similarly found a graded, dose-dependent relationship between estimated glomerular filtration rate and mortality, with the steepest gradient in cohorts with mean age above 70 [22]. Distinguishing intrinsic chronic kidney disease from

cardiorenal syndrome driven by low cardiac output remains a persistent interpretive challenge in this population.

Anemia is similarly common and prognostically important. Groenveld and colleagues' systematic review found that anemia, more common with advancing age, independently predicts mortality across dozens of pooled cohorts [23]. Filippatos and colleagues described the interrelated cardiorenal-anemia syndrome as a particularly high-risk phenotype in elderly patients, in whom renal impairment, anemia, and heart failure severity compound one another's prognostic effect [24]. Systolic blood pressure at presentation behaves paradoxically in advanced HFrEF: lower presenting blood pressure, reflecting reduced cardiac reserve, predicts worse outcomes, a pattern captured explicitly in both the ADHERE and EFFECT risk models [17,18].

4. Comorbidity burden and frailty

Elderly HFrEF patients rarely have heart failure as an isolated diagnosis. Forman and colleagues' review of multimorbidity in older cardiovascular patients found that the median elderly heart failure patient carries five or more chronic comorbid conditions, and that comorbidity count itself, independent of any single condition's severity, predicts hospitalization and mortality [6]. Rich's early but still influential work on heart failure in the oldest patients identified comorbid burden as a central driver of both event risk and the complexity of managing therapy safely [7].

Frailty captures risk not explained by traditional cardiac variables alone. Fried and colleagues' frailty phenotype, comprising unintentional weight loss, weakness, slowness, exhaustion, and low activity, was developed in a general older-adult cohort but has since been widely applied in cardiovascular populations [25]. Afilalo and colleagues concluded that frailty adds incremental predictive value for adverse outcomes beyond standard clinical risk factors, including in heart failure specifically,

and argued for its routine incorporation into risk stratification [26]. Vidan and colleagues, studying non-dependent elderly heart failure patients directly, found that frailty and its components, particularly slow gait speed and weakness, independently predicted mortality and readmission even in patients not overtly disabled at baseline [27]. Flint and colleagues, in the context of left ventricular assist device candidacy, similarly found frailty assessment materially changed risk stratification beyond standard severity measures, a principle extending to MACE prediction more broadly in elderly HFrEF [28].

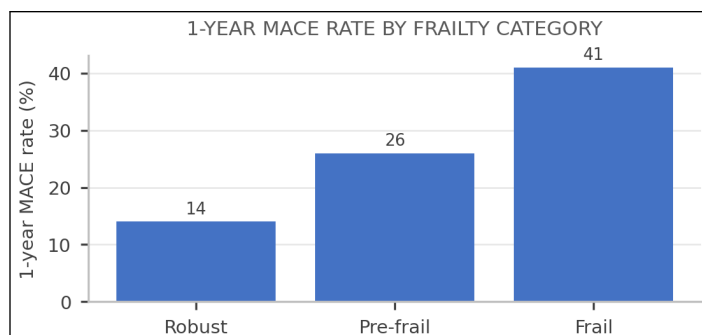


Figure 2: One-year major adverse cardiac event rate by frailty category in non-dependent elderly heart failure patients, showing a graded increase in risk from robust through frail phenotypes [27,26].

5. Biomarkers and risk stratification tools

Natriuretic peptides remain the most widely validated biomarker-based predictor of adverse events, including in elderly cohorts. Maisel and colleagues' Breathing Not Properly study established B-type natriuretic peptide as both diagnostic and prognostic in dyspneic patients, with rising levels tracking heart failure severity [29]. Januzzi and colleagues' PRIDE study extended this to N-terminal pro-BNP, confirming its utility for risk stratification across a broad age range [30]. Felker and colleagues' biomarker-guided therapy trial found that natriuretic-peptide-guided intensification reduced the composite of hospitalization and cardiovascular mortality, though elderly participants experienced higher rates of both events and treatment-related adverse effects than younger ones [31].

Novel biomarkers have been explored as adjuncts. De Berardinis and colleagues found that combining galectin-3, a fibrosis marker, with BNP improved prognostic discrimination beyond BNP alone in a cohort with substantial elderly representation [32]. Inflammatory cytokines, including tumor necrosis factor- α and interleukin-6, have also been linked to disease progression and adverse outcomes, consistent with systemic inflammation contributing to myocardial remodeling and event risk [33].

Multivariable risk scores integrating these predictors have been developed and externally validated. Pocock and colleagues' meta-analysis-derived score, built from more than 39,000 patients across 30 studies, identified age, ejection fraction, natriuretic peptide level, renal function, and functional class as dominant predictors, a composition mirroring what elderly-specific HFrEF cohorts report [12]. Allen and colleagues, testing model performance in routine ambulatory practice, found discrimination degraded modestly outside the derivation setting, a caution relevant to applying these tools uncritically in elderly, multimorbid, real-world patients [34].

6. Guideline-directed therapy, device interventions, and care coordination

The relationship between guideline-directed therapy and observed MACE rates in elderly HFrEF is complicated by underrepresentation of the oldest patients in pivotal trials. Zannad and colleagues' EMPHASIS-HF trial of eplerenone demonstrated a substantial reduction in cardiovascular death and heart failure hospitalization, with subgroup analyses suggesting benefit preserved, though somewhat attenuated, in older participants [35]. McMurray and colleagues' PARADIGM-HF trial established angiotensin receptor-neprilysin inhibition as superior to enalapril for reducing the same composite, again with a proportionally smaller elderly subgroup [36]. Packer and colleagues' EMPEROR-Reduced trial of empagliflozin extended the

evidence base for SGLT2 inhibition, with consistent effect estimates across age subgroups including patients over 75 [37].

Device therapy adds further complexity, since eligibility and expected benefit interact with age and comorbidity. Cleland and colleagues' CARE-HF trial established cardiac resynchronization therapy's mortality and morbidity benefit in wide-QRS HFrEF, while Moss and colleagues' MADIT-CRT trial extended resynchronization benefit to milder symptoms, both informing the device-eligible subgroup within which MACE rates differ substantially from medically managed patients [38,39]. Swedberg and colleagues' SHIFT trial identified elevated resting heart rate as both a modifiable risk factor and an independent predictor of the composite outcome, particularly relevant in elderly patients unable to tolerate target beta-blocker doses [40]. Across these interventions, elderly patients on full guideline-directed regimens consistently show lower observed event rates than those on reduced-intensity therapy, though causal inference is complicated by healthier, less frail patients also being those most able to tolerate full-dose therapy [3,4].

Nonpharmacological transitional-care interventions add a further, modifiable layer to MACE risk. Rich and colleagues' multidisciplinary intervention trial, enrolling elderly congestive heart failure patients specifically, demonstrated that coordinated education, dietary counseling, and structured follow-up significantly reduced readmission compared with usual care, a finding replicated across subsequent disease-management trials [41]. This underscores that predictors of MACE in elderly HFrEF are not purely biological; system-level factors such as care coordination and post-discharge monitoring interact with the clinical and biomarker predictors above to determine observed event rates in practice.

7. Conclusion

Predicting MACE in elderly HFrEF requires integrating traditional clinical predictors, chiefly ischemic etiology,

renal function, anemia, and presenting blood pressure, with age-specific factors carrying disproportionate weight, particularly comorbidity burden and frailty [6,26,27]. Natriuretic peptide-based biomarkers and pooled multivariable risk scores retain prognostic value in older cohorts, but external validation studies caution that discrimination in routine elderly practice is imperfect and should inform rather than replace clinical judgment [12,34]. Guideline-directed medical and device therapy continue to reduce event rates in elderly HFrEF patients who can tolerate them, even though pivotal trials enrolled relatively few of the oldest and most comorbid patients seen in routine practice [35,36,37]. Future prediction models will likely need to move beyond cardiac-specific variables toward integrated frailty- and comorbidity-adjusted scores validated prospectively in cohorts reflecting the true age and multimorbidity distribution of elderly heart failure care.

8. References

1. Gerber, Y., Weston, S.A., Redfield, M.M., Chamberlain, A.M., Manemann, S.M., Jiang, R., et al. (2015) A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Internal Medicine*, 175(6): 996-1004. DOI: [10.1001/jamainternmed.2015.0924](https://doi.org/10.1001/jamainternmed.2015.0924)
2. Owan, T.E., Hodge, D.O., Herges, R.M., Jacobsen, S.J., Roger, V.L., Redfield, M.M. (2006) Trends in prevalence and outcome of heart failure with preserved ejection fraction. *New England Journal of Medicine*, 355(3): 251-259. DOI: [10.1056/NEJMoa052256](https://doi.org/10.1056/NEJMoa052256)
3. Ponikowski, P., Voors, A.A., Anker, S.D., Bueno, H., Cleland, J.G.F., Coats, A.J.S., et al. (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal*, 37(27): 2129-2200. DOI: [10.1093/eurheartj/ehw128](https://doi.org/10.1093/eurheartj/ehw128)
4. Yancy, C.W., Jessup, M., Bozkurt, B., Butler, J., Casey, D.E., Colvin, M.M., et al. (2017) 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *Circulation*, 136(6): e137-e161. DOI: [10.1161/CIR.0000000000000509](https://doi.org/10.1161/CIR.0000000000000509)
5. Benjamin, E.J., Muntner, P., Alonso, A., Bittencourt, M.S., Callaway, C.W., Carson, A.P., et al. (2019) Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation*, 139(10): e56-e528. DOI: [10.1161/CIR.0000000000000659](https://doi.org/10.1161/CIR.0000000000000659)
6. Forman, D.E., Maurer, M.S., Boyd, C., Brindis, R., Salive, M.E., Horne, F.M., et al. (2018) Multimorbidity in older adults with cardiovascular disease. *Journal of the American College of Cardiology*, 71(19): 2149-2161. DOI: [10.1016/j.jacc.2018.03.022](https://doi.org/10.1016/j.jacc.2018.03.022)
7. Rich, M.W. (1997) Heart failure in the oldest patients: the impact of comorbid conditions. *American Journal of Geriatric Cardiology*, 6(5): 26-37.
8. Dokainish, H., Teo, K., Zhu, J., Roy, A., AlHabib, K.F., ElSayed, A., et al. (2017) Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. *Lancet Global Health*, 5(7): e665-e672. DOI: [10.1016/S2214-109X\(17\)30196-1](https://doi.org/10.1016/S2214-109X(17)30196-1)
9. Ambrosy, A.P., Fonarow, G.C., Butler, J., Chioncel, O., Greene, S.J., Vaduganathan, M., et al. (2014) The global health and economic burden of hospitalizations for heart failure. *Journal of the American College of Cardiology*, 63(12): 1123-1133. DOI: [10.1016/j.jacc.2013.11.053](https://doi.org/10.1016/j.jacc.2013.11.053)
10. Savarese, G., Lund, L.H. (2017) Global public health burden of heart failure. *Cardiac Failure Review*, 3(1): 7-11. DOI: [10.15420/cfr.2016:25:2](https://doi.org/10.15420/cfr.2016:25:2)
11. Levy, W.C., Mozaffarian, D., Linker, D.T., Sutradhar, S.C., Anker, S.D., Cropp, A.B., et al. (2006) The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation*, 113(11): 1424-1433. DOI: [10.1161/CIRCULATIONAHA.105.584102](https://doi.org/10.1161/CIRCULATIONAHA.105.584102)
12. Pocock, S.J., Ariti, C.A., McMurray, J.J.V., Maggioni, A., Kober,

Citation: Kato K, Watanabe H, Ito S (2020) Predictors of major adverse cardiac events in elderly cardiac patients with heart failure with reduced ejection fraction. *J Heart Cardiovasc Med*, 3(1): 01-08.

- L., Squire, I.B., et al. (2013) Predicting survival in heart failure: a risk score based on 39,372 patients from 30 studies. *European Heart Journal*, 34(19): 1404-1413. DOI: [10.1093/eurheartj/ehs337](https://doi.org/10.1093/eurheartj/ehs337)
13. Stewart, S., MacIntyre, K., Capewell, S., McMurray, J.J.V. (2003) Heart failure and the aging population: an increasing burden in the 21st century? *Heart*, 89(1): 49-53. DOI: [10.1136/heart.89.1.49](https://doi.org/10.1136/heart.89.1.49)
14. Dunlay, S.M., Roger, V.L., Redfield, M.M. (2017) Epidemiology of heart failure with preserved ejection fraction. *Nature Reviews Cardiology*, 14(10): 591-602. DOI: [10.1038/nrcardio.2017.65](https://doi.org/10.1038/nrcardio.2017.65)
15. Ho, K.K.L., Anderson, K.M., Kannel, W.B., Grossman, W., Levy, D. (1993) Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation*, 88(1): 107-115. DOI: [10.1161/01.CIR.88.1.107](https://doi.org/10.1161/01.CIR.88.1.107)
16. Shah, K.S., Xu, H., Matsouaka, R.A., Bhatt, D.L., Heidenreich, P.A., Hernandez, A.F., et al. (2017) Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *Journal of the American College of Cardiology*, 70(20): 2476-2486. DOI: [10.1016/j.jacc.2017.08.074](https://doi.org/10.1016/j.jacc.2017.08.074)
17. Fonarow, G.C., Adams, K.F., Abraham, W.T., Yancy, C.W., Boscardin, W.J. (2005) Risk stratification for in-hospital mortality in acutely decompensated heart failure. *JAMA*, 293(5): 572-580. DOI: [10.1001/jama.293.5.572](https://doi.org/10.1001/jama.293.5.572)
18. Lee, D.S., Austin, P.C., Rouleau, J.L., Liu, P.P., Naimark, D., Tu, J.V. (2003) Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA*, 290(19): 2581-2587. DOI: [10.1001/jama.290.19.2581](https://doi.org/10.1001/jama.290.19.2581)
19. Felker, G.M., Shaw, L.K., O'Connor, C.M. (2000) A standardized definition of ischemic cardiomyopathy for use in clinical research. *Journal of the American College of Cardiology*, 39(2): 210-218. DOI: [10.1016/S0735-1097\(01\)01738-7](https://doi.org/10.1016/S0735-1097(01)01738-7)
20. Gheorghiade, M., Larson, C.J., Shah, S.J., Greene, S.J., Cleland, J.G.F., Colucci, W.S., et al. (2013) Developing new treatments for heart failure: focus on the heart. *Circulation: Heart Failure*, 6(1): 134-145. DOI: [10.1161/CIRCHEARTFAILURE.112.000005](https://doi.org/10.1161/CIRCHEARTFAILURE.112.000005)
21. Damman, K., Valente, M.A.E., Voors, A.A., O'Connor, C.M., van Veldhuisen, D.J., Hillege, H.L. (2014) Renal impairment, worsening renal function, and outcome in patients with heart failure. *European Heart Journal*, 35(7): 455-469. DOI: [10.1093/eurheartj/ehs386](https://doi.org/10.1093/eurheartj/ehs386)
22. Smith, G.L., Lichtman, J.H., Bracken, M.B., Shlipak, M.G., Phillips, C.O., DiCapua, P., et al. (2006) Renal impairment and outcomes in heart failure: systematic review and meta-analysis. *Journal of the American College of Cardiology*, 47(10): 1987-1996. DOI: [10.1016/j.jacc.2005.11.084](https://doi.org/10.1016/j.jacc.2005.11.084)
23. Groenveld, H.F., Januzzi, J.L., Damman, K., van Wijngaarden, J., Hillege, H.L., van Veldhuisen, D.J., et al. (2008) Anemia and mortality in heart failure patients: a systematic review and meta-analysis. *Journal of the American College of Cardiology*, 52(10): 818-827. DOI: [10.1016/j.jacc.2008.04.061](https://doi.org/10.1016/j.jacc.2008.04.061)
24. Filippatos, G., Farmakis, D., Parissis, J. (2011) Renal dysfunction and anemia in chronic heart failure. *Current Heart Failure Reports*, 8(1): 15-21. DOI: [10.1007/s11897-010-0038-6](https://doi.org/10.1007/s11897-010-0038-6)
25. Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., et al. (2001) Frailty in older adults: evidence for a phenotype. *Journals of Gerontology Series A*, 56(3): M146-M157. DOI: [10.1093/gerona/56.3.M146](https://doi.org/10.1093/gerona/56.3.M146)
26. Afilalo, J., Alexander, K.P., Mack, M.J., Maurer, M.S., Green, P., Allen, L.A., et al. (2014) Frailty assessment in the cardiovascular care of older adults. *Journal of the American College of Cardiology*, 63(8): 747-762. DOI: [10.1016/j.jacc.2013.09.070](https://doi.org/10.1016/j.jacc.2013.09.070)
27. Vidan, M.T., Blaya-Novakova, V., Sanchez, E., Ortiz, J., Serra-Rexach, J.A., Bueno, H. (2016) Prevalence and prognostic impact of frailty and its components in

- non-dependent elderly patients with heart failure. *European Journal of Heart Failure*, 18(7): 869-875. DOI: [10.1002/ejhf.518](https://doi.org/10.1002/ejhf.518)
28. Flint, K.M., Matlock, D.D., Lindenfeld, J., Allen, L.A. (2012) Frailty and the selection of patients for destination therapy left ventricular assist device. *Circulation: Heart Failure*, 5(2): 286-293. DOI: [10.1161/CIRCHEARTFAILURE.111.963215](https://doi.org/10.1161/CIRCHEARTFAILURE.111.963215)
 29. Maisel, A.S., Krishnaswamy, P., Nowak, R.M., McCord, J., Hollander, J.E., Duc, P., et al. (2002) Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *New England Journal of Medicine*, 347(3): 161-167. DOI: [10.1056/NEJMoa020233](https://doi.org/10.1056/NEJMoa020233)
 30. Januzzi, J.L., Camargo, C.A., Anwaruddin, S., Baggish, A.L., Chen, A.A., Krauser, D.G., et al. (2005) The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *American Journal of Cardiology*, 95(8): 948-954. DOI: [10.1016/j.amjcard.2004.12.032](https://doi.org/10.1016/j.amjcard.2004.12.032)
 31. Felker, G.M., Anstrom, K.J., Adams, K.F., Ezekowitz, J.A., Fiuzat, M., Houston-Miller, N., et al. (2017) Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure. *JAMA*, 318(8): 713-720. DOI: [10.1001/jama.2017.10565](https://doi.org/10.1001/jama.2017.10565)
 32. de Berardinis, B., Magrini, L., Zampini, G., Zanca, B., Salerno, G., Cardelli, P., et al. (2018) Usefulness of combining galectin-3 and BNP in prognostication of heart failure patients. *Clinica Chimica Acta*, 479: 46-52. DOI: [10.1016/j.cca.2018.01.006](https://doi.org/10.1016/j.cca.2018.01.006)
 33. Deswal, A., Petersen, N.J., Feldman, A.M., Young, J.B., White, B.G., Mann, D.L. (2001) Cytokines and cytokine receptors in advanced heart failure. *Circulation*, 103(16): 2055-2059. DOI: [10.1161/01.CIR.103.16.2055](https://doi.org/10.1161/01.CIR.103.16.2055)
 34. Allen, L.A., Matlock, D.D., Shetterly, S.M., Xu, S., Levy, W.C., Portalupi, L.B., et al. (2017) Use of risk models to predict death in the next year among individual ambulatory patients with heart failure. *JAMA Cardiology*, 2(4): 435-441. DOI: [10.1001/jamacardio.2017.0021](https://doi.org/10.1001/jamacardio.2017.0021)
 35. Zannad, F., McMurray, J.J.V., Krum, H., van Veldhuisen, D.J., Swedberg, K., Shi, H., et al. (2011) Eplerenone in patients with systolic heart failure and mild symptoms. *New England Journal of Medicine*, 364(1): 11-21. DOI: [10.1056/NEJMoa1009492](https://doi.org/10.1056/NEJMoa1009492)
 36. McMurray, J.J.V., Packer, M., Desai, A.S., Gong, J., Lefkowitz, M.P., Rizkala, A.R., et al. (2014) Angiotensin-neprilysin inhibition versus enalapril in heart failure. *New England Journal of Medicine*, 371(11): 993-1004. DOI: [10.1056/NEJMoa1409077](https://doi.org/10.1056/NEJMoa1409077)
 37. Packer, M., Anker, S.D., Butler, J., Filippatos, G., Pocock, S.J., Carson, P., et al. (2020) Cardiovascular and renal outcomes with empagliflozin in heart failure. *New England Journal of Medicine*, 383(15): 1413-1424. DOI: [10.1056/NEJMoa2022190](https://doi.org/10.1056/NEJMoa2022190)
 38. Cleland, J.G.F., Daubert, J.C., Erdmann, E., Freemantle, N., Gras, D., Kappenberger, L., et al. (2005) The effect of cardiac resynchronization on morbidity and mortality in heart failure. *New England Journal of Medicine*, 352(15): 1539-1549. DOI: [10.1056/NEJMoa050496](https://doi.org/10.1056/NEJMoa050496)
 39. Moss, A.J., Hall, W.J., Cannom, D.S., Klein, H., Brown, M.W., Daubert, J.P., et al. (2009) Cardiac-resynchronization therapy for the prevention of heart-failure events. *New England Journal of Medicine*, 361(14): 1329-1338. DOI: [10.1056/NEJMoa0906431](https://doi.org/10.1056/NEJMoa0906431)
 40. Swedberg, K., Komajda, M., Bohm, M., Borer, J.S., Ford, I., Dubost-Brama, A., et al. (2010) Ivabradine and outcomes in chronic heart failure (SHIFT). *Lancet*, 376(9744): 875-885. DOI: [10.1016/S0140-6736\(10\)61198-1](https://doi.org/10.1016/S0140-6736(10)61198-1)
 41. Rich, M.W., Beckham, V., Wittenberg, C., Leven, C.L., Freedland, K.E., Carney, R.M. (1995) A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *New England Journal of Medicine*, 333(18): 1190-1195. DOI: [10.1056/NEJM199511023331806](https://doi.org/10.1056/NEJM199511023331806)