Ten-Year Survival of Heart Failure Patients with Left Ventricular Ejection Fraction of 40-59%: A Potential Phenotypic Classification?

Luiz Claudio Danzmann,[1,2,3] Luiz Carlos Bodanese,[2,4] Aline Petracco Petzold,[4] Anna Paula Tscheika,[2] Ellen Hettwer Magedanz,[2] Lucas Celia Petersen,[2] Evgeny Belyavskiy,[5] Fernanda Lourega Chieza[3,4]

Universidade Luterana do Brasil,[1] Canoas, RS – Brazil
Hospital São Lucas da PUCRS,[2] Porto Alegre, RS – Brazil
Santa Casa de Misericórdia de Porto Alegre,[3] Porto Alegre, RS – Brazil
Pontifícia Universidade Católica do Rio Grande do Sul,[4] Porto Alegre, RS – Brazil
Charité Universitätsmedizin Berlin,[5] Berlin – Germany

Abstract

Definitions of left ventricular ejection fraction (LVEF) cut-off values for HF with mildly reduced LVEF (HFmrEF) have been a subject of debate, in the face of evidence that some drugs used in the treatment of HF with LFEV < 40% (HFrEF) are also effective in patients with LVEF < 60%.

The aim of this study was to compare overall survival and cardiovascular survival in HF patients with LVEF of 40-59% in patients with HFrEF and HF with LVEF ≥ 60%.

Patients with decompensated HF who met the Framingham diagnostic criteria at hospital admission between 2009 and 2011 were included. Patients were divided into HFrEF, HF with LVEF 40-59%, and HF with LVEF ≥ 60%. The Kaplan-Meier was used to determine ten-year overall survival and cardiovascular survival. The statistical significance was established at p<0.05.

A total of 400 patients were included, with a mean age of 69 ± 14 years. Cardiovascular survival in patients with HF and LVEF of 40-59% was not significantly different than in patients with HFrEF (adjusted Hazard Ratio [HR] 0.86; 95% Confidence Interval [CI] 0.61-1.22, Ptrend = NS), but was statistically different compared with patients with LVEF ≥ 60% (adjusted HR of 0.64; 95% CI 0.44-0.94, Ptrend = 0.023).

No difference was found in 10-year survival between the LVEF groups. Patients with HF and LVEF ≥ 60% had significantly higher cardiovascular survival compared with the other groups.

Introduction

The management of heart failure (HF) patients is based on left ventricular ejection fraction (LVEF) classification. Recent guidelines[1,2] suggest the following phenotypes of HF: HF with reduced LVEF (<40%) (HFrEF), HF with mildly reduced LVEF (40-49%) (HFmrEF), HF with preserved LVEF (≥50%) (HFpEF). However, the upper limit for HFmrEF is still a matter of debate regarding the most appropriate criteria of normality for LVEF.[3]

Clinical studies have suggested that patients with HFmrEF have similar benefits from therapies shown to be effective for HFrEF.[4,5] Prespecified analysis of the PARAGON-HF[6] study reveals a reduction in clinical outcomes in patients with LVEF > 45% and ≤ 57% with sacubitril/valsartan, reinforcing the hypothesis that a higher upper limit for HFmrEF could be more adequate for result prediction.[4]

The aim of the present study was to compare overall and cardiovascular survival between HF patients with LVEF of 40-59% and HF patients with LVEF ≥ 60% in a 10-year follow-up period.

Keywords

Heart Failure; Mortality; Survival; Stroke Volume.

Mailing Address: Luiz Claudio Danzmann •
Avenida Ipiranga, 6690/402. Postal Code 96610-000, Jardim Botânico, Porto Alegre, RS - Brazil
E-mail: luiz.danzmann@gmail.com
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Methods

This was a cohort study of adult patients (>18 years old) with diagnosis of HF according to the Framingham criteria, confirmed by echocardiogram between January 2009 and December 2011, who were followed for 10 years. The study population was divided into three groups – HFrEF, HF with LVEF 40-59% and HF with LVEF ≥ 60%.

Patient survival was assessed by review of medical records or by telephone contact. In case of data inconsistency, a search in the civil registration system was made.

The following outcomes were evaluated during the follow-up period: overall survival and survival free of cardiovascular outcomes (acute myocardial infarction, rehospitalization for HF, stroke, and arrhythmias).

Statistical analysis

Comparisons of quantitative characteristics at baseline were made using the ANOVA test, and the Kaplan-Meier test was used for survival analysis. The log-rank test was used to determine differences in survival distribution, followed by univariate and multivariate Cox regression, adjusted for age, hypertension, diabetes mellitus, coronary artery disease (CAD), body mass index (BMI), chronic obstructive pulmonary disease (COPD) and chronic renal disease (CRD). Hazard ratio (HR) values and respective 95% confidence interval (CI) was determined, and a p<0.05 was defined as statistically significant.

Results

Of the initial sample of 423 patients from the metropolitan region of Porto Alegre, 400 were included (133 with LVEF<40, 145 with LVEF 40-59% and 122 with LVEF ≥60%); 60.1% had New York Heart Association functional class III/IV. A total of 324 (81%) died. The five-year survival rate was 32.8%. No statistically significant association was found between the LVEF groups and overall mortality (Figure 1).

In the Kaplan-Meier analysis, patients with HFrEF had a median survival of 4.5 years, patients with LVEF of 40-59% had a median survival of 5.7 years, and patients with LVEF ≥ 60% had a median survival of 8.8 years.

Univariate and multivariate analysis adjusted for age, hypertension, DM, CAD, BMI, CPOD and CRD was performed. Regarding cardiovascular survival, statistically difference was observed between the LVEF 40-59% and LVEF ≥ 60% groups only (adjusted HR = 0.64; 95% CI 0.44-0.94, Ptrend = 0.023) (Table 1, Figure 1 and Figure 2).

Discussion

Our results did not show significant differences in survival between the groups of patients categorized by LVEF. This result reproduces findings from other studies on populations of patients hospitalized for HF, which also did not describe LVEF as a marker of overall survival.[7,8] Cardiovascular survival was significantly higher in the group of patients with LVEF ≥ 60% compared with the other LVEF groups, which corroborates previous studies with similar populations.[8]

Most characteristics of patients with LVEF 40-59% showed intermediate distribution as compared with the other groups. However, the prevalence of CAD in patients with HFrEF and LVEF 40-59% was higher compared with patients with LVEF ≥ 60% (43.8% x 53.5% x 64.4, respectively; Ptrend = 0.004). This fact had already been associated with lower cardiovascular survival in populations with HF and systolic dysfunction.[7]

The low rate of prescription of prognostic-modifiers drugs for HF reflects a serious difficulty in applying guideline recommendations in clinical practice.[7] Nevertheless, the differences detected between the groups in our study are similar to those reported in a recent European registry.[8]

Table 1 - Overall and cardiovascular mortality

	Overall mortality		Cardiovascular mortality	
Groups	HR (not adjusted)	HR (adjusted)*	HR (not adjusted)	HR (adjusted)*
LVEF 40-59%	0.89 (0.69-0.15)	0.89 (0.68-1.17)	0.86 (0.62-1.20)	0.86 (0.61-1.22)
LVEF ≥ 60%	0.80 (0.61-1.07)	0.78 (0.59-1.04)	0.68 (0.48-0.98)	0.64 (0.44-0.94)
Tendency p value	0.125	0.094	0.039	0.023

**Cox regression adjusted for age, hypertension, diabetes mellitus, coronary artery disease, body mass index, chornic obstructive pulmonary disease and chronic renal disease. LVEF: left ventricular ejection fraction; HR: hazard ratio.*

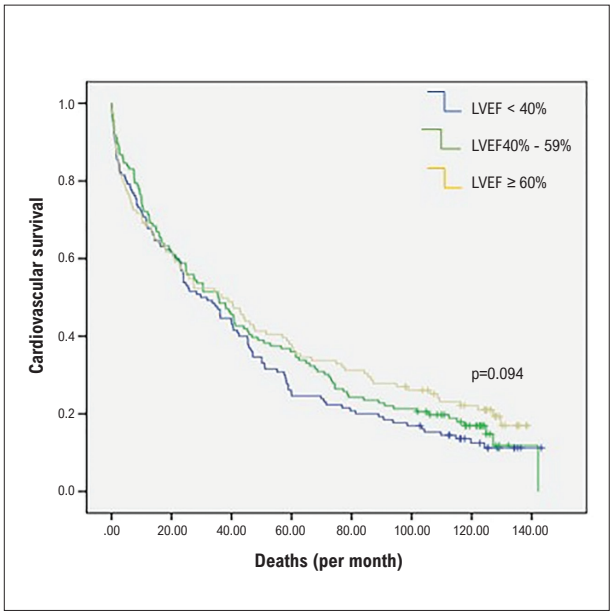

Figure 1 – *Kaplan-Meier curve for all-cause mortality. LVEF: left ventricular ejection fraction.*

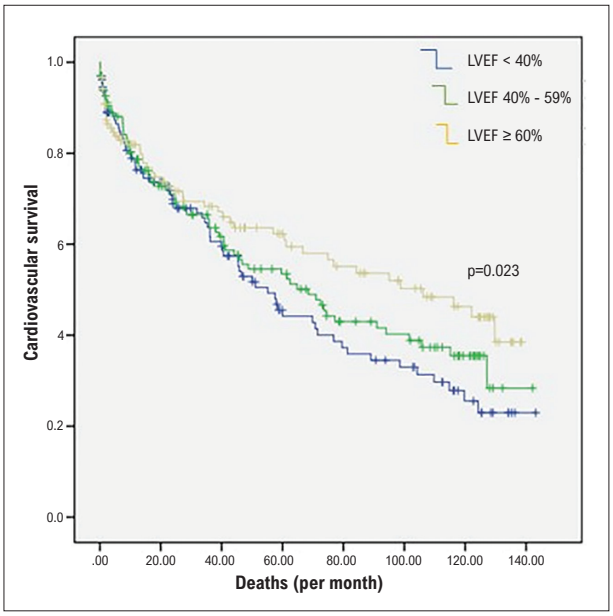

Figure 2 – *Kaplan-Meier curve for cardiovascular mortality. LVEF: left ventricular ejection fraction.*

Finally, the plausibility of the idea of raising the cut-off values of LVEF in HFrEF is also supported by results of the recent EMPEROR-Preserved study[9] that showed greater efficacy of empagliflozin over placebo in reducing the outcomes of cardiovascular death and/or hospitalization in patients with LVEF>40%. The effect was greater in the subgroup of patients with LVEF<60%, even though the interaction p between the groups was not statistically significant. This result configures an epidemiological alignment with our findings and results of previously mentioned studies.[4-8]

Conclusion

Results of the 10-year follow-up of our cohort of HF patients demonstrated that, in patients with LVEF 40-59%, the overall survival was not different from that in the other two LVEF groups, and cardiovascular survival was significantly lower than in patients with LVEF ≥60%. These data suggest epidemiological plausibility for redefinition of the LVEF cutoffs for HFmrEF.

Author Contributions

Conception and design of the research: Danzmann LC, Bodanese LC, Magedanz EH, Chieza FL; Acquisition of data: Danzmann LC, Bodanese LC, Petzold AP, Magedanz EH, Petersen LC, Chieza FL; Analysis and interpretation of the data: Danzmann LC, Bodanese LC, Petzold AP, Tscheika AP, Magedanz EH, Chieza FL; Statistical analysis: Danzmann LC, Bodanese LC, Magedanz EH, Chieza FL; Obtaining financing: Danzmann LC, Bodanese LC, Petzold AP, Magedanz EH, Chieza FL; Writing of the manuscript: Danzmann LC, Bodanese LC, Petzold AP, Tscheika AP, Magedanz EH, Chieza FL; Critical revision of the manuscript for important intellectual content: Danzmann LC, Bodanese LC, Tscheika AP, Magedanz EH, Petersen LC, Belyavskiy E.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Pontifícia Universidade Católica do Rio Grande do Sul under the protocol number 19638919.1.0000.5336. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. 2021:S1071-9164(21)00050-6. doi: 10.1016/j.cardfail.2021.01.022.
2. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.
3. Galderisi M, Cosyns B, Edvardsen T, Cardim N, Delgado V, Di Salvo G, et al. Standardization of Adult Transthoracic Echocardiography Reporting in Agreement with Recent Chamber Quantification, Diastolic Function, and Heart Valve Disease Recommendations: An Expert Consensus Document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2017;18(12):1301-10. doi: 10.1093/ehjci/jex244.
4. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, et al. Heart Failure with Mid-Range Ejection Fraction in CHARM: Characteristics, Outcomes and Effect of Candesartan Across the Entire Ejection Fraction Spectrum. Eur J Heart Fail. 2018;20(8):1230-39. doi: 10.1002/ejhf.1149.
5. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of Ejection Fraction on Outcomes and Efficacy of Spironolactone in Patients with Heart Failure with Preserved Ejection Fraction. Eur Heart J. 2016;37(5):455-62. doi: 10.1093/eurheartj/ehv464.
6. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2019;381(17):1609-20. doi: 10.1056/NEJMoa1908655.
7. Petersen LC, Danzmann LC, Bartholomay E, Bodanese LC, Donay BG, Magedanz EH, et al. Survival of Patients with Acute Heart Failure and Mid-range Ejection Fraction in a Developing Country - A Cohort Study in South Brazil. Arq Bras Cardiol. 2021;116(1):14-23. doi: 10.36660/abc.20190427.
8. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and One-Year Outcomes in Patients with Chronic Heart Failure and Preserved, Mid-Range and Reduced Ejection Fraction: An Analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2017;19(12):1574-85. doi: 10.1002/ejhf.813.
9. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385(16):1451-61. doi: 10.1056/NEJMoa2107038.

***Supplemental Materials**

For additional information, please click here.