KARDIOLOGIA POLSKA
Polish Heart Journal
The Official Peer-reviewed Journal of the Polish Cardiac Society since 1957
Online first
This is a provisional PDF only. Copyedited and fully formatted version will be made available soon
ISSN 0022–9032 e-ISSN 1897–4279

Reviving a failing heart in real-life: are the results of the REVIVED trial applicable to the all-comer population?

Authors: Łukasz Pyka, Bartosz Hudzik, Kamil Bujak, Mariusz Gąsior

Article type: Short communication

Received: February 15, 2023

Accepted: May 19, 2023

Early publication date: July 2, 2023

Reviving a failing heart in real-life: are the results of the REVIVED trial applicable to the all-comer population?

Short title: REVIVED trial results vs. real-life outcomes

Łukasz Pyka, Bartosz Hudzik, Kamil Bujak, Mariusz Gąsior

3rd Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland

Correspondence to:
Łukasz Pyka, MD,
3rd Department of Cardiology, Silesian Center for Heart Diseases,
Faculty of Medicine in Zabrze, Medical University of Silesia,
M Skłodowskiej-Curie 9, 41–800 Zabrze, Poland,
phone: +48 32 373 3 860,
e-mail: l.t.pyka@gmail.com

INTRODUCTION

The long-awaited ISCHEMIA trial results have put in doubt the efficacy of percutaneous coronary revascularization (PCI) in improving outcomes for stable coronary artery disease (CAD) patients [1]. In the ischemic heart failure (HF) population, coronary artery bypass (CABG) surgery was shown in the pivotal STICH trial to improve survival in as-treated analysis (as crossover rates were at 9.0%–10.8%) and at 10 years in the extended follow-up analysis [2,3]. However, such results have never been confirmed for PCI in randomized trials. The authors of the REVIVED-BCIS2 trial [4] set out to demonstrate such benefit in a similar population of patients on contemporary optimal medical treatment (OMT). The trial showed no benefit of percutaneous coronary revascularization, starting a broad discussion on the role of PCI as well as the trial's limitations. Issues such as stenosis severity, evidence of ischemia, or low CCS score were raised. The aspects of complete revascularization or the presence of chronic total occlusion, previously shown to impact outcomes in smaller studies [5, 6], are yet to be published. Moreover, it must be stressed that the overall outcomes of both study arms were poor, with a high all-cause mortality of 37.2%–38% after a median 41-month follow-up.

Considering the issues mentioned above, we aimed to relate the results of the REVIVED-BCIS2 to real-world clinical practice by comparing the clinical characteristics and long-term outcomes of this trial population with a cohort of consecutive HF patients from our institution.

METHODS

Of all ischemic HF patients admitted to Silesian Center for Heart Diseases in Zabrze, Poland, between 2013–2019, we have selected patients with left ventricular ejection fraction (LVEF) of 35% or less who underwent PCI for the chronic coronary syndrome. Patients with acute coronary syndromes, acute decompensated HF, requiring inotrope or mechanical circulatory support were excluded from further analysis. A total of 627 patients met the inclusion criteria, forming a real-world group.

Data on clinical characteristics and treatment of the real-world group were collected from the hospital's electronic database. In addition, data on long-term all-cause mortality in this group were obtained from the national healthcare provider's (NFZ) database and were available for all patients.

REVIVED was a prospective, randomized, open-label trial on ischemic HF patients, comparing two treatment modalities – conservative and invasive (PCI). For the purpose of this analysis we have selected only the PCI treated REVIVED study cohort. Study-level data on patients' characteristics of the REVIVED cohort (n = 347), i.e. frequencies and means with corresponding standard deviations, were extracted from the published report [4]. Moreover, reconstructed individual patient data on the incidence of all-cause death were extracted from Kaplan-Meier survival curves presented in the same paper using the freely available online tool: IPDfromKM Shiny app (https://www.trialdesign.org/one-page-shell.html#IPDfromKM).

Statistical analysis

Continuous variables were expressed as mean and standard deviation and were compared between the real-world group and REVIVED cohort using a one-sample t-test. Categorical variables were presented as percentages, and between-group differences for these variables were assessed using the $\chi 2$ test. The cumulative incidence of all-cause death during 8-year follow-up between groups was depicted using the Kaplan-Meier method and compared by log-rank test. Additionally, a landmark analysis was performed with a landmark set at one year. The hazard ratio and corresponding 95% confidence interval for all-cause mortality were obtained from the unadjusted Cox regression model. The proportional hazards assumption was confirmed using the Schoenfeld residuals. The $P < 0.05$ (two-tailed) was considered statistically

significant. Statistical analyses were performed using R version 4.2.2 (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

RESULTS AND DISCUSSION

The real-world population was younger (66 [9] vs. 70 [9]; *P* <0.001), with no differences in proportion of male patients (85.6% vs. 87.0%; *P* = 0.54) and similar body-mass index (28.4% (5.3%) vs. 28.4 (5.5%); *P* = 0.84), yet much more morbid. We have observed more frequently a history of PCI (49.1% vs. 19.0%; *P* <0.001) and CABG (13.2% vs. 3.4%; *P* <0.001), more hypertension (77.3% vs. 53.0%; *P* <0.001), and the similar prevalence of diabetes (41.4% vs. 39.1%; *P* = 0.48). Real-world patients were much more symptomatic, with more severe angina (CCS III/IV 29.9% vs. 2.0%; *P* <0.001) and dyspnea (NYHA III/IV 53.9% vs. 23.0%; *P* <0.001), with differences in median NT-proBNP concentrations (3685 [IQR, 869–5590] vs. 1376 [IQR, 697–3426] pg/ml) and lower LVEF (24% [6.1%] vs. 27% [6.6%]; *P* <0.001). The prevalence of left main lesions was similar in both cohorts (10.5% vs. 14.4%; *P* = 0.07). After discharge, the real-life cohort presented a similar frequency of myocardial infarction (10.4% vs. 10.7%; *P* = 0.85). Implantable cardioverter-defibrillators were implanted post-discharge more frequently in the registry population (54.8% vs. 27.9%; *P* <0.001).

All-cause mortality at 8 years follow-up was lower in the REVIVED cohort (hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.54–0.83; *P* <0.001) (Figure 1A). The landmark analysis revealed that mortality rates were similar during the first 12 months but lower in the REVIVED patients during the subsequent 7 years (Figure 1B).

Understandingly, the registry population is different. However, despite a much worse clinical profile, the outcomes in the early follow-up were similar. In the first year after PCI, both the potential benefit of the procedure as well as its risks bear the most influence on outcomes. The worse outcomes of the real-life cohort in longer-term follow-up might be, in our opinion, more related to the worse clinical profile as well as the more stringent care of patients enrolled in the clinical trial. This underlines the need to improve real-life patient care and introduce a more systematic approach to the treatment of HF.

Obviously the timeframe of the presented analysis resulted in the lack of utilizaiton of novel pharmacotherapy modalities, which have been shown to improve outcomes and are recommended by experts and guidelines [7]. We believe that generally better long-term outcomes would have been observed in both study populations if all modern heart failure pharmacological options had been utilized.

Nonetheless, the outcomes in both cohorts are worrisome. Thus, the question remains if the outcomes of ischemic HF patients might be improved by coronary revascularization. In fact, the REVIVED-BCIS trial showed no difference in terms of long-term outcomes between PCI and medical therapy alone. However, some questions were raised regarding patient selection in this trial. The REVIVED patients were obligatorily tested for myocardial viability to be enrolled, yet most of them were asymptomatic or had little angina, especially compared to real-world patients. On the other hand, in light of the evidence, contemporary PCI should be driven by ischemia in the case of asymptomatic patients, but proof of ischemia was not compulsory for patients' inclusion in this trial. Perhaps, therefore, testing for ischemia might be essential for identifying HF patients who might benefit the most from revascularization. In patients without confirmed ischemia, coronary artery disease might be only a bystander, not the cause of HF. In these cases, revascularization might be unnecessary and bears only potential procedure-related complications.

Limitations

Our study compares real-life registry patients with a randomized study cohort, which is, at the same time, the major strength and limitation of this analysis. Moreover, we had no access to complete patient-level REVIVED data. Therefore, we could not adjust the survival analysis for the differences in the baseline clinical characteristics.

CONCLUSIONS

The results of our analysis showed that real-world HF patients had higher comorbidity and angina symptom burden than patients enrolled in the REVIVED trial but had a similar one-year mortality rate. Although slightly better in the REVIVED cohort, the long-term prognosis was generally poor in both groups, showing an urgent need for further research to find optimal management strategies in ischemic patients, including a better selection of patients who might benefit from PCI.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med. 2020; 382(15): 1395–1407, doi: 10.1056/NEJMoa1915922, indexed in Pubmed: 32227755.
2. Velazquez EJ, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med. 2011; 364(17): 1607–1616, doi: 10.1056/NEJMoa1100356, indexed in Pubmed: 21463150.
3. Howlett JG, Stebbins A, Petrie MC, et al. CABG improves outcomes in patients with ischemic cardiomyopathy: 10-year follow-up of the STICH trial. JACC Heart Fail. 2019; 7(10): 878–887, doi: 10.1016/j.jchf.2019.04.018, indexed in Pubmed: 31521682.
4. Perera D, Clayton T, O'Kane PD, et al. Percutaneous revascularization for ischemic left ventricular dysfunction. N Engl J Med. 2022; 387(15): 1351–1360, doi: 10.1056/NEJMoa2206606, indexed in Pubmed: 36027563.
5. Pyka Ł, Hawranek M, Tajstra M, et al. Complete percutaneous revascularisation feasibility in ischaemic heart failure is related to improved outcomes: insights from the COMMIT-HF registry. Kardiol Pol. 2017; 75(5): 453–461, doi: 10.5603/KP.a2017.0018, indexed in Pubmed: 28150287.
6. Tajstra M, Pyka Ł, Gorol J, et al. Impact of chronic total occlusion of the coronary artery on long-term prognosis in patients with ischemic systolic heart failure: insights from the COMMIT-HF registry. JACC Cardiovasc Interv. 2016; 9(17): 1790–1797, doi: 10.1016/j.jcin.2016.06.007, indexed in Pubmed: 27609252.
7. Lelonek M, Grabowski M, Kasprzak JD, et al. An expert opinion of the Heart Failure Association of the Polish Cardiac Society on the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure: Heart

failure guidelines from a national perspective. Kardiol Pol. 2022; 80(2): 239–246, doi: 10.33963/KP.a2022.0021, indexed in Pubmed: 35076082.

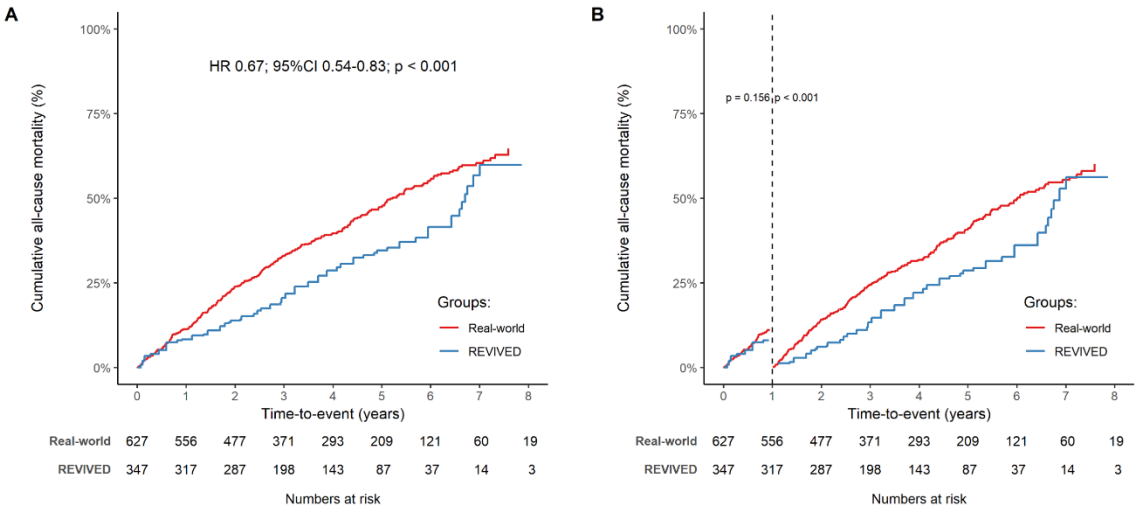

Figure 1. Kaplan-Meier curves presenting cumulative incidence of all-cause death in REVIVED and real-world cohort of heart failure patients, during the whole long-term follow-up (**A**) and in the landmark analysis (**B**)