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

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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, the pivotal STICH trial showed that coronary artery bypass (CABG) surgery improved 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 for PCI have never been confirmed in randomized trials.

The authors of the REVIVED-BCIS2 trial [4] set out to demonstrate such a benefit in a similar population of patients on current 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 Canadian Cardiovascular Society (CCS) score were raised. The results on 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 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 trial 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 the Silesian Center for Heart Diseases in Zabrze, Poland, between 2013 and 2019, we have selected patients with left ventricular ejection fraction (LVEF) of 35% or less who underwent PCI for 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 and open-label trial on ischemic HF patients, comparing two treatment modalities – conservative and invasive (PCI). For our analysis, we selected only the PCI-treated REVIVED study cohort. Study-level data on patient 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 report 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 means and standard deviations and were

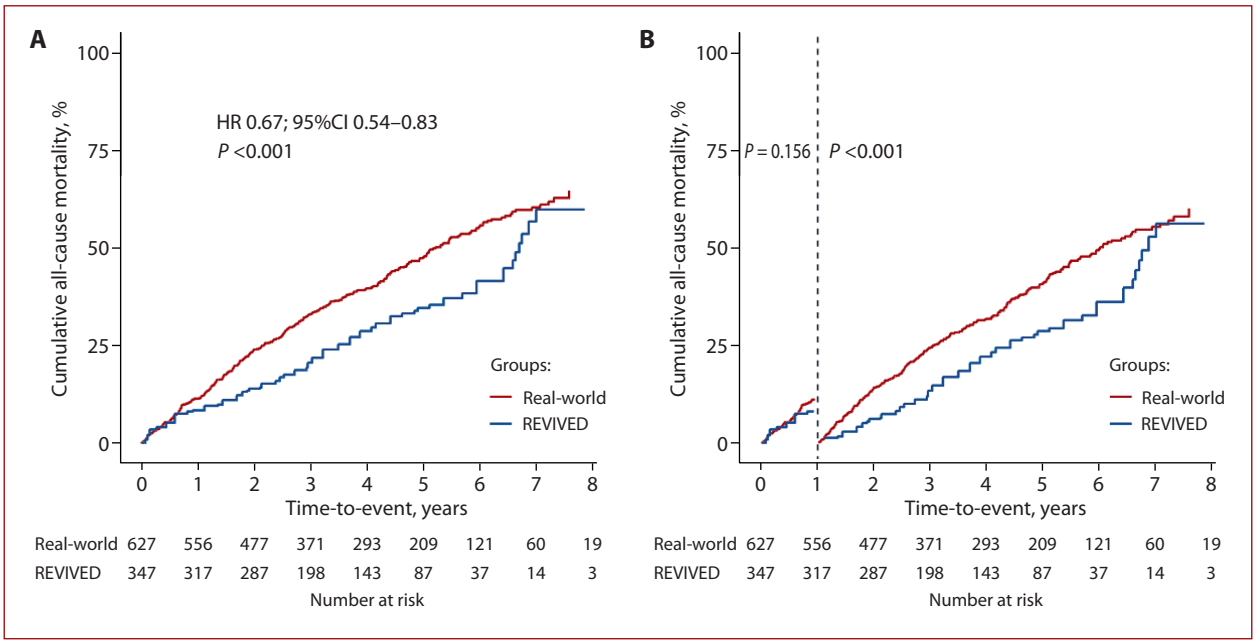

Figure 1. Kaplan-Meier curves presenting cumulative incidence of all-cause death in the REVIVED and real-world cohorts of heart failure patients during long-term follow-up (**A**) and in the landmark analysis (**B**)

compared between the real-world group and the 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 χ2 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 the log-rank test. Additionally, a landmark analysis was performed with the 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*-value <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 the proportion of male patients (85.6% vs. 87.0%; *P* = 0.54) and with 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 a 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 (New York Heart Association [NYHA] class III/IV 53.9% vs. 23.0%; *P* <0.001), with differences in median NT-proBNP levels (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 coronary artery 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-year 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).

Understandably, the registry population was 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, related to the worse clinical profile as well as the more stringent care for 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.

The timeframe adopted in our analysis did not allow for including novel pharmacotherapy modalities, which have been shown to improve outcomes and are recommended by experts and guidelines [7]. We believe that 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, currently PCI should be driven by ischemia in the case of asymptomatic patients, but evidence of ischemia was not in the inclusion criteria for this trial. Therefore, testing for ischemia might be essential in identifying HF patients who benefit the most from revascularization. In patients without confirmed ischemia, coronary artery disease might be only an adventitious finding, not the cause of HF. In these cases, revascularization might be unnecessary due to potential procedure-related complications.

Limitations

Our study compared 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 develop optimal management strategies in ischemic patients, including a better selection of patients who might benefit from PCI.

Article information

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