Revascularization and Outcomes in Ischemic Left Ventricular Dysfunction After Heart Failure Admission:The RevascHeart Study

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Abstract

Aims: Despite numerous trials on revascularization in patients with heart failure (HF) and ischemic left ventricular (LV) dysfunction, its role remains unsettled. Guideline-directed medical therapy (GDMT) for HF has shown benefits on outcomes. This multicenter study aims to compare long-term mortality between revascularization and GDMT in patients with ischemic LV dysfunction following admission for HF.

Methods and results: Between 2012 and 2023, 408 patients admitted for HF with an ejection fraction (LVEF) of 40% or less and documented coronary artery disease (CAD) were included. Patients were categorized into two groups based on their initial treatment decision: revascularization (PCI or CABG) or GDMT. The primary outcome was rate of all-cause or cardiovascular mortality, and secondary outcomes included type of revascularization (PCI vs CABG) and LV reverse remodeling. After a median 44.6-month follow-up, 100 patients (33%) died in revascularization group, compared to 44 (43%) in GDMT group. Multivariate analysis showed no significant benefit of revascularization on all-cause mortality (HR 0.81, 95% CI 0.48-1.39, p=0.45) or cardiovascular mortality (HR 0.97, 95% CI 0.62-1.52, p=0.90) compared to GDMT. Neither CABG (HR 0.74, 95% CI 0.51-1.08, p=0.13) nor PCI (HR 0.98, 95% CI 0.62-1.55, p=0.93) demonstrated a mortality reduction compared to GDMT. Both groups experienced significant reductions in LV size and improvements in LVEF, greater in the revascularization group.

Conclusions: Revascularization did not outperform GDMT in ischemic LV dysfunction following HF admission in this retrospective analysis. Larger prospective studies are needed to clarify the potential role of revascularization in improving outcomes.

Key words: ischemic left ventricular dysfunction, ischemic heart failure, revascularization, GDMT

Introduction

Coronary artery disease (CAD) is the primary cause of systolic dysfunction[1], which can eventually lead to heart failure (HF). Stemming from the historical concept of myocardial hibernation, there emerged a hypothesis proposing that revascularization could reverse ventricular dysfunction by promoting left ventricular reverse remodeling (LVRR), potentially improving prognosis in ischemic LV dysfunction[2].

To date, the only randomized trial showcasing the prognostic impact of revascularization, specifically through coronary artery bypass grafting (CABG), on systolic dysfunction of ischemic origin is the 10 year extended follow up of STICH trial[3], conducted between 2002 and 2007. Based on these findings, current guidelines recommend myocardial revascularization for patients with severe LV systolic dysfunction and CAD suitable for intervention (Class I, Level of Evidence: B). In cases of multivessel disease with acceptable surgical risk, CABG is the preferred strategy (Class I, Level of Evidence: B)[4].

More recently, the REVIVED-BCIS trial[5], incorporating contemporary GDMT for HF, did not replicate the survival advantage of revascularization, this time employing percutaneous coronary intervention (PCI). Moreover, no impact of PCI was seen on LVRR.

When attempting to translate these findings into clinical practice, the stringent inclusion and exclusion criteria of both trials restrict their generalizability. For instance, the STICH trial excluded individuals with left main coronary artery (LMCA) disease or factors predicting poor treatment adherence (such as alcohol dependence or psychiatric disorders). Thus, we conducted a multicenter registry to ascertain the advantages of revascularization in patients with significant CAD, LV systolic dysfunction and a recent HF admission in real-world clinical settings.

Methods

Study population

This multicenter retrospective cohort study encompassed consecutive patients admitted for HF with LV systolic dysfunction and documented significant coronary artery disease at six tertiary hospitals between 2012 and 2023. These hospitals collectively represent all cardiac surgery centers in Catalonia. Patients were identified using the diagnostic coding system upon discharge from participating hospitals. Those admitted for heart failure and who underwent invasive coronary angiography within 6 months before or after admission were considered. Inclusion criteria were patients aged 18 or older, with a history of previous HF admission, an LVEF of 40% or less (determined by transthoracic echocardiography during the index hospitalization), and extensive CAD defined as LMCA ≥50%, proximal LAD ≥70%, or two or more major epicardial vessels ≥70%.

Patients were excluded if they had experienced a recent acute coronary syndrome (within two months prior to HF admission), significant valvular heart disease (excluding functional mitral or tricuspid regurgitation), or any prior cardiac surgical intervention (such as CABG or surgical valve replacement) (Figure 1).

Subsequently, the population was divided into two groups based on their treatment approach: 1) those selected by the heart team for revascularization (REVASC group: CABG or PCI), either during hospital admission or shortly thereafter as outpatients along with GDMT (Revascularization group), and 2) those managed solely with GDMT (GDMT group).

We registered the reason for the therapeutic decision and evaluated the vital status, cause of death, HF admissions, acute coronary syndrome (ACS) admissions, strokes, need for heart transplant, implantation of intracardiac defibrillators (ICD) or cardiac resynchronization

therapy (CRT), occurrences of ventricular arrhythmias, and MitraClip implantation for each participant in the study, utilizing local and shared national electronic records. Additionally, information on New York Heart Association (NYHA) and Canadian Cardiovascular Society (CCS) functional classification scales, GDMT for HF, echocardiography results, and NT-proBNP levels at 1 year after inclusion and at the last available follow-up were recorded.

The study was approved by Hospital de la Santa Creu i Sant Pau ethics committee and conformed with the principles outlined in the *Declaration of Helsinki*. The authors from each participating center guarantee the integrity of data.

Study endpoints

The primary objective of this study was to compare the rates of all-cause and cardiovascular mortality in patients with ischemic LV dysfunction between the revascularization and the GDMT alone groups. The secondary objectives were to evaluate and compare the incidence and extent of LVRR between both groups and to compare the rates of a combined endpoint (MACE) (all-cause mortality, acute myocardial infarction, stroke, HF readmission) between REVASC and GDMT.

Statistical analysis

Continuous variables are reported as the mean ± standard deviation (SD), or median and interquartile range (IQR), as appropriate. Categorical variables are reported as the number and percentage. To compare the baseline characteristics among REVASC and GDMT groups, a descriptive analysis was performed using the chi-squared test, *t*-test, or Wilcoxon rank sum test, as appropriate. The Kaplan–Meier method was used to analyse the cumulative incidence of events over time, whereas log-rank tests were applied to evaluate differences between the groups. Cox proportional-hazards regression analyses were used to compare the clinical

outcomes. Variables with an association with the outcome in the univariate Cox regression with a value of $P < 0.10$ were selected for the multivariate analysis and a Cox regression model. Subgroup analyses were conducted according to type of revascularization (PCI vs. CABG) and use of guideline directed medical treatment (GDMT) (combination of betablocker -BB-, angiotensin-converting enzyme inhibitor -ACEI- or angiotensin receptor blocker -ARB- and mineralocorticoid receptor antagonist -MRA-). To account for non-CV mortality competing risk, we used Fine–Gray proportional hazard model. To quantify the magnitude of LVRR, we analysed patients with a control echocardiogram at around 12 months after the index hospitalization. The change in LVEF (ΔLVEF) and LV end-diastolic diameter (ΔLVEDD) was estimating by subtracting the values recorded at 12 months from the baseline value. To compare the magnitude of LVRR among REVASC and GDMT groups a paired *t*-test or Wilcoxon rank sum test (as appropriate) was performed. Two-sided significance levels of 0.05 were used in all analyses. Data were analysed using STATA SE Version 15.0 (StataCorp LLC, College Station, TX, USA). Results are reported following the CONSORT guidelines.

Results

From January 2012 to December 31, 2023, 408 patients from six tertiary hospitals were enrolled, predominantly men (83%), with a median age of 67.1 years (interquartile range [IQR] 59-74). Baseline characteristics, as shown in Table 1, were stratified between the REVASC and GDMT groups. There were no significant differences observed between the REVASC and GDMT groups in terms of age, gender, cardiovascular risk factors, or ejection fraction. However, GDMT patients had a higher burden of comorbidities, as indicated by the Charlson Comorbidity Index (CCI), along with a higher prevalence of prior myocardial infarction and PCI. Additionally, they were more often on BB or MRA, exhibited poorer renal function, a more dilated left ventricle, and a higher incidence of LV ischemic fibrosis. In contrast, REVASC patients presented with a more complex coronary anatomy, often involving the LMCA and proximal left anterior descending artery (LAD).

The primary reasons for maintaining patients on GDMT (n=103) included absence of viability (26%), poor distal vessel conditions (20%), lack of ischemia (17%), and patient comorbidities (16%). 305 participants (75%) formed the REVASC group. Within this group, 184 individuals (45%) underwent revascularization while hospitalized, and 66 (16%) received it shortly after discharge, with a median interval of 27 days from discharge to the revascularization procedure. CABG was the preferred technique for revascularization, performed in 225 cases (74%). Table 2 presents baseline characteristics categorized by revascularization modality. Patients who underwent CABG tended to be younger, had fewer comorbidities, were more commonly diabetic, possessed a higher LVEF, less frequently exhibited significant mitral or tricuspid regurgitation, and had a more intricate coronary anatomy. The median time to revascularization was notably longer in the CABG group compared to PCI (29 days vs. 16.5 days, $p<0.01$). Within the CABG group, the median number of conduits was 3, with the left internal mammary artery (LIMA) utilized in 222 patients (Supplementary Table 1). Revascularization was more

frequently complete in the CABG group (64%) compared to PCI (21%). Detailed procedural specifications and outcomes according to the mode of revascularization can be found in Supplementary Table 2. Guideline directed pharmacological treatments for HF did not differ among treatment groups at 1 year, except for iSGLT2 that was more prevalent in CABG group (49% vs 37% -PCI- vs. 27% -GDMT-, p<0.01) (Supplementary Table 3).

In the REVASC group, 100 patients (33%) experienced death from any cause, compared to 44 patients (43%) in GDMT group (unadjusted hazard ratio [HR] 0.80; 95% CI, 0.56 to 1.2; p=0.23 (Table 3, Supplementary Figure 1), after a median follow-up of 44.6 months (interquartile range [IQR] 22-69). No significant differences were found in cardiovascular mortality between the groups (unadjusted HR, 0.87; 95% CI, 0.57 to 1.34; p=0.54). Furthermore, there were no significant differences in the causes of mortality between the two groups (Table 3). The GDMT group exhibited a higher need for subsequent revascularization procedures (median time to revascularization was 557 [157-1568] days), HF admissions, and heart transplants. However, there were no differences in the incidence of acute coronary syndrome observed between the groups. After adjusting for baseline characteristics, multivariate analysis showed no significant benefit of revascularization on all-cause mortality (HR 0.81, 95% CI 0.48-1.39, p=0.45) or cardiovascular mortality (HR 0.97, 95% CI 0.62-1.52, p=0.90) compared to GDMT. Neither CABG (HR 0.74, 95% CI 0.51-1.08, p=0.13) nor PCI (HR 0.98, 95% CI 0.62-1.55, p=0.93) demonstrated a mortality reduction compared to GDMT (Table 4, Figure 2), nor a reduction in MACE (0.83, 95% CI 0.55-1.26, p=0.39) (Supplementary table 4, supplementary Figure 2). In a sub-group analysis of patients who underwent both baseline and 12-month echocardiograms, it was found that both the REVASC and GDMT groups experienced reverse ventricular remodeling. However, the extent of change was notably greater in the revascularized group for both parameters. Specifically, the left

ventricular ejection fraction (LVEF) improved by a mean of 11 points in the REVASC group compared to 8 points in the GDMT group ($p<0.01$), as detailed in Table 5.

Discussion

This contemporary study of patients with ischemic LV dysfunction after a HF admission revealed three key findings. Firstly, revascularization (REVASC) did not show a significant association with reduced all-cause or cardiovascular mortality compared to GDMT during a median follow-up period of 44.6 months. Secondly, when mortality was analyzed based on the revascularization technique, neither CABG nor PCI displayed superiority over GDMT after multivariable analysis. Lastly, while both REVASC and GDMT led to LVRR, REVASC demonstrated notably better outcomes in terms of improving LVEF and reducing diameters (graphical abstract).

The lack of discernible benefit from revascularization in our cohort may be attributed to several factors. First, the advancement of contemporary GDMT, encompassing key pharmacological interventions, has demonstrated substantial efficacy in improving outcomes among patients with HF with reduced ejection fraction (HFrEF)[6–9]. Although our study commenced before the widespread adoption of angiotensin receptor-neprilysin inhibitor (ARNI) and sodium-glucose cotransporter 2 inhibitors (SGLT2i), the utilization of these medications has increased in recent years, potentially contributing to improved patient outcomes. Second, a significant proportion of patients in our cohort were diagnosed with de novo HF during the index hospital admission. These individuals might have experienced rapid improvement in ventricular function with GDMT regardless of revascularization. Indeed, findings from the ISCHEMIA trial[10] suggest that an initial revascularization strategy does not confer superiority over conservative management in patients with higher LVEF. Lastly, the coexistence of CAD and ventricular dysfunction does not invariably imply a causal relationship. A recent study[11] indicates that up to 17% of patients with CAD and systolic dysfunction exhibit magnetic resonance imaging (MRI) findings consistent with non-ischemic

or mixed cardiomyopathy. Consequently, this subgroup of patients may derive less benefit from revascularization interventions.

The ongoing debate surrounding revascularization in ischemic LV dysfunction received renewed attention with the publication of the REVIVED-BCIS trial[5]. This study involved 700 patients with a LVEF≤ 35%, extensive CAD, and substantial proven viability in dysfunctional segments. Notably, the trial reported a high rate of complete revascularization (71%) and adherence to clinical practice guidelines for HF therapies. The authors concluded that among well-treated patients from a GDMT perspective, PCI did not offer benefits in terms of all-cause mortality or hospitalization for HF. However, it's essential to acknowledge that our study's patient population differs significantly from that of REVIVED or STICH. In our cohort, patients were enrolled after a HF admission, with de novo HF observed in 85% of cases, and most underwent revascularization within 30 days post-admission. In contrast, the REVIVED and STICH trials excluded patients with recent HF decompensation, with the former enrolling only about 30% of patients with a previous HF decompensation. These details are crucial for understanding the relevance of our study results and their role in adding evidence to the complex decision-making process regarding the choice and timing of specific therapies and interventions in real-world clinical practice.

A significant observation from this retrospective analysis is the high percentage of patients recommended for revascularization by the heart team, reaching 75%. Interestingly, a prominent reason for exclusion from revascularization was the absence of viability. This finding is particularly intriguing considering that viability assessment is designated a recommendation level of IIb-B in clinical practice guidelines[12]. Moreover, sub-studies[13,14] focused on this matter have revealed that viability does not enable the identification of a subgroup of patients who would experience greater benefits from revascularization.

Another notable aspect of our study is its insight into the positive influence of GDMT and revascularization on ventricular remodeling in ischemic LV dysfunction. Previous research [15–19] has underscored the potential of medications like beta-blockers, ACE inhibitors, ARNI, and SGLT2 inhibitors to induce reverse cardiac remodeling and mitigate mitral regurgitation. In our investigation, both GDMT and revascularization were associated with a reduction in LVEDD and an enhancement in LVEF. Interestingly, the improvements in LVEDD and LVEF were notably more pronounced in patients who underwent revascularization. This finding stands in contrast to the outcomes of both the STICH[20] and REVIVED-BCIS trials[5], where revascularization showed no significant effect on LVEF. One possible explanation for this disparity could be that more patients receiving GDMT alone were initially on BB, MRA and ARNI compared to the REVASC group, thereby reducing potential for further optimization of HF drugs in this group. Moreover, in our study, GDMT patients more frequently had a history of MI and a higher extent of nonviable myocardium, both of which are associated with a reduced likelihood of LVEF improvement.[21].

The ongoing STICH3C trial22 will randomize over 700 patients with ischemic LVD (including LM disease) to PCI vs. CABG over contemporary GDMT and will shed light on this complex scenario.

Limitations

This study is not exempt from limitations. There is a potential for selection bias that may have favored the overrepresentation of revascularized patients in our cohort. This bias could stem from our patient search strategy, which included data from cardiac imaging, cath lab, and cardiac surgery units. Additionally, patient allocation to REVASC or GDMT was based on clinical grounds, and it is important to note that the revascularization mode assignment was not randomized. Therefore, despite performing a multivariate analysis, there remains a possibility of bias that could have influenced the clinical outcomes.

Finally, our study included patients between 2012 and 2023, during which ARNI and ISGLT2 were not part of GDMT during the entire study period. Therefore, the benefit of GDMT may be underestimated in our research.

Conclusions

In this large multi-center retrospective study, with long-term follow-up of patients suffering from ischemic LV dysfunction and recent HF admission, we found no evidence to support a survival advantage for revascularization (CABG or PCI) over GDMT. Although both groups exhibited signs of reverse remodeling, the improvements were more pronounced in patients who underwent revascularization. These results, in the context of contemporary GDMT, only add more fuel to the already contentious debate surrounding revascularization in ischemic LV dysfunction. Despite our findings suggesting that revascularization does not outperform GDMT, further research focusing on patients admitted with HF and ischemic LV dysfunction is crucial to conclusively settle the debate over revascularization.

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Conflict of interest

None declared.

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Figure legends

Figure 1. Flowchart of patient selection. *Each patient could fullfill more than one exclusion criteria.*

Figure 2. Kaplan- Meier survival graph representing all-cause mortality and cardiovascular mortality according to revascularization status

Suppl. Figure 1. Kaplan Meier survival curves for all-cause mortality and cardiovascular mortality according to revascularization status

Suppl. Figure 2. Kaplan Meier curves for the combined endpoint according to revascularization and mode.