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PCI has no role in patients with heart failure and reduced ejection fraction: pros and cons

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Introduction

Heart failure with reduced ejection fraction (HFrEF) is a complex clinical syndrome associated with significant morbidity and mortality. Coronary artery disease is a common comorbidity among HFrEF patients, but its presence does not necessarily imply causation of HFrEF. Although myocardial revascularisation with percutaneous coronary intervention (PCI) can improve symptoms and quality of life in patients with angina, there is not sufficient evidence to support using PCI to improve clinical outcomes of unselected patients with chronic coronary syndromes. As such, whether PCI could be beneficial in patients with HFrEF or in specific subgroups is still controversial.

Pros

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Coronary artery disease is the most common cause of chronic heart failure with reduced ejection fraction, a condition also described as ischaemic cardiomyopathy. Left ventricular systolic dysfunction in these cases is due to a combination of (irreversible) myocardial infarction and (reversible) hibernation. The prospect of reversing hibernation has underpinned the rationale for revascularisation of ischaemic cardiomyopathy for several decades, but whether this improves prognosis or systolic function has not been tested in a robust manner until relatively recently. The Surgical Treatment for Ischemic Heart Failure (STICH) trial was the first randomised evaluation of this concept and revealed that, in selected patients, surgical revascularisation itself was associated with an approximately 3-fold excess of death in the first few weeks following the procedure, but that, over the longer term (median follow-up of 10 years), a survival benefit does become apparent[1]. It has been postulated that PCI might reverse hibernation and improve clinical outcomes, without incurring the early hazard that accompanies surgery. Despite the lack of evidence to support this assertion, European Society of Cardiology (ESC) guidelines in 2021 gave PCI a Class IIb recommendation (which was a downgrading of the previous Class IIa recommendation)[2]. In fact, a review of routine health records data from the UK has revealed that PCI is undertaken more commonly than bypass surgery in ischaemic cardiomyopathy[3].

The REVIVED-BCIS2 trial provides the first randomised data on the safety and efficacy of PCI for ischaemic cardiomyopathy[4]. Seven hundred patients (mean age 70 years) with severe left ventricular dysfunction (median ejection fraction 28%), extensive coronary disease (median British Cardiovascular Intervention Society Jeopardy

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Score 10 [maximum possible score is 12]) and evidence of hibernation in at least 4 myocardial segments that could be revascularised by PCI were randomised to PCI or optimal medical therapy (OMT) alone. Thirty-eight percent of patients in the OMT group died or were hospitalised for heart failure, and the event rate in the PCI group was nearly identical throughout the median follow-up of 3.4 years (hazard ratio [HR] 0.99, 95% confidence interval [CI]: 0.78-1.27; p=0.96). This lack of benefit was consistent across all prespecified subgroups, regardless of whether there was complete or incomplete revascularisation of the coronary disease present. Furthermore, while there was an absolute improvement in the median left ventricular ejection fraction of almost 5% in the first 6 months, there was no difference in the change in left ventricular function between groups. These results clearly demonstrate that patients with severe ischaemic cardiomyopathy, who are well treated with guideline-directed medical therapy, should not routinely be offered PCI for improving their prognosis. The lack of incremental improvement in left ventricular function, compared to OMT alone, provides a mechanistic explanation for the lack of prognostic benefit of PCI. But what about symptoms? Patients enrolled in REVIVED-BCIS2 had a median Kansas City Cardiomyopathy Questionnaire (KCCQ) Summary Score of 60 (the score ranges from 0 to 100: higher scores indicate a better quality of life, 60 indicates significantly impaired quality of life). The KCCQ score improved more in the PCI group than those treated with OMT in the first 6 and 12 months, but this difference was not sustained, such that patients in both groups had similar scores at 24 months from randomisation. Hence, PCI does not seem to provide a durable improvement in quality of life and, therefore, should not be routinely considered for improvement of heart failure symptoms. It should be noted that most patients enrolled in REVIVED-BCIS2 were free of limiting angina. Hence, PCI may continue to be an effective therapy for patients with ischaemic cardiomyopathy who have limiting angina, although this is yet to be tested in a randomised trial.

Conflict of interest statement

D. Perera has no conflicts of interest relevant to this article.

Cons

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It is well known that left ventricular (LV) dysfunction is associated with higher mortality, more heart failure and a lower quality of life (QOL) compared to patients without LV dysfunction. Since the most common cause of LV dysfunction is multivessel coronary artery disease (CAD), it makes sense that revascularisation could improve hibernating myocardium and reduce further ischaemic events. Many studies of revascularisation in symptomatic patients with severe CAD and LV dysfunction have shown improvement in ejection fraction (EF), clinical outcomes and late mortality. The PROTECT 2 study[5] reported an absolute increase in EF of 13.2% (p<0.001) due to reverse remodelling. This occurred more frequently in patients with more extensive revascularisation (odds ratio 7.52, 95% CI: 1.31-43.25) and was associated with significantly fewer major adverse events and improved symptoms. Similarly, Velagaleti et al reported data from 10,000 patients undergoing revascularisation in the Veterans Administration hospitals (USA) and found for each 5% improvement in EF, there was an associated reduction in death or congestive heart failure (CHF)[6]. Unfortunately, in this study, older patients seemed to have less benefit. In the STICH trial, the primary endpoint of death from any cause at 5 years was similar in groups assigned to coronary artery bypass grafting and medical therapy. However, after an extended 10-year follow-up (STICHES trial), a survival benefit with revascularisation emerged[1].

However, the recently published REVIVED-BCIS2 study has challenged the benefit of PCI in patients with LV dysfunction. In this study, EF improved in both the PCI and no PCI groups, and there was no difference in death or readmission for heart failure. Interestingly, in REVIVED-BCIS2, EF improved in both groups, and an improvement of >4.7% was associated with a reduction in death or CHF (HR 0.62, 95% CI: 0.41-0.95; p=0.029), confirming the importance of improving LVEF by guideline-directed therapies +/− revascularisation. How to best select patients for revascularisation is uncertain, given that myocardial viability testing at baseline was not predictive of benefit (similar to STICH), suggesting that our methods of measurement are not accurate or that other mechanisms play a role.

Despite not meeting its primary endpoint, REVIVED-BCIS2 did show that PCI was associated with an improvement in quality of life, similar to other trials of coronary revascularisation. This is particularly important given the minimal symptoms that were present at baseline. Moreover, similar to other PCI trials, the rate of spontaneous myocardial infarction (MI) was reduced: 18 (5.2%) in the PCI group versus 33 (9.3%) in the no PCI group (p=0.04 per my calculation with Fisher's exact test). Reduction in MI is particularly important in patients with LV dysfunction who may not be able to tolerate further loss of myocardium. Also, there was a trend for reduced need for automatic implantable cardioverter defibrillator termination of ventricular arrhythmias in the PCI group. These benefits alone may indicate a role for PCI in the management of these patients.

The REVIVED-BCIS2 study has limitations that make it difficult to apply its findings to broad clinical practice. First and

foremost, physicians want to provide the best care for their patients. It is likely that in many patients, critical multivessel CAD may have been treated with revascularisation outside of the study, as per guideline recommendations. However, it appears that neither an exclusion log nor a registry of non-randomised patients were maintained. Operators are often biased and will only randomise patients whom they do not believe need revascularisation, thus, a negative study becomes a self-fulfilling prophecy.

In addition, it is well known that patients with minimal symptoms are unlikely to have improvement in clinical outcomes. Despite being a trial of low EF, only 25% of patients enrolled in the REVIVED-BCIS2 study had New York Heart Association Class >II symptoms. Furthermore, 67% of patients had no angina and 31% had CCS class I-II angina. No patients had acute coronary syndromes (which is the predominant reason patients receive PCI globally).

One really does not know if coronary ischaemia is the cause of LV dysfunction. It is common to have a non-ischaemic cardiomyopathy with coincident coronary artery disease, and these patients are unlikely to benefit from revascularisation. Better methods of delineating the cause of LV dysfunction are greatly needed.

Furthermore, the jeopardy score in the REVIVED-BCIS2 study does not account for diffuse disease, since segments with <70% narrowing received a jeopardy score of zero. The study does not mention use of fractional flow reserve for intermediate-severity lesions, so it is likely that not all ischaemic areas were revascularised. It is concerning that the median number of lesions treated was only 2 and that half of the patients in REVIVED-BCIS2 had a revascularisation index of <80%. We know incomplete revascularisation is associated with an increase in long-term morbidity and mortality[7]. Perhaps greater use of haemodynamic support devices may have allowed more complete revascularisation.

It is also possible that the sample size was too small. The expectation of a 30% reduction in the primary endpoint (hazard ratio 0.70) is very ambitious in randomised trials − a target most therapies would not be able to achieve. Also, the duration of follow-up (3.4 years median) may have been too short. This is especially important since the primary endpoint in STICH was negative at 5 years, yet by 10 years, a mortality benefit was observed. In the REVIVED-BCIS2 study, cardiovascular mortality was numerically lower in the PCI group (21.9% vs 24.9%; HR 0.88, 95% CI: 0.65-1.20), and it is possible that these curves may have further diverged over time.

Finally, since this trial was conducted within the UK only, the results may be specific to Western Europe. This is an important limitation since the STICHES trial (which found a late mortality benefit for bypass surgery in patients with LV dysfunction) showed no benefit in patients who were white, those aged >60 years or in patients from Western Europe, precisely the patients enrolled in REVIVED-BCIS2.

Thus, PCI for LV dysfunction remains alive and well. PCI may not be necessary in all patients, but routine PCI does seem to reduce spontaneous MI, improve QOL and may reduce defibrillator shocks. Decision-making in such patients is complex, and we do not have the best tools to determine viability or predict future benefits of revascularisation. However, I strongly believe that all patients with LV dysfunction should have their coronary anatomy defined. If the patient has ischaemic symptoms or haemodynamically significant lesions, then revascularisation should be strongly considered.

Conflict of interest statement

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References

1. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, Michler RE, Bonow RO, Doenst T, Petrie MC, Oh JK, She L, Moore VL, Desvigne-Nickens P, Sopko G, Rouleau JL; STICHES Investigators. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. *N Engl J Med.* 2016;374:1511-20.

2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599-726.

3. Pathak S, Lai FY, Miksza J, Petrie MC, Roman M, Murray S, Dearling J, Perera D, Murphy GJ. Surgical or percutaneous coronary revascularization for heart failure: an in silico model using routinely collected health data to emulate a clinical trial. *Eur Heart J.* 2023;44:351-64.

4. Perera D, Clayton T, O'Kane PD, Greenwood JP, Weerackody R, Ryan M, Morgan HP, Dodd M, Evans R, Canter R, Arnold S, Dixon LJ, Edwards RJ, De Silva K, Spratt JC, Conway D, Cotton J, McEntegart M, Chiribiri A, Saramago P, Gershlick A, Shah AM, Clark AL, Petrie MC; REVIVED-BCIS2 Investigators. Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction. *N Engl J Med.* 2022;387:1351-60.

5. Daubert MA, Massaro J, Liao L, Pershad A, Mulukutla S, Magnus Ohman E, Popma J, O'Neill WW, Douglas PS. High-risk percutaneous coronary intervention is associated with reverse left ventricular remodeling and improved outcomes in patients with coronary artery disease and reduced ejection fraction. *Am Heart J.* 2015;170:550-8.

6. Velagaleti RS, Vetter J, Parker R, Kurgansky KE, Sun YV, Djousse L, Gaziano JM, Gagnon D, Joseph J. Change in Left Ventricular Ejection Fraction With Coronary Artery Revascularization and Subsequent Risk for Adverse Cardiovascular Outcomes. *Circ Cardiovasc Interv.* 2022;15:e011284.

7. Garcia S, Sandoval Y, Roukoz H, Adabag S, Canoniero M, Yannopoulos D, Brilakis ES. Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. *J Am Coll Cardiol.* 2013;62:1421-31.