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Title: Revascularisation and HFpEF – Time for Randomised Trials

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## Revascularisation and HFpEF – Time for Randomised Trials

Reducing mortality and hospitalisation has been the goal of almost every major clinical trial of coronary revascularisation yet achieving such benefits has been elusive in patients with stable coronary artery disease. Improving outcomes in heart failure with preserved ejection fraction (HFpEF) has also proven to be challenging with the first positive trial only being published in 2021[1]. As coronary artery disease is thought to be a major driver of the pathogenesis of HFpEF and is recognised to be highly prevalent in this population, it would seem reasonable to propose revascularisation as a treatment option for HFpEF[2]. In heart failure with reduced ejection fraction (HFrEF) revascularisation by coronary artery bypass grafting (CABG) reduced long-term mortality in the STICH trial[3]. The efficacy of percutaneous coronary intervention (PCI) in HFrEF has been investigated in the REVIVED-BCIS2 trial which will be presented in 2022[4]. It is therefore remarkable that there are no randomised trials published, or even recruiting, to investigate what looks to be an obvious therapeutic option for patients with HFpEF.

In this issue of the Journal, Deo and colleagues report the outcomes of patients with heart failure who underwent CABG in the Veteran Affairs Medical Centres in the United States between 2005 and 2019, focusing on those with HFpEF [5]. The occurrence of death, hospitalisation for heart failure (HHF) and myocardial infarction were compared between heart failure patients across the spectrum of ejection fraction as well as a control population without a history of heart failure. Estimated five-year mortality was highest in patients with HFrEF, intermediate in patients with mid-range ejection fraction (HFmrEF) and similar between patients with HFpEF and those without heart failure. Patients with HFpEF had higher risk of HHF in the first year after CABG, following which their clinical course appeared to mirror those without heart failure.

The reassuring outcomes of patients with HFpEF in the current analysis are at odds with prior data where outcomes were substantially worse than comparator populations (for example in Swedish and Japanese HFpEF cohorts undergoing coronary artery surgery, as well as decades of studies in other cohorts)[6,7]. This discordance in outcomes likely

reflects the identification of the current HFpEF cohort as well as the highly selected HFpEF population undergoing revascularisation for conventional indications. Patients undergoing CABG for conventional revascularisation indications are also very different than general community and hospitalised HFpEF populations; in the present study <1% of patients were female and the median age was far younger than contemporary registries and randomised trials in HFpEF. The current analysis identified patients with HFpEF based on ICD-10 codes rather than a conventional HFpEF diagnostic tools including cardiac biomarkers and echocardiography. Furthermore a left ventricular ejection fraction greater than 55% was chosen in contrast to recent guideline definitions (>50% in the European (2021) and American (2022) heart failure guidelines)[8,9].

The current data might lead the reader to conclude that CABG is “safe” in patients with HFpEF but this is not a conclusion that can be drawn from this low risk cohort. Only randomised trials will determine the safety and efficacy of CABG in HFpEF. These trials should enrol patients who have HFpEF and coronary artery disease where there is equipoise with respect to the whether or not CABG may confer benefit, likely limiting eligibility to those who are ambulatory and whose HFpEF syndrome appears to be driven by coronary artery disease. Harm is important to remember during revascularisation as a treatment for HF, as illustrated by the STICH trial where 9% of patients had either died or remained in hospital 30 days after CABG. Any benefit of CABG has to “catch up” after the harm sustained during the index revascularisation procedure.

Bypass surgery is a major undertaking for HF patients. Revascularisation with PCI avoids general anaesthetic, sternotomy and intensive care and may be achievable in more of the HFpEF population. As with CABG, however, the efficacy of PCI as a treatment for heart failure cannot be assumed and needs to be tested in randomised trials. Whilst PCI generally confers a lower procedural risk than CABG, increasing comorbidity in this population leads to important safety considerations. Prolonged courses of antiplatelet therapy in a HFpEF population with a high prevalence of iron deficiency confer a significant bleeding risk, particularly when combined with anticoagulants for atrial fibrillation. Contrast induced nephropathy is more likely in a HFpEF population with a high prevalence of chronic

kidney disease. Only trials of PCI versus CABG versus medical therapy alone will inform the clinical community of the pros and cons of revascularisation in HFpEF.

Rates of coronary angiography and revascularisation are known to be low even in patients with newly diagnosed, hospitalised HFrEF in insured populations in the United States, with only 11% undergoing angiography within 3 months of diagnosis and 2.1% undergoing revascularisation in the largest and most recent registry)[10]. At present no data are available to describe how many people with HFpEF undergo angiography or revascularisation.

The mechanism of benefit of revascularisation in HFrEF is not understood. CABG was thought to improve LV systolic function but CABG did not improve systolic function in STICH [11,12]. Perhaps CABG reduces ventricular arrhythmias and spontaneous myocardial infarction. In HFpEF revascularisation might result in clinical benefit by a variety of mechanisms. There is some preliminary evidence that coronary revascularisation might prevent a deterioration in systolic function in this population[13]. Reduction in ischaemia may be a driver of benefit, particularly in relation to improving exertional symptoms[14]. Atrial arrhythmias are common in HFpEF and are associated with higher morbidity and higher mortality. Reducing ischaemia may reduce the burden of atrial arrhythmias, either directly or via improvements in diastolic function. Improving diastolic function or increasing cardiac output may reduce left atrial and venous pressure or reduce pulmonary congestion and improve renal perfusion.

In summary the current study highlights an important question but cannot inform practice. We remain at the foothills of understanding whether or not patients with HFpEF and significant coronary disease should undergo coronary revascularisation, what modality of revascularisation should be used. Even the simple question of whether investigation for coronary disease should be offered remains unclear. As a consequence, current revascularisation guidelines make no mention of HFpEF even as an entity [15,16]. Definitive answers will only be developed through randomised trials, yet none are in progress. In the interim, the involvement of heart failure cardiologists in heart team discussions on coronary

revascularisation is essential to ensuring that the specific needs of patients with HFpEF are considered.

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