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Rethinking Revascularization in Left Ventricular Systolic Dysfunction

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Patients with chronic heart failure with reduced ejection fraction (HFrEF) now have multiple therapeutic options, including oral medications and cardiac devices, that improve quality of life, reduce the risk of readmission, and/or improve mortality. In the span of only decades, the goals of treatment has moved dramatically upstream from supportive care towards HF stabilization, reversal, and prevention. Those caring for HF patients now face new challenges of integrating sophisticated genetic, biomarker and imaging information in the pursuit of patient-centered care while delivering guideline-directed therapies across an increasingly fragmented health care landscape for HF patients who are likely to have multiple comorbidities and an expanded treatment time horizon.

For one, consider the number of oral medications available to patients. A recent study examined the difference between a patient's medication regimen at hospital admission for HF and that recommended by HF quality measures at discharge.¹ Among patients with HFrEF discharged between 2008 and 2013, 82% of patients needed to start at least 1 medication to meet HF quality measures and 55% need to start >1 medication. These numbers do not include additional medications indicated for non-HF comorbidities such as coronary artery disease, and with the recent update on new pharmacological therapy,² two more oral medications have been added to guideline recommendations. Second, some of the art in managing chronic HFrEF today involves the careful avoidance of medication stacking and polypharmacy. Many oral medications in chronic HFrEF modulate maladaptive neurohormonal pathways, such as the renin-angiotensin-aldosterone axis, and tolerance of all the available therapies for this pathway is limited by overlapping side effect profiles (e.g., hypotension and hyperkalemia).

In this context, it is important to recognize that coronary revascularization addresses an important therapeutic pathway with a unique treatment target for many patients with HFrEF. In this issue of *Circulation: Heart Failure*, Wolff et al report the results of meta-analysis of available data comparing surgical and percutaneous revascularization strategies to each other and to medical therapy alone in patients with left ventricular systolic dysfunction (LVSD).³

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Compared to medical therapy alone, there data support a significant mortality reduction with coronary bypass surgery (hazard ratio (HR) 0.67 [95% confidence interval (CI) 0.51 to 0.86]; $P < 0.001$) and percutaneous coronary intervention (PCI) (HR 0.73, [CI 0.62 to 0.85]; $P < 0.001$). When comparing different methods of revascularization, coronary bypass surgery was associated with a survival benefit compared to PCI (HR 0.82 [CI 0.75 to 0.90]; $P < 0.001$). These findings will both better inform the daily interactions between patients and providers and may impact treatment guidelines regarding the strength of recommendation particularly for surgical revascularization for LVSD.

While the authors are to be commended for adding this meta-analysis to a growing body of literature on revascularization in patients with LVSD, important caveats must be acknowledged. This study draws on data from a limited number of mostly observational studies. Only 3 of the 21 (14%) studies included in the meta-analysis were randomized clinical trials (RCTs) with the STICH trial⁴ providing 1212 of 1779 (68%) of the RCT patients and the vast majority of patient life-years of follow-up. While well-done meta-analyses are valuable tools in evidence development, the majority of the pooled data here are still limited by the challenges of observational studies. Observational (non-randomized) studies of procedural interventions and surgeries are particularly susceptible to treatment selection bias even after adjustment for measured confounders.

A second important consideration is to acknowledge that data included in the meta-analysis by Wolff et al were published between 1983 and 2016. As previously described, there have been significant advances in medical therapy for HFrEF over time. The same is true for medical therapy for coronary artery disease (e.g., improved risk factor modification) and revascularization techniques (e.g., use of fractional flow reserve to guide revascularization as well as improvements in stent technology). Importantly, the use of evidence-based medications known to impact survival are not summarized across the comparator groups and are not available for many of the studies included. Although the authors performed sensitivity analyses to account for changing medication use patterns over the years, caution is required before generalizing these findings to a patient seen today receiving contemporary guideline-directed medical therapy.

With these caveats in mind, the current evidence squarely supports surgical revascularization and accelerated evidence development for PCI in appropriate patients on a background of guideline directed medical therapy. However, important challenges must be considered as the cardiovascular community embarks on a more proactive approach to revascularization for LVSD. For one, the scope of the potential benefit to patients in the United States is unknown. Part of the reason for this is that the prevalence of coronary disease among patients with HF is somewhat unclear, with estimates ranging from 36% to 68% depending on the population of interest and study design.⁵ Further illustrating this point, a recent study noted significant underutilization of testing to evaluate for coronary disease among patients with new-onset HF.⁶ In a study of claims data from 2010 to 2014 from over 67,000 patients hospitalized with new-onset HF, only 18% received an invasive or noninvasive test for ischemic heart disease during the index hospitalization, and only 27% received a test within 90 days following the index admission. Secondly, although epicardial coronary disease is well known to play an important role in the pathophysiology of HF, there are remarkably

limited data in patients with HF detailing the interplay of coronary artery disease progression, myocardial dysfunction and contemporary medical therapy. Surprisingly, traditional constructs that informed decision making for revascularization such as the presence of angina, myocardial ischemia and/or viability did not perform as expected in STICH⁷⁻⁹ and may not represent appropriate nodal points to define candidacy for revascularization in LVSD. Whether this reflects the high utilization of guideline directed medical therapy in both the surgical revascularization and medical therapy only arms in STICH or because these constructs are not sufficiently predictive in LVSD or due to yet undefined factors remains unclear and is deserving of further study. Accordingly, the current approach to the diagnosis of coronary artery disease as a prerequisite to revascularization consideration is highly variable, predominantly reactive, likely deficient and its systematic modification represents a major opportunity to improve outcomes in HFrEF.

With these considerations in mind, how should the findings by Wolff et al. impact current clinical practice and research? These data supporting revascularization should lead to studies assessing cost-effective approaches for timely, accurate diagnosis and refined estimates of the current burden of ischemic heart disease in US patients with HFrEF. Quality improvement efforts in HF could adopt testing to evaluate for coronary disease among patients with new-onset HF as a quality metric to accelerate translation. In addition, on the backdrop of STICH results and supported by this report, we believe RCTs are now urgently needed to define the role of PCI as an alternative to surgical revascularization in candidates for both procedures as well as against medical therapy alone among those patients who perhaps due to co-morbidity or preference are not surgical candidates such as the Study of Efficacy and Safety of PCI to Improve Survival in HF (REVIVED-BCIS2), currently enrolling in the United Kingdom.¹⁰ Finally, the data by Wolff et al should embolden providers to search proactively for coronary artery disease in patients presenting with LVSD and include revascularization in the conversation as a treatment option if established. These discussions should be informed by evaluation of a multidisciplinary Heart Team and must be guided by patient expectations and preferences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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