

# An Age-Old Question

## What Is Too Old for Coronary Artery Bypass Grafting in Heart Failure?

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**T**he dilemma of how best to treat patients with severe coronary artery disease (CAD) and reduced left ventricular ejection fraction continues to perplex clinicians. One lone, but notable randomized trial, STICH (Surgical Treatment for Ischemic Heart Failure)<sup>1</sup>, and its 10-year follow-up report, STICHES (STICH Extension Study)<sup>2</sup>, has helped clarify this clinical challenge. When a clinician is faced with clinical equipoise in a patient with a low ejection fraction and revascularizable CAD, coronary artery bypass grafting (CABG) in combination with optimal medical therapy (MED) provides an eventual reduction in cardiovascular mortality and hospitalizations, and an increase in overall survival, as long as an appreciable but not unanticipated early hazard of surgical mortality is accepted. Yet, it is important to understand that the conclusions are more nuanced than just presented. Despite this landmark study, the complexity of routine clinical practice poses several common quandaries that continue to be debated. Perhaps none is more difficult than what to do with the older patient with heart failure and a reduced ejection fraction attributable to CAD.

In the current issue, Petrie and coinvestigators present a post hoc analysis from the STICHES report in which they ask the relevant clinical question of whether all age groups studied in the STICHES trial derived the same benefits of CABG added to MED in comparison with MED alone.<sup>3</sup> For this analysis, the authors divided the STICHES cohort into age-based quartiles: Q1≤54 years, Q2>54 and ≤60 years, Q3>60 and ≤67 years, and Q4>67 years. When examining outcomes based on these quartiles, cardiovascular-related mortality was high and did not vary between the oldest and youngest quartiles in either randomized group. Consistent with the original report, CABG added to MED reduced cardiovascular mortality across all age quartiles in a statistically significant manner. Not surprisingly, they also observed that the oldest patients experienced greater all-cause mortality than the younger patients, regardless of randomized group. The reduction in all-cause mortality by CABG + MED did not reach statistical significance in the >67 years of age quartile (0.82; 95% confidence interval, 0.63–1.06), although younger patients (eg, <54 years) did experience a clear reduction in all-cause mortality (0.66; 95% confidence interval, 0.49–0.89). This observation was likely driven by the fact that cardiovascular-related deaths comprised a smaller proportion of all deaths in the oldest cohort. These differences in proportional cardiovascular mortality with respect to all-cause mortality are consistent with the greater comorbidity burden in the oldest quartile.

This particular analysis provides important and unique information to clinicians who struggle with providing advice to older patients with ischemic cardiomyopathy because cardiac surgery in the elderly has become commonplace. The strengths of this study are several and should be emphasized. STICHES is the only randomized trial of contemporary CABG for the treatment of severe ischemic left ventricular dys-

The opinions in this article are not necessarily those of the editors or of the American Heart Association.

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function that is available for such an analysis. The sample size was large, the study was well conducted, and the follow-up was remarkably long for any prospective study, much less a randomized trial. Compliance with MED in both arms was impressively maintained over the decade following the trial. Age was also a prespecified analysis at the time of study design. In addition, despite the necessary lack of blinding with randomization, the adjudication of events was done in a blinded fashion.

The investigators also appropriately provided limitations to the study. These issues are relevant and bear repeating. Women were underrepresented, the analysis was post hoc, and the selection bias limits generalizability. Two other acknowledged points deserve emphasis: (1) the number of truly older patients was small, eg, only 201 patients (16%) were >70 years of age (75 [6%] patients were >75 years of age) and (2) study sites were highly selected in that surgical expertise had to be demonstrated.

In light of these 2 issues, how well does this study inform us about the benefits of CABG+MED in older patients with heart failure and a reduced ejection fraction and CAD in routine clinical practice?

Older age is a well-recognized, powerful, and principal driver of mortality risk in cardiac surgery.<sup>4</sup> Although a testament to the surgical centers in this trial, the lack of increased mortality in the older cohort and comparable bypass times and intensive care unit stays suggests that either the patients were highly selected, the surgical teams remarkably skilled, or the patients were simply not that old from an operative mortality standpoint. In any of these scenarios, the findings are not clearly generalizable to routine clinical practice. The predominant enrollment of younger patients in this trial (eg, median age of 60 years) may reflect the lack of clinical equipoise clinicians had when enrolling older patients into this trial, which parenthetically had to be extended and the sample size reduced because of slow enrollment.<sup>1</sup>

What constitutes older is certainly in the eye of the beholder. Heart transplantation is no longer uncommon in the 65- to 70-year age group, and the use of left ventricular assist devices in this age group and older is frequently encountered. Contemporary registries of populations with heart failure and a reduced ejection fraction suggest that the median age is commonly >70 years, although the age in clinical trials is often in the mid-60s. Moreover, older age cutoffs in cardiac surgery vary tremendously by center and in the literature. Importantly, older patients die of processes that are not likely modifiable by CABG (although CABG did not appear to accelerate these processes). Frailty is an important case in point.

For older (and likely most) patients, the relevance of cardiovascular mortality versus all-cause mortality will be difficult to appreciate or reconcile. Some have pro-

posed that defining older age cutoffs in cardiac surgery would be more relevant if associated with prognosis. Using this approach, Afilalo and colleagues<sup>5</sup> used data from the Society of Thoracic Surgeons and POSSE (Pre-Operative Surgical Stratification by Echocardiography) to determine an inflection point of mortality with respect to age and concluded that  $\geq 75$  years of age was the optimal cutoff to identify older patients at greater risk with isolated CABG. In comparison, a review of the top graph in Figure 2 from the current article by Petrie et al would suggest that, between the ages of 60 and 70 years, the hazard ratio and confidence intervals for all-cause mortality appear to straddle unity. Extrapolation of mortality in patients in their 60s to those older is made even more challenging when one recognizes that the relationship between age and adverse outcomes is exponential rather than simply nonlinear.<sup>6</sup>

The issue of an early hazard is also not discussed in any detail. In the primary report, the all-cause mortality in the surgical arm was greater than in the medical arm and did not cross over until year 2. From a population perspective, the eventual benefit is compelling over the long term. However, from a patient perspective, the short-term hazard is a relevant concern that should not be discounted. An examination of the Kaplan-Meier plot for all-cause mortality for CABG+MED shows a mortality of what appears to be >10% in the first few months in the 60- to 67-year age group.

Another important consideration in older patients is the quality of their daily lives. A quality-of-life analysis from the original STICH report did note that patients who had CABG added to MED felt better,<sup>7</sup> but the effect attenuated over time. Although it is tempting to extrapolate this observation to older patients, surveys have suggested that the impact of quality of life relative to mortality is highly individual<sup>8</sup> in patients with heart failure. Hopefully, future reports with respect to age and quality of life from this study will be forthcoming from this investigative group.

Some details of the STICH and STICHES reports are worth recalling to put these findings into perspective. The original report from 2011 noted that angina was common and symptoms of heart failure were modest, but left ventricular volumes were large. How long symptomatic heart failure was present was not reported. The use of implantable cardioverter defibrillators was low in both arms despite the average age of 60 years. Survival was good for a heart failure study with a 10-year all-cause mortality of  $\approx 40\%$  to  $50\%$ . Both the surgical and medical therapies were carefully supervised and regularly reviewed. In particular, to be selected as an operator in STICH, surgeons had to provide data on at least 25 patients with an ejection fraction of  $\leq 40\%$ , demonstrating an operative mortality of  $\leq 5\%$ . The period of time over which this experience was gleaned was not reported. It would be of interest to examine

the number of contemporary cardiac surgeons who achieve this bar.

The authors should be congratulated on the completion and extended follow-up of one of the most important trials ever to have been conducted in cardiovascular disease, one not likely to be repeated again. They have clearly made the case that age alone should not disqualify a patient for the potential benefits of CABG added to MED for heart failure with a reduced ejection fraction and CAD, but it is not to be ignored. Clinicians can feel more at ease that there is a cardiovascular mortality benefit to CABG in patients with significant ischemic left ventricular dysfunction across a spectrum of age (and particularly those <67 years of age) when there is clinical equipoise. However, it is still not clear if these benefits will extrapolate to overall mortality in older patients. It would appear that this age-old question will remain unanswered for now.

## DISCLOSURES

None.

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## FOOTNOTES

*Circulation* is available at <http://circ.ahajournals.org>.

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## An Age-Old Question: What Is Too Old for Coronary Artery Bypass Grafting in Heart Failure?

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