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Commentary: Bias in cardiac surgery trial design

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CENTRAL MESSAGE

Proposed randomized trials of transcatheter versus surgical degenerative mitral repair are biased towards the transcatheter arm.

In their analysis in this issue of the *Journal* of 1155 patients who underwent degenerative mitral repair between 2004 and 2018, the Northwestern team of Imielski and colleagues[1] found residual mild mitral regurgitation was a risk factor for progression to moderate to severe regurgitation. Because residual regurgitation was uncommon (6% of patients), however, reoperation was rare. The echocardiographic follow-up averaged only 3 years, and clinical follow-up was 5 years and 91% complete. So these results may be consistent with 20-year outcomes from Toronto and Cleveland—with similarly low rates of residual mild regurgitation, recurrence of significant regurgitation was 13% in long-term follow-up, predicted by mild residual regurgitation, and associated with reduced survival.[2,3]

These findings underline the importance of leaving the operating room with minimal residual regurgitation. More importantly, they underline the importance of leaving the *catheterization laboratory* with minimal regurgitation—which is currently difficult to achieve consistently in patients with degenerative regurgitation with the MitraClip (Abbott, Abbott Park, Ill), for which reported rates of 2+ or greater residual regurgitation approach 30%.[4] With that in mind, how could you design a pivotal trial of transcatheter versus surgical repair so that it favored transcatheter repair in degenerative mitral regurgitation?

There are 5 ways:

1. Pick a primary end point favoring the percutaneous approach. For example, in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) MitraClip trial, blood transfusion was included in the composite end point, weighted equally with mortality and stroke.[5] A composite end point including unplanned rehospitalization is another example of an end point that generally favors percutaneous devices over surgery, because 20% to 30% of patients are readmitted postoperatively for diuresis or atrial fibrillation.
2. Specify short follow-up. In addition to facilitating earlier Food and Drug Administration approval, 2-year follow-up favors the least invasive option and minimizes the opportunity to observe how incomplete or ineffective treatment affects long-term survival and quality of life.
3. Choose a noninferiority design. It is easier (requires less efficacy and fewer patients) to show that outcomes are not significantly worse than to demonstrate that they are significantly better.
4. Select the best interventionalists, in this case, the minority who reliably achieve the greatest freedom from residual regurgitation. Device companies maintain detailed registries, including residual regurgitation, data that inform their choice of participating trialists.
5. Select patients equally carefully. Although the patient inclusion criteria need to be sufficiently broad (for example age >75 years, or 1 comorbidity) to ensure that the device is approved for the largest possible population, the anatomic inclusion criteria should play to the device's strengths—for example, patient selection based on echocardiographic evaluation by a core laboratory.

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Most, if not all, of these are features of the MITRA-HR trial,[6] and they also match initial descriptions of the Food and Drug Administration pivotal trial of MitraClip for degenerative mitral regurgitation. Consequently, these trials will likely provide a platform supporting MitraClip in degenerative disease in what are essentially patients at low surgical risk—the same patients that Imielski and colleagues[1] and others demonstrate are so well served by surgery. Unlike the aortic valve, a setting in which low-risk patients lose little by deferring surgery for transcatheter replacement, low-risk patients with degenerative mitral disease are trading length and quality of life for expediency with current transcatheter repair. This is because residual regurgitation is common after transcatheter repair, challenging to rerepair, and effectively consigns such patients to valve replacement—which significantly reduces life expectancy relative to a durable surgical repair.

Astonishingly, we are about to provide ''evidence'' supporting this.

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