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EDITORIAL COMMENT

Evaluating Catheter-Based Mitral Valve Therapies

Lessons Learned and Future Directions*

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In this issue of the *Journal*, the EVEREST II (Endovascular Valve Edge-to-Edge REpair Study II) investigators have reported the 5-year results of their randomized trial comparing percutaneous edge-to-edge mitral valve repair, using the MitraClip device (Abbott, Menlo Park, California), with mitral valve surgery (1). The primary outcomes of the trial

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have been previously published (2). We congratulate the investigators for concluding an important pivotal study in the emerging field of transcatheter mitral valve therapy and for providing key information on percutaneous edge-to-edge mitral repair. We have already learned 4 principal lessons from the EVEREST II trial: 1) the clip procedure is safe; 2) the clip may be applied to both degenerative and functional subtypes (although with less efficacy in reducing mitral valve regurgitation compared with surgery); 3) patients may safely undergo surgical reintervention if the clip fails; and 4) improvements in symptoms occur after successful clip treatment. The U.S. Food and Drug Administration (FDA) has now approved the device for use in the United States for patients with significant symptomatic degenerative mitral regurgitation (MR) who are too high risk for surgery. The role of clip therapy in functional MR has not been established and is the subject of an ongoing U.S. trial (3), but the device is widely used in Europe for this indication (4).

The current report provides new data on the midterm performance of the clip in the EVEREST II study. Device failure and need for surgical intervention were uncommon after the first year post-clip implant, and importantly, midterm mitral stenosis occurred in <1% of implants. Clip repairs did have a higher midterm incidence of reoperation and recurrence of moderate or severe regurgitation compared with surgery; however, patient survival was the same (1).

The EVEREST II trial was pioneering and, despite concerns regarding the trial design and conduct (5), the experience and observations from this study provide future investigators with a framework on which to conduct trials of transcatheter mitral valve therapy (**Table 1**). We have previously discussed the unique features that will set apart trials of transcatheter mitral valve replacement (TMVR) from those of transcatheter aortic valve replacement (6). The EVEREST II study demonstrates that trials of percutaneous mitral valve repair pose even greater challenges. Several lessons gleaned from the EVEREST II study can help form the framework for future trials of transcatheter mitral valve therapy.

STUDY POPULATIONS

A major limitation of EVEREST II was the inclusion of both degenerative MR (for which the role of surgery is certain) and functional MR (where the role of surgery and transcatheter intervention remain uncertain). This greatly limited interpretation and applicability of the results. The trial was unable to draw conclusions regarding the role of the clip in either functional or degenerative etiology, because neither was specifically studied. Even within the degenerative

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TABLE 1 Key Elements for Future Trials of Percutaneous Mitral Valve Repair

1. Study populations should not be heterogeneous.
2. Inclusion criteria should mirror current guidelines and practice.
3. High-quality repair centers are critical.
4. Maintaining patient compliance should be a major focus.
5. Young and low-risk patients should be excluded from trials of irreversible devices.
6. Endpoints should be clinically relevant.
7. Inclusion criteria should mandate planned surgical repair of the valve.

group, there is a spectrum of pathology and lesions that have different implications for valve repairability (7). Although there is an obvious attraction to study all-comers, doing so risks the same predicament of EVEREST II, as it can be impossible to draw reliable conclusions about relevant clinical subsets. To demonstrate *effectiveness* of a percutaneous mitral therapy, study of a well-defined etiology (such as degenerative) and lesion subset (such as P2 prolapse due to chordal rupture) will likely yield results that are more definitive.

INCLUSION CRITERIA

To allow generalizability of results, inclusion criteria should closely mirror current practice and agreed indications for intervention. In EVEREST II, the inclusion criteria included asymptomatic or symptomatic patients with moderate to severe (3+) regurgitation (8), whereas current and previous guidelines recommend mitral valve surgery for only patients with severe (4+) regurgitation (9–11). Only 24% of patients in EVEREST II had severe MR, as defined by their core laboratory assessment (2). The majority (71%) had moderate to severe regurgitation—some of these patients, particularly those without symptoms, may not meet agreed criteria for intervention in current practice. Indeed, although indication for surgery was a prerequisite for trial entry, about one-third (13 of 41) of patients who had a failed attempt at device placement did not undergo subsequent surgical operation during the initial study period (5), raising the question as to how strong an indication for surgery had existed in those patients in the first place. It therefore becomes difficult to extrapolate the EVEREST II results, as there is the possibility that the clip was used on less-severe stages of disease. Of note, 5% of patients in the study had mild or moderate MR, and should not have met criteria for study inclusion; this highlights the importance of core laboratory adjudication of echocardiographic images *before* recruitment of patients into trials.

QUALITY OF CENTERS

Although the paper did not provide a breakdown of volume and outcomes among trial centers (1), this was a likely variable. The mean number of clip procedures per center was 5 and the mean number of surgical procedures was 2.5. Most probably there was considerable variation with relatively few high enrollers and others as low enrollers. Procedural outcomes may be linked to experience with the new technology and with previous experience, such that low enrollers may remain in early stages of the learning curve for an entire study. Additionally, a high enroller with suboptimal techniques and outcomes could negatively influence measured effectiveness of a new device. Although it is desirable to include many centers to allow quick enrollment in a trial, a more restricted number of participating centers with balanced recruitment volume and procedural quality will likely give a more robust assessment of effectiveness of a novel device, albeit at the expense of a longer recruitment period. It may be argued that including more centers presents a pragmatic real-world experience, but it should be remembered that the role of trials of new devices is *not* to determine how they perform in the real world, but to determine whether they are safe and effective when used in a proscribed and ideal manner.

To test the effectiveness of percutaneous versus surgical *repair*, trialists should choose surgical centers on the basis of expertise in mitral valve repair, rather than expertise in mitral valve surgery (which includes also valve replacement), as the skills for replacement and repair are not interchangeable. The EVEREST II investigators do not report whether specific surgical expertise or volume in mitral valve *repair* was a prerequisite for the 37 participating centers (2,8). Public information from the FDA in their executive summary of EVEREST II, however, indicated that a high proportion of patients with adverse events in the surgical arm were operated on by surgeons who performed <15 mitral valve repairs per year (5). Utilizing low-volume mitral valve repair surgeons to perform trial procedures may not allow measurement of the true effectiveness and safety of surgery. Of note, the surgical arm of the EVEREST II trial had a 14% valve replacement rate, and the only significant predictor for valve replacement in the surgical cohort was the presence of bileaflet prolapse, which was present in 47% of the replaced valves (12). In experienced repair centers, bileaflet prolapse should not be a strong predictor for replacement, as

high-volume mitral repair surgeons routinely repair such valves at a rate exceeding 95% (13–16). In addition, bleeding, which was the main complication in the primary safety composite outcome (2), was weighted toward low-volume centers (5). All these suggest that center volume and experience could have confounded the results of EVEREST II. For future trials, surgical center selection should be on the basis of the ability to deliver guideline-recommended therapy for the mitral disease being studied at a rate pre-specified by investigators. At a minimum, the researchers should disclose the full dataset, including enrollment volumes and key variations per site.

PATIENT COMPLIANCE

Maintaining consent in trials of percutaneous devices versus surgery can be difficult, as the EVEREST II trial demonstrates. Compared with 3% in the clip arm, 16% of those randomized to surgery withdrew from the study after randomization (2). Although these patients were included in an intention-to-treat analysis (2), in reality they cannot be seen as a reflection of the effectiveness of a *procedure* (but rather the effectiveness of a strategy). From the device perspective, what is most important is the effectiveness of the procedure in patients who actually received the procedure, or in whom it was attempted. In *effectiveness* or *safety* trials comparing percutaneous valve therapy to surgery, the results of all analyses (intention to treat, as treated, per protocol, and so on) should be presented to fully evaluate the trial.

Late follow-up also was an issue in EVEREST II. The 12-month completeness of follow-up was 94%, whereas at 5 years it was 87% in the clip group and 70% in the surgical group (1). The higher late follow-up rates in the clip group could be indicative of bias in perception by patients or bias in follow-up by recruiting centers. Such biased follow-up could have bearing on study outcomes (better follow-up could translate into superior medical management and surveillance, for example). Trial design should take into account these considerations. Preferably, the source of patients for entry should be patients who have already accepted surgical treatment (and are then introduced to a concept of a trial of a less-invasive approach), as opposed to patients with a disease who are primarily seeking the least invasive therapy. Randomization after anesthetic induction is one strategy that can circumvent withdrawals after randomization.

INCLUSION OF YOUNG AND LOW-RISK PATIENTS

Early technical failures are inevitable with any percutaneous (or surgical) repair. As failures will generally necessitate surgical intervention, the frequency of failures and the outcomes of patients with failed techniques or devices is particularly relevant. In EVEREST II, 21% of patients who were randomized to a clip subsequently underwent surgical operation within the first year because of residual regurgitation (12). Of these patients, 46% had the valve replaced, and 54% were repaired (12). The overall valve replacement rate in the first year for patients who received the clip was 10%. Therefore, a young asymptomatic patient with mitral valve prolapse undergoing clip placement could have up to a 10% probability of ending up with a valve replacement. In contrast, the same patient having surgery in a reference center should expect a valve replacement rate below 1% (13).

The key factor driving replacements (as opposed to repair) after failed percutaneous clip repair appears to have been leaflet injury by the clip (5,12). Therefore, the possibility of permanent injury to the valve should be considered when selecting patients for trials of repair devices. If devices have an effect on the valve that is irreversible, or only partially reversible, then testing should be avoided in young and asymptomatic patients (as surgical valve replacement is particularly undesirable and negatively impacts life-expectancy). Such devices should preferably be tested on patients at high surgical risk, patients in whom valve replacement would not be an unreasonable option (such as rheumatic or functional etiology), or patients in whom the consequences of valve replacement may be less pronounced (such as older patients). All TMVR devices, by definition, would also fall into the category of devices with an irreversible effect on the valve. Devices under development for investigation and use on low-risk patients should not permanently damage the valve in a way that could compromise subsequent surgical repair.

ENDPOINTS

The essence of mitral valve intervention is resolution of MR. All patient benefits stem directly from this effect. In primary MR, “the disease” is MR (11), and its elimination should be the primary effectiveness endpoint. However, its elimination in secondary MR, although necessary, is not sufficient to evaluate the clinical utility of surgical or transcatheter mitral valve

intervention. Primary effectiveness endpoints in secondary MR should be chosen to demonstrate clinical improvement.

The EVEREST II investigators used a composite primary endpoint of death, freedom from surgery for mitral valve dysfunction, and freedom from grade 3+ or 4+ MR (73% in the surgery group vs. 55% in clip group) (2). This primary endpoint was controversial and was challenged by the FDA, which believed freedom from 2+ (moderate) or greater regurgitation was a more appropriate measure (5). Indeed, a post-hoc analysis of EVEREST II data with freedom from more than 2+ (rather than 3+) regurgitation as the main driver of the composite endpoint in a modified intention-to-treat population found that only 31% of clip patients would have met the more stringent primary endpoint, compared with 77% of surgical patients (5). Future trials should provide similar sensitivity analyses to test key assumptions around primary endpoints, so readers can attain a complete picture of the data.

It is also problematic to have death as part of an effectiveness endpoint for mitral repair devices, as mitral valve repair is not typically performed to enhance short-term survival. In a strict sense, death should be part of a safety endpoint, as should other major adverse major clinical events. Composite safety endpoints should generally include death, major adverse cardiac and cerebrovascular events, major infective complications, major vascular complications, major organ dysfunction, major bleeding episodes, and other events specific to the procedures or mitral disease being studied.

The inclusion of 2 units (U) or more blood transfusion as part of the primary safety composite endpoint in EVEREST II heavily skewed the safety outcomes in favor of the clip (15% adverse events with clip vs. 48% with surgery). If blood transfusion (which was present in 45% of those who had surgery) is excluded, the adverse event rates were 5% for the clip and 10% for surgery (2). A major driver for blood use in the surgical arm was the addition of concurrent procedures (such as coronary bypass, maze, or other valve surgery) in almost one-half the surgical patients—considering that no clip patients received concomitant procedures, this adds another unmeasurable source of bias to the study (5). Ideally, the 2 arms of a percutaneous versus surgery trial should differ only in the mode of delivery of valve therapy, and not also in concomitant application of other procedures. Where bleeding is used as part of a safety endpoint, investigators should consider the approach proposed by the Mitral Valve Academic Research Consortium (MVARC) (17), which requires the presence of overt bleeding and also considers drop in hemoglobin and clinical sequelae of bleeding, rather than transfusion alone, to classify bleeding as an adverse event. MVARC defines criteria for minor, major, extensive, life-threatening, and fatal bleeding events, and on the basis of MVARC classification, 2 U of blood transfusion (used in the EVEREST II as part of the safety endpoint) would constitute a minor bleeding event, 3 U transfusion would be major, and 4 U transfusion (or a hemoglobin drop of 4 g/l in 24 h) would be extensive bleeding. Bleeding into critical organ space (such as causing cardiac tamponade or cerebral effects) would be life-threatening, regardless of whether blood was transfused. The bleeding endpoint chosen should be relevant for the procedure being studied—for surgical procedures where minor blood loss is obligatory, minor bleeding should not constitute a safety endpoint (but extensive bleeding should), whereas for a trial of 2 percutaneous approaches, even a minor bleed may be deemed relevant.

Finally, investigators should resist the temptation to evaluate device effectiveness on the basis of 1-year follow-up alone. We have learned more about the clip therapy from this 5-year report that would not have been known if the study closed after the 12-month primary report. Other investigators should follow the model of EVEREST II and maintain follow-up for at least 5 years after study closure, as this midterm information is critical for durability evaluation.

INCLUSION CRITERIA

The EVEREST II investigators specified the key study inclusion criterion as patients who are candidates for mitral valve repair *or* replacement. The clip, however, is a mitral valve *repair* device and should be an alternative to surgical repair and not surgical replacement. Thus, the results are confounded because: 1) allowing valve replacement candidates resulted in a lower frequency of surgical repair both directly (by allowing surgeons a priori to decide preoperatively that a patient would have a replacement) and indirectly (by permitting surgeons to convert intraoperatively to replacement without impact on study endpoints); and 2) percutaneous repair will likely be less efficacious in those patients whom a surgeon has decided a priori would have a valve replacement (if undergoing surgery). In surgical arms of repair device trials, a surgical valve replacement should be seen as a failure to meet an effectiveness endpoint in the same way that a valve replacement after a failed percutaneous device is deemed a therapeutic failure. In EVEREST II, the 14% in the surgical

arm who received valve replacement should have been deemed surgical failures to make a fair comparison with percutaneous repair. Future trials of percutaneous or surgical *repair* devices should pre-specify surgical repairability as an inclusion criteria, and any valve replacement (surgical or percutaneous) should be seen as a failure.

We applaud the EVEREST II investigators for pioneering a new field of investigation and therapy in mitral valve regurgitation. The lessons we have learned from this trial will allow us to better conduct and understand trials on newer percutaneous repair devices, which will likely emerge over the next decade.

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