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VIEWPOINT

# Randomized Trials Are Needed for Transcatheter Mitral Valve Replacement



Jason H. Rogers, MD,<sup>a</sup> Paul Sorajja, MD,<sup>b</sup> Vinod H. Thourani, MD,<sup>c</sup> Rahul Prakash Sharma, MD,<sup>d</sup> Bassem Chehab, MD,<sup>e</sup> Jennifer Cowger, MD, MS,<sup>f</sup> David Heimansohn, MD,<sup>g</sup> Vinay Badhwar, MD,<sup>h</sup> Mayra Guerrero, MD,<sup>i</sup> Gorav Ailawadi, MD<sup>j</sup>

## ABSTRACT

Transcatheter mitral valve replacement (TMVR) is a new therapy for treating symptomatic mitral regurgitation (MR) and stenosis. The proposed benefit of TMVR is the predictable, complete elimination of MR, which is less certain with transcatheter repair technologies such as TEER (transcatheter edge-to-edge repair). The potential benefit of MR elimination with TMVR needs to be rigorously evaluated against its risks which include relative procedural invasiveness, need for anticoagulation, and chronic structural valve deterioration. Randomized controlled trials (RCTs) are a powerful method for evaluating the safety and effectiveness of TMVR against current standard of care transcatheter therapies, such as TEER. RCTs not only help with the assessment of benefits and risks, but also with policies for determining operator or institutional requirements, resource utilization, and reimbursement. In this paper, the authors provide recommendations and considerations for designing pivotal RCTs for first-in-class TMVR devices.

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**T**ranscatheter mitral valve replacement (TMVR) is a rapidly evolving therapy for the treatment of symptomatic mitral regurgitation (MR) and mitral stenosis (MS). Numerous TMVR devices are currently under investigation (1). A major potential benefit of TMVR is the predictable, complete elimination of MR, which is less certain with transcatheter edge-to-edge repair (TEER). The potential benefit of MR elimination with TMVR needs to be evaluated against its risks, including relative procedural invasiveness, need for anticoagulation, and long-term structural valve deterioration.

Randomized controlled trials (RCTs) provide a vehicle for evaluating the safety and effectiveness of novel pharmacologic, surgical, or transcatheter therapies against the existing standard of care and can also help determine operator or institutional requirements, resource utilization, and reimbursement. RCTs to evaluate first-in-class technologies such as TMVR must consider the mitral pathologies and existing treatment options to define appropriate control groups. We herein review considerations and proposed recommendations for designing pivotal RCTs for TMVR devices, incorporating the recently

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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**ABBREVIATIONS  
AND ACRONYMS**

- GDMT** = guideline-directed medical therapy
- LV** = left ventricular
- MAC** = mitral annular calcification
- MR** = mitral regurgitation
- MS** = mitral stenosis
- NYHA** = New York Heart Association
- PMR** = primary mitral regurgitation
- RCT** = randomized controlled trial
- RMVD** = rheumatic mitral valve disease
- SMR** = secondary mitral regurgitation
- TEER** = transcatheter edge-to-edge repair
- TMVR** = transcatheter mitral valve replacement

updated U.S. guidelines for the treatment of valvular heart disease (2).

**MITRAL VALVE PATHOLOGIES AND  
AVAILABLE TREATMENT MODALITIES**

The complex mitral valve apparatus consists of 2 leaflets (anterior and posterior) in an anatomical continuum with the left ventricle via chordae tendineae and circumferentially to the atrioventricular groove via a fibrous, saddle-shaped annulus. Anatomical abnormalities of the mitral valve apparatus or related cardiac anatomy such as the left atrium or left ventricle can result in MR, MS, or both. Both MR and MS significantly affect normal cardiovascular function and, when symptomatic, require treatment. MR exists in 2 basic forms: primary mitral regurgitation (PMR) (due to a primary abnormality of the mitral valve apparatus) and secondary mitral regurgitation (SMR) (due to left ventricular [LV] dysfunction and annular dilatation).

For patients with symptomatic PMR (Carpentier class II, increased leaflet motion) mitral valve surgery has a Class 1B recommendation, with surgical mitral valve repair preferred over mitral valve replacement. The guidelines specifically state that mitral valve replacement should not be performed in patients with PMR when leaflet pathology is limited to the posterior leaflet (the most common form of PMR), unless repair has been attempted and failed. For patients with PMR who are at high or prohibitive risk for mitral valve surgery, TEER has a Class 2A recommendation.

For patients with chronic SMR (Carpentier class IIb, restricted leaflet motion in systole alone) and heart failure with reduced ejection fraction, guideline-directed medical therapy (GDMT) has a Class 1 recommendation. On the basis of the results of COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation Trial), TEER was recently added as a Class 2A recommendation for patients who have chronic severe SMR related to LV dysfunction, persistent symptoms (New York Heart Association [NYHA] functional class II, III, or IV) while on optimal GDMT for heart failure, appropriate leaflet anatomy, LV ejection fraction between 20% and 50%, LV end-systolic diameter ≤ 70 mm, and pulmonary artery systolic pressure ≤ 70 mm Hg (3). Mitral valve surgery for isolated SMR is only recommended as a Class 2B indication for patients who are symptomatic despite GDMT; when

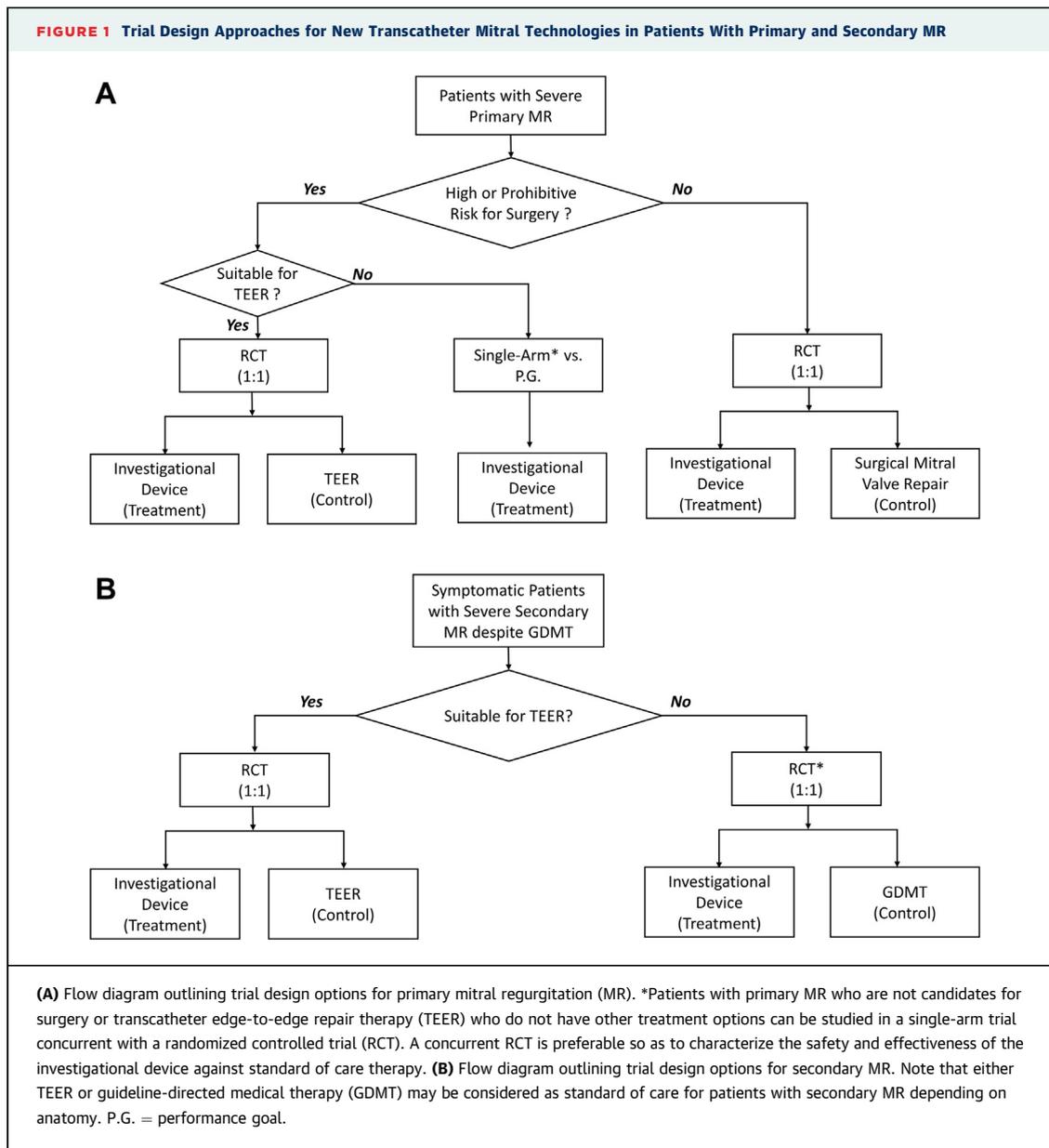
**TABLE 1 Treatment Options for Patients With Mitral Valve Disease**

Etiology of MR/MS	Available Treatment Options
Severe primary MR (Carpentier class IIA)	<ul style="list-style-type: none"> <li>• Surgical mitral valve repair if candidate for surgery (Class 1 recommendation)</li> <li>• TEER if high or prohibitive risk (Class 2A recommendation)</li> <li>• Surgical mitral valve replacement if unreparable valve</li> </ul>
Severe secondary MR (Carpentier class IIIB)	<ul style="list-style-type: none"> <li>• GDMT (Class 1 recommendation)</li> <li>• TEER if subjects are symptomatic despite GDMT and meet commercial TEER indications (Class 2A)</li> <li>• Surgical mitral valve replacement or repair may be considered if patients are symptomatic despite GDMT (Class 2B)</li> </ul>
Severe MR due to severe MAC (Carpentier class IIIA)	<ul style="list-style-type: none"> <li>• Unmet clinical need; surgery is high risk; patients may be managed with medical therapy with limited efficacy</li> </ul>
Rheumatic severe MS	<ul style="list-style-type: none"> <li>• PMBC (Class 1)</li> <li>• Surgical mitral valve replacement or repair if patient is not suitable for PMBC (Class 1)</li> </ul>
Nonrheumatic calcific severe MS due to severe MAC	<ul style="list-style-type: none"> <li>• Surgical valve intervention should be considered only after extensive discussion of the high procedural risk and the individual patient's preference and values (Class 2B)</li> </ul>

GDMT = guideline-directed medical therapy; MAC = mitral annular calcification; MR = mitral regurgitation; MS = mitral stenosis; PMBC = percutaneous mitral balloon commissurotomy; TEER = transcatheter edge-to-edge repair.

surgery is performed concomitant with coronary artery bypass grafting, mitral replacement is generally preferred over restrictive annuloplasty (mitral repair).

MR may also occur as a consequence of restricted leaflet motion in both systole and diastole (Carpentier class IIIa) because of either rheumatic mitral valve disease (RMVD) or severe mitral annular calcification (MAC). These conditions may also result in severe MS. The primary treatment option for many patients with RMVD is percutaneous mitral balloon commissurotomy. Mitral valve surgery (repair, replacement, or commissurotomy) is recommended as a Class 1 indication for patients with RMVD who are not candidates for percutaneous mitral balloon commissurotomy or who require other concomitant cardiac procedures. Although RMVD is the most common form of MS and more prevalent in developing nations, MS and MR due to severe MAC are increasingly prevalent in elderly patients in developed countries. Treatment options for patients with severe MAC are limited because the extent of calcification alters the anatomy of the annulus, the leaflet tips, as well as left atrial and LV compliance, often resulting in an increased



transvalvular gradient. The prognosis of patients with severe MAC is quite poor without intervention (4), but surgical intervention requires extensive debridement of the calcium, which is technically challenging and increases operative risk (5,6). Guidelines support intervention for severe MS as only a Class 2B indication for severely symptomatic patients (NYHA functional class III or IV) when the MS is attributable to MAC. The high risk of available treatment options for patients with severe MAC and the relative lack of data on the treatment of patients with severe MAC with MR represents a significant unmet clinical need.

### CLINICAL TRIAL CONSIDERATIONS FOR NOVEL TMVR DEVICES

The design of clinical trials for novel TMVR devices must take into account the complexity and heterogeneous nature of mitral valve pathologies and available treatment options. Table 1 shows the available treatment options for patients with mitral valve disease. Although there can be benefits associated with complete MR elimination from valve replacement versus valve repair, the risks of valve replacement must be weighed against other available therapies.

<b>TABLE 2 Pros and Cons Associated With Potential Control Groups for TMVR Trials</b>		
<b>Surgery</b>	<b>GDMT</b>	<b>TEER (MitraClip)</b>
<b>Pros</b>		
The comparative precedent for TMVR is surgical replacement in patients with secondary/mixed MR	GDMT is the standard of care for patients who are not suitable for surgery or TEER with the MitraClip (particularly for secondary MR)	The MitraClip is the preferred standard of care for selected patients with secondary MR
TMVR offers a less invasive approach for mitral valve replacement		There are unanswered questions on the benefits and risks (Table 1) of TMVR vs TEER, which an RCT will answer
<b>Cons</b>		
Surgery is a Class 2B indication for treatment of isolated secondary MR	COAPT demonstrated that correcting secondary MR with TEER in patients with heart failure provides significant clinical benefit	TMVR and TEER have different mechanisms of action, different impact on MR elimination, and different safety profiles, making randomization important but challenging
Surgery for isolated secondary MR is performed rarely: ~4.3% of all surgical procedures	Physicians will offer available therapies (eg, TEER) to symptomatic patients on GDMT, and patients will prefer TEER rather than remaining on GDMT alone	
With release of the COAPT results and subsequent approval of the MitraClip for secondary MR, reimbursement, and ultimately guideline support, TEER with the MitraClip is the preferred standard of care for appropriate patients with secondary MR		
<b>Conclusion</b>		
Conducting an enrollable RCT vs surgery is not feasible	Implementing an RCT with GDMT alone as a control is not an enrollable trial given proven benefit of TEER (MitraClip)	Compared with surgery and GDMT, randomization to TEER (MitraClip) is the only practical and feasible randomization pathway for TMVR
COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation Trial; RCT = randomized controlled trial; TMVR = transcatheter mitral valve replacement; other abbreviations as in Table 1.		

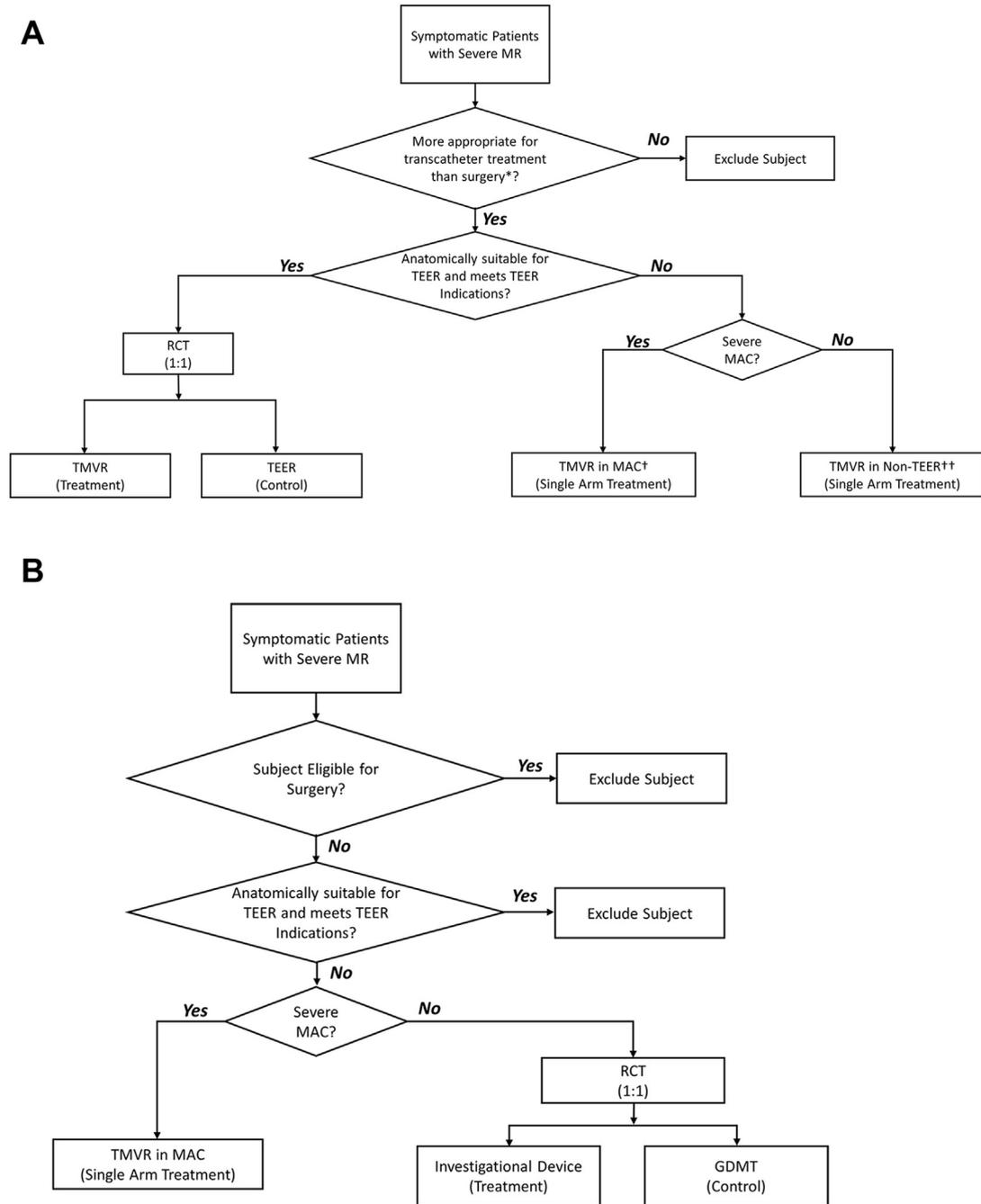
As treatment options are available for both MR and MS, novel transcatheter mitral valve interventional devices (repair or replacement) should be evaluated in RCTs to adequately assess safety and effectiveness against current standard of care. For transcatheter technologies targeted to patients with PMR, RCTs must be considered against surgical mitral valve repair for surgical candidates or TEER for patients who are at high risk for surgical mortality. For transcatheter technologies targeted to patients with severe SMR, randomized clinical trials may be considered against GDMT, TEER, or surgery depending on patient anatomy or surgical candidacy. Single-arm trials for patients with an unmet clinical need (eg, those with severe MAC or with PMR who are not candidates for surgery or TEER) may be considered but are most meaningful if performed within an overall construct that includes an RCT to best interpret the safety and effectiveness of novel first-in-class transcatheter devices against the standard of care. Single-arm trials may also exhibit a tendency toward “enrollment creep,” as randomizable patients may be enrolled in the single arm if a concomitant RCT arm is not available. Figures 1A and 1B show trial design

approaches for new transcatheter mitral technologies in patients with PMR and SMR.

For novel TMVR technologies, standard-of-care treatment that serves as an appropriate control group is rapidly evolving. A summary of strengths and limitations of potential control groups can be found in Table 2. For PMR, either surgery or TEER may serve as the control group depending upon surgical candidacy. TEER in particular is now being routinely used in patients with PMR who are at prohibitive or high surgical risk and in patients with SMR who are symptomatic despite GDMT. With the recent guideline inclusion of TEER as Class 2A and Medicare coverage for both PMR and SMR, TEER has become the de facto standard of care today for many high- or prohibitive-risk patients with PMR or SMR.

As the only commercially available transcatheter therapy for both PMR and SMR, TEER serves as a logical control group for TMVR RCTs. The broad applicability and availability of TEER and improved outcomes with newer generation devices for different subsets of patients with MR poses challenges as well as opportunities to conduct RCTs (Figure 2A). For patients who are not suitable for TEER (see the

**FIGURE 2** Trial Design Options for a First-in-Class TMVR Device



**(A)** Option 1: trial design for a first-in-class transcatheter mitral valve replacement (TMVR) device with an RCT arm against TEER. \*Patients must be high or prohibitive risk for surgery. †There is an unmet clinical need for patients with severe mitral annular calcification (MAC). As such, there is no appropriate control group for this patient cohort, and these patients may be studied in a single-arm study as long as it is concurrent with an RCT against TEER or GDMT **(B)**. ††A single-arm trial in non-TEER patients may be considered in this construct, as the safety and effectiveness of the TMVR design will be evaluated in an RCT against TEER. If the RCT arm was not present, this group must be randomized to GDMT **(B)**. **(B)** Option 2: trial design for a first-in-class TMVR device with an RCT arm against GDMT. Abbreviations as in [Figure 2](#).

**TABLE 3 Potential Benefits and Risks That Are Evaluable in Randomized Clinical Trials of TMVR Versus TEER**

Transapical TMVR	Transfemoral TEER
<b>Benefits</b>	
Complete, predictable, and durable elimination of MR	Transfemoral approach to repair the mitral valve with expedited patient recovery
Strong early safety profile	Excellent safety profile
Agnostic to MR pathophysiology	Established outcomes and operator familiarity with >100,000 global implantations
Early data that are beneficial for left ventricular remodeling	No requirement for anticoagulation  Supported by randomized clinical trial data
<b>Risks</b>	
Implanted via left thoracotomy	Only applicable to anatomies conducive to edge-to-edge repair
Large-bore apical delivery system	Results in smaller mitral valve area
Requires anticoagulation for at least the short term	Risk for residual or recurrent MR
New operator and site requirements for performance and delivery	Outcomes may vary with operator experience
Anatomic exclusions to therapy (ie, LVOT obstruction)	
LVOT = left ventricular outflow tract; other abbreviations as in Tables 1 and 2.	

section on trial execution considerations), RCTs against GDMT should be considered, as a significant majority of patients who qualify for TMVR will have SMR, for which GDMT is standard of care (Figure 2B). RCTs against surgery may also be considered (for patients who are surgical candidates), but such trials will be difficult to enroll, as surgery is rarely performed for isolated SMR (7). Single-arm trials may be appropriate provided the trial structure includes a concurrent RCT (eg, TEER in Figure 2A, GDMT in Figure 2B).

### ENDPOINT CONSIDERATIONS

The Mitral Valve Academic Research Consortium guidance documents elegantly outline endpoints that should be considered for transcatheter mitral valve trials (8,9). Depending upon the trial’s objectives, primary, secondary, and descriptive endpoints may be chosen from the options provided within the Mitral Valve Academic Research Consortium documents. As patients with untreated MR are at high risk for mortality and progressive heart failure symptomatology, the primary endpoint for TMVR trials should include endpoints that are related to heart failure (ie, mortality and/or heart failure hospitalizations). As noted in the Mitral Valve Academic Research Consortium document, quality of life (eg,

Kansas City Cardiomyopathy Questionnaire score) may be considered as a component of a composite primary endpoint depending upon the trial’s intent but should not be used in isolation. Trials with TEER as a control group can be designed to demonstrate either superiority or noninferiority depending upon the device features (eg, transapical TMVR devices may consider noninferiority designs, and transeptal devices may be designed to demonstrate superiority). Results from such trials must also be used to define anatomies for which TMVR may be more suitable than TEER and vice versa. Trials against GDMT must be designed to demonstrate superiority. Effect size for superiority trials of TMVR versus TEER may be based on the incremental impact of MR elimination over MR reduction on mortality and heart failure hospitalization. Effect size for superiority trials of TMVR versus GDMT may be based on the results observed in COAPT. Noninferiority trials must be designed to ensure there is no violation of the “constancy assumption” (designing trials similar to the past trial that demonstrated effectiveness of the TEER control compared with GDMT placebo) and must demonstrate that outcomes with the TMVR device are not worse than TEER by a clinically significant margin (10).

Secondary endpoints should typically include those pertaining to safety (eg, composite of major adverse events, stroke, bleeding, myocardial infarction), device effectiveness (eg, MR severity), measures of success (technical success, device success, patient success), LV dimensions (eg, LV end-diastolic and end-systolic volumes), quality of life (eg, Kansas City Cardiomyopathy Questionnaire score), and functional capacity (eg, 6-minute walk distance, NYHA functional class). Secondary endpoints must be adjusted for multiple testing, and all other endpoints should be evaluated descriptively.

### TRIAL EXECUTION CONSIDERATIONS

Trial oversight at multiple junctures for pivotal TMVR trials is critical. An independent clinical events committee and a data monitoring committee should be used to adjudicate adverse events and monitor the safety of trial participants. Imaging core laboratories are recommended for the anatomical and functional pathophysiological assessment of the mitral valve derived from echocardiographic and computed tomographic imaging studies.

Perhaps the most critical component for oversight of TMVR trials is evaluation of surgical candidacy, GDMT, and TEER suitability. Such oversight needs to be provided by a subject eligibility committee, which

must be composed of representatives from cardiac surgery, heart failure, and interventional cardiology. The role of the mitral heart team surgeon is to ensure that the patient is an appropriate candidate for surgery (if the trial is randomizing to surgery) or not a candidate for surgery (if the trial is in a patient population not suitable for surgery). If the trial is randomizing against GDMT, the heart failure cardiologist needs to ensure that the patient is optimized on GDMT. The recent favorable data from the use of angiotensin receptor blockers/nephrilysin inhibitors and sodium-glucose cotransporter-2 inhibitors in patients with systolic heart failure mandate aggressive pharmaceutical therapy before and after valve intervention.

The role of an expert TEER operator is becoming more important in contemporary trials randomizing against MitraClip therapy. An expert opinion document has recently been published that outlines the anatomical criteria for TEER suitability (11). This document was developed on the basis of a request of the US Food and Drug Administration to harmonize TEER suitability criteria across TMVR trials by various manufacturers. Whether the TMVR RCT component is executed in a patient population that is suitable for TEER (Figure 2A) or not suitable for TEER (Figure 2B), rigorous assessment of TEER suitability must be made by the expert TEER operators of the subject eligibility committee on the basis of the published criteria (11). At least 2 experienced TEER operators should vote on TEER suitability to ensure that appropriate patients are being enrolled. The subject eligibility committee should review the transesophageal echocardiographic studies along with quantitative assessment of the transesophageal and transthoracic echocardiographic studies by the echocardiography core laboratory to determine TEER suitability and thereby determine next steps for the trial. For the trial framework outlined in Figure 2A, the subject eligibility committee will determine whether the patient is in the randomized arm (against TEER) or in one of the non-randomized arms (for non-TEER patients). Similarly, for the trial framework outlined in Figure 2B, the subject eligibility committee will determine eligibility for the trial, as both the RCT and the single arms are in patients who are not suitable for TEER.

### ANTITHROMBOTIC THERAPY CONSIDERATIONS

Current guidelines (2) recommend antithrombotic therapy with a vitamin K antagonist (warfarin) for the first 3 to 6 months following surgical mitral valve replacement (Class 2A) to allow the endothelium to cover the bioprosthetic material and minimize the

risk for thromboembolic complications. The larger stent frames and additional prosthetic material for TMVR systems in comparison with surgical valves require consideration of antithrombotic therapy with warfarin for at least 6 months postimplantation, with a target international normalized ratio of 2.5 to 3.5 to minimize the risk for thromboembolic complications. Although the specific anticoagulation requirements (international normalized ratio range and duration) may change with expanded experience and are individualized to the device features, patients who cannot tolerate anticoagulation are excluded from TMVR studies thus far.

### FINAL CONSIDERATIONS AND RECOMMENDATIONS

We acknowledge that there are challenges to the execution of an RCT with current-generation TMVR technologies. The clinical community may be reluctant to randomize patients because of the current requirement for transapical access (Table 3). As a complicating matter, the anatomical criteria used in determining TEER candidacy have uncertainty (11) attributable to recent device iterations as well as continued operator experience with the therapy, both of which have been shown to lead to greater effectiveness and better safety (12). However, such reluctance for either randomization or the choosing of criteria for randomization are addressable with study oversight and should not cause abandonment of RCTs for the evaluation of TMVR technologies, as single-arm-only trials have major limitations. For example, even in a well-structured single-arm trial with strong oversight, the subject eligibility committee may be at risk for selection “creep” by enrolling patients with debatable anatomical criteria that are within TEER indications for use, if a TEER treatment arm within a concurrent RCT does not exist.

Although TMVR may result in longer post-procedural recovery compared with TEER and require anticoagulation therapy, it is important to note that the safety profile for some TMVR devices has been excellent, with long-term clinical outcomes comparable with TEER registry data (13-15). As a rapidly emerging field, pivotal RCTs are needed to study the risks and benefit of MR elimination versus MR reduction of TMVR versus TEER in patients with MR, whether the etiology is simple or complex. Furthermore, with emerging data on mitral therapies, stand-alone single-arm trials for novel TMVR therapies using performance goals as the sole basis for evidence generation have limitations and are most powerful when complemented with a concurrent RCT to minimize patient selection bias and

maximize study validity against standard of care in a broad population. Establishing clear indications on the basis of high-quality scientific evidence could be expected to reduce off-label use of approved therapies. Perhaps most important, without such comparative data from RCTs, we will lack a comprehensive understanding of the roles of various therapies for patients with MR.

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