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Evidence Generation and Implementation of Transcatheter Interventions for Atrioventricular Valvular Heart Disease in Heart Failure: Current Status and Future Directions

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ABSTRACT: Mitral regurgitation and tricuspid regurgitation are the most common valvular heart diseases in patients with heart failure and have independent prognostic value. Transcatheter interventions are now available for the treatment of valvular heart disease, and their efficacy and safety have been tested in randomized controlled trials. However, evidence is still limited and sometimes inconclusive because several aspects of these trials limit their interpretation or consistency. These include heterogeneity in the pathogenesis and clinical characteristics of patients, the dynamic nature of secondary atrioventricular valve disease severity, the role of heart failure medications and devices, dependency on procedural results and operators' skills, smaller number of patients enrolled and the power to detect differences in trials, and limitations to use patients' reported outcomes with unblinded study protocols. These specific aspects of trials in patients with atrioventricular valve disease are reviewed in this article with a focus on possible solutions to generate further evidence for the efficacy and safety for transcatheter treatments of atrioventricular valve disease in patients with heart failure.

Key Words: heart failure ■ heart valve disease ■ mitral valve insufficiency ■ tricuspid valve insufficiency

Mitral regurgitation (MR) and tricuspid regurgitation (TR) are the most common valvular heart diseases (VHDs) in patients with heart failure (HF).[1–8] Their prognostic role has been established,[2,4,6,7,9–11] and many treatment options are now available for these patients. However, evidence for the efficacy and safety of transcatheter interventions in patients with HF and MR or TR is challenged by either limited or conflicting data from randomized controlled trials, leading to varying degree of acceptance by the clinical community. The interaction among specialists in HF, imaging, interventional cardiology, and cardiac surgery is crucial for evidence generation, implementation, and management of patients with HF with MR or TR to generate the most reliable and valid data and, in turn, maximize the utility of these interventions in the right patient population. The aim of this document is to analyze current studies on the treatment of MR and TR, discuss the limitations of current data, provide a road map on how to bridge the gap in data, and create collaboration among the various specialties involved in this scientific domain.

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Nonstandard Abbreviations and Acronyms

6MWTD	6-minute walking test distance
A-SMR	atrial secondary mitral regurgitation
ARNI	angiotensin receptor neprilysin inhibitor
COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation
GDMT	guideline-directed medical therapy
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	left ventricular
LVEF	left ventricular ejection fraction
MATTERHORN	Multicenter Mitral Valve Reconstruction for Advanced Insufficiency of Functional or Ischemic Origin
MITRA-FR	Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation
MR	mitral regurgitation
M-TEER	mitral transcatheter edge-to-edge repair
NT-proBNP	N-terminal probrain natriuretic peptide
NYHA	New York Heart Association
PROM	patient-reported outcome measure
RESHAPE-HF2	Randomized Investigation of the MitraClip Device in Heart Failure: Second Trial in Patients With Clinically Significant Functional Mitral Regurgitation
RV	right ventricular
SMR	secondary mitral regurgitation
STR	secondary tricuspid regurgitation
TEER	transcatheter edge-to-edge repair
TR	tricuspid regurgitation
TRILUMINATE Pivotal	Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System Pivotal
TRISCEND	Edwards EVOQUE Tricuspid Valve Replacement: Investigation of Safety and Clinical Efficacy After Replacement of Tricuspid Valve with Transcatheter Device
TRISCEND II	Edwards EVOQUE Transcatheter Tricuspid Valve Replacement: Pivotal Clinical Investigation of Safety and Clinical Efficacy Using a Novel Device
T-TEER	transcatheter tricuspid edge-to-edge repair
TTVI	tricuspid transcatheter valve intervention
TTVR	transcatheter tricuspid valve replacement
TVI	transcatheter valve intervention
VHD	valvular heart disease
V-SMR	ventricular secondary mitral regurgitation

BACKGROUND: EPIDEMIOLOGY AND PROGNOSTIC IMPACT

The prevalence of moderate or severe secondary MR (SMR) in patients with HF ranges between 31% and 61%,[1,9,12,13] with the highest percentages in patients with HF with reduced ejection fraction (HFrEF), those who are hospitalized with worsening HF, and those with advanced HF.[9,11,14] Prevalence of moderate or severe TR ranges between 10 and 36% depending on HF phenotype and TR etiology.[2,6,8,13] Among outpatients the proportion of moderate/severe TR is higher in patients with HF with preserved ejection fraction compared with those with HFrEF.[6,7]

Both MR and TR are associated with worse HF symptoms, poorer quality of life, and higher risk for mortality and hospitalization.[6,9,12] These associations are independent of other confounders, including those related to HF severity.[6,9,12,15] It can thus be expected that transcatheter valve interventions (TVIs) may improve symptoms and outcome. The evidence from randomized trials remain limited, however, in part because of inherent characteristics of the trials, including patients enrolled, the design of the trials, and in some cases conflicting results. Here, we discuss factors that are specific for atrioventricular valve interventions trials that may limit the evidence on the efficacy and safety of these interventions. These include heterogeneity of the patient phenotypes with MR or TR and HF, as well as trial designs and end points. Possible future improvements for evidence generation so that data on efficacy and safety can be more readily available and acceptable by the clinical community are given in Table 1.

Table 1. Consideration for Designing Trials in Patients With Secondary VHD and Chronic HF

Problem	Possible solutions
Heterogeneity of atrioventricular VHD	Careful phenotypic characterization based on anatomic and clinical criteria Trials including or excluding selected patients phenotypes: Atrial vs ventricular SMR COAPT-like vs non–COAPT-like patients with SMR Atrial vs ventricular STR TR and left-side related VHD Characterization of pulmonary hypertension pathogenesis in patients with STR Severe/end-stage HF
Use of GDMT	Mandate GDMT before randomization/procedure Mandate optimization of GDMT after the procedure Mandate multidisciplinary team preprocedural assessment
Size of the study group	Include also worsening HF events without patient hospitalization Use recurrent events analysis or hierarchical win-ratio analyses
End points	Mortality: unbiased but requires large study groups HF hospitalizations/events: may be biased and requires large study groups Quality of life: is biased but may yield useful data Hemodynamic parameters/RV function: useful for a mechanistic end point Biomarkers: unbiased and may be used as surrogate for mortality Postprocedural changes in cardiac function assessed by echocardiography or cardiac MRI: may be used as surrogates for mortality

COAPT indicates Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; GDMT, guideline-directed medical therapy; HF, heart failure; MRI, magnetic resonance imaging; RV, right ventricular; SMR, secondary mitral regurgitation; STR, secondary tricuspid regurgitation; TR, tricuspid regurgitation; and VHD, valvular heart disease.

CLINICAL PHENOTYPES

Clinical phenotypes of patients with MR or TR and concomitant HF may have a major impact on the results of trials with TVI (Figure 1).

Mitral Regurgitation

MR is traditionally classified as primary or secondary.[16,17] Primary MR may cause HF. Surgery is the standard of care in symptomatic patients with primary MR at low or intermediate risk.[18] EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) compared conventional surgery with transcatheter edge-to-edge repair (TEER) in 279 patients with moderately severe to severe MR, 27% with functional MR. The percutaneous procedure was less effective than surgery with respect to the primary end point, although mainly for a higher need of surgical repair, but had superior safety and similar improvement in clinical and instrumental end points at 12 months with results confirmed at 5 years.[19,20] A significant interaction was found according to type of MR with better results for surgery only in patients with primary MR.[19]

Thus, according to current guidelines, TEER of the mitral valve (M-TEER) remains a safe alternative in patients with primary MR and contraindications for surgery or high operative risk.[18,19,21]

A head-to-head comparison of M-TEER and surgery for the treatment of primary MR is being further investigated in randomized trials enrolling high-risk (MITRA-HR study [Multicentre Study of MITRACLIP Transcatheter Mitral Valve Repair in Patients With Severe Primary Mitral Regurgitation Eligible for High-risk Surgery]; NCT03271762) and intermediate-risk (REPAIR-MR study [MitraClip REPAIR MR Study]; NCT04198870) patients.[22,23] The development of new devices and results of most recent trials are likely to expand the indications to TVI for a larger number of patients at low to intermediate surgical risk.

SMR is the most frequent form of MR in HF. It is subdivided into atrial and ventricular induced MR.[24] Both MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) enrolled patients with ventricular SMR (V-SMR), as shown by a left ventricular (LV) ejection fraction (LVEF) of 15% to 40% and 20% to 50%, respectively.[25,26] Different enrollment criteria, inclusion of patients with less severe SMR, more severe LV dilatation and dysfunction, and more advanced HF in MITRA-FR compared with COAPT have been cited as reasons of diverging results between the 2 trials.[27–29] The 5-year follow-up of the COAPT trial confirmed the large prognostic benefit of M-TEER at 5 years. Patients undergoing crossover after 2 years (allowed per protocol) did derive a similar benefit of the initial cohort compared with guideline-directed medical therapy (GDMT) alone, which provided internal validation of the reported results.[30] RESHAPE-HF2 (Randomized Investigation of the MitraClip Device in Heart Failure: Second Trial in Patients With Clinically Significant Functional Mitral Regurgitation) confirmed the benefits of M-TEER in patients with

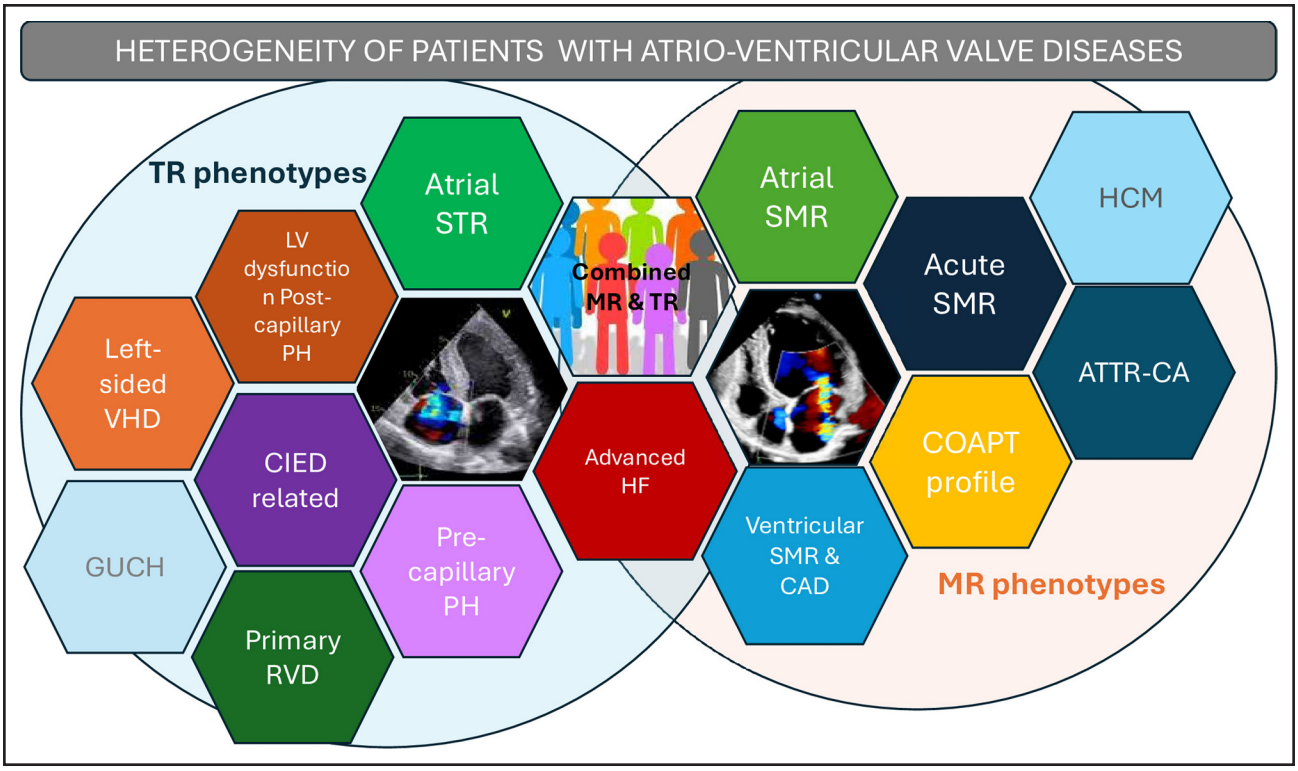

Figure 1. Different phenotypes of patients with MR and TR.
ATTR-CA indicates transthyretin cardiac amyloidosis; CAD, coronary artery disease; CIED, cardiac implantable electronic devices, COAPT, Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation trial; GUCH, grown-up congenital heart disease; HCM, hypertrophic cardiomyopathy; HF, heart failure; LV, left ventricular; MR, mitral regurgitation; PH, pulmonary hypertension; RVD, right ventricular dysfunction; SMR, secondary mitral regurgitation; STR, secondary tricuspid regurgitation; TR, tricuspid regurgitation; and VHD, valvular heart disease.

HFrEF and moderate to severe V-SMR, who remained symptomatic despite optimized GDMT.[31,32]

Real-world registries showed that a non–COAPT-like profile was associated with lower rates of procedural success, more frequent in-hospital complications, longer length of hospitalization, and worse prognosis after M-TEER compared with patients with a COAPT-like profile.[33–35] However, non–COAPT-like patients may show improvement in quality of life and exercise capacity similar to the COAPT-like patients.[33,35,36] TVI of severe MR may also be useful as bridge to LV assist device implantation or heart transplantation.[16,37,38] In addition, M-TEER may benefit patients with moderate SMR and improve LV remodeling[39–41]; however, these extensions to adjacent populations need evaluation with randomized trials. The MATTERHORN (Multicenter Mitral Valve Reconstruction for Advanced Insufficiency of Functional or Ischemic Origin), a randomized, controlled, parallel-group study, investigated the efficacy and safety of percutaneous mitral valve repair by means of the MitraClip device for patients with moderate to severe SMR compared with surgical therapy. M-TEER was noninferior to mitral valve surgery with respect to a composite of death, rehospitalization for HF, stroke, reintervention, or implantation of an LV assist device at 1 year ($P<0.001$ for noninferiority).[42]

Atrial SMR (A-SMR) is characterized by preserved LV geometry and LVEF with atrial remodeling and myopathy. Results for the effects of M-TEER in A-SMR cannot be extrapolated from the COAPT and MITRA-FR trials because these trials enrolled patients with V-SMR. Data on the efficacy of TVI in patients with A-SMR still come mainly from observational studies.[43–46] In these studies, M-TEER and indirect mitral valve annuloplasty were shown to be feasible and safe,[43–45] and the efficacy of M-TEER was similar in A-SMR and V-SMR.[43,44,46] Few patients enrolled in the MATTERHORN trial were categorized as having A-SMR (34 patients, of whom 16 versus 18 were randomized to TEER versus surgery, respectively). A nonprespecified post hoc analysis of the trial reproduced the overall results of MATTERHORN in both the A-SMR and V-SMR subgroups.[47]

Tricuspid Regurgitation

Different phenotypes of TR have been classified by the Tricuspid Valve Academic Research Consortium, and they have a major impact on treatment.[48–51] Primary TR results from anatomic abnormality of the tricuspid valve apparatus and may cause HF. Secondary TR (STR) results from annular dilation caused by right

ventricular (RV) enlargement and dysfunction due to pulmonary hypertension or right atrial enlargement. It includes atrial STR due to right atrial/tricuspid annular dilatation and ventricular STR due to LV disease, left-sided VHD, pulmonary disease, RV dysfunction/remodeling, or cardiac implantable electronic devices.[49] Cardiac implantable electronic device–related STR is further subdivided into 2 subtypes based on whether the cardiac implantable electronic device interferes or does not interfere with the tricuspid valve apparatus function.[49,50]

The cause of TR and comorbidities may have a major role in the management of severe TR before transcatheter or surgical correction.[48,50,52] Surgery is currently recommended in symptomatic patients with severe primary TR and without severe RV dysfunction and should be considered in selected asymptomatic or mildly symptomatic patients with an initial RV dilation or RV function decline.[18] In addition, tricuspid valve repair during left-sided surgery is recommended for severe STR and should be considered for mild or moderate STR with annulus dilation.[18] On the other hand, the benefits of surgical repair of isolated STR are not yet established, and the procedure might be burdened by a nonnegligible risk of periprocedural mortality and morbidity when patients are treated at a late stage.[53,54] The TRI-SCORE has been recently proposed to estimate in-hospital mortality in patients undergoing isolated TR surgery.[53] With the progressive development of novel devices that offer also the possibility of percutaneous tricuspid valve replacement and the high surgical risk of many patients with TR, it seems that transcatheter treatment will be adopted more frequently. However, also in this case, randomized controlled trials are required to directly compare outcomes between transcatheter treatment and surgery, as was done for aortic valve replacement and more recently for MR. Restoration of normal sinus rhythm may be effective for atrial STR caused by annular dilation associated with atrial fibrillation.[55] Atrial STR has been associated with lower mortality compared with ventricular STR, independently of other clinical and echocardiographic characteristics.[52,56,57] In the real-world multicenter TriValve registry (Transcatheter Tricuspid Valve Therapies), among 298 patients with STR undergoing transcatheter tricuspid edge-to-edge repair (T-TEER), 65 (22%) had atrial STR and 233 (78%) had ventricular STR. Procedural success and TR reduction were similar in the 2 groups.[58]

STR is often associated with left-sided VHD.[52,59–63] In a prospective transcatheter aortic valve replacement registry, more than one-half of patients with moderate or greater TR had a reduction in TR after aortic valve replacement.[64] The magnitude of TR improvement after M-TEER is variable, but improvement may occur in a meaningful proportion of patients, as shown in observational studies.[62,65,66]

Patients with TR and other comorbidities, including atrial fibrillation and left-sided VHD, deserve a specific approach, if not specific trials, because these concomitant conditions affect each other. Whether TR and either atrial fibrillation or left-sided VHD should be corrected with TVI at the same time or sequentially is not settled.

Severity and Cause of HF

The severity of HF may be a major determinant of the efficacy of TVI and a major factor for trial design. Treatment of MR or TR at late stages of HF may not be as beneficial.[67–71] COAPT criteria for the selection of patients for M-TEER were based mainly on the exclusion of patients with more severe HF or severe LV or RV dysfunction.[16,72–74] Although the procedural success of TVI is independent of baseline LVEF,[75] observational data have shown that the prognostic impact of MR or TR severity is greater in patients with mild to moderate compared with more severe impairment of cardiac function, as shown by LVEF and NT-proBNP (N-terminal probrain natriuretic peptide) concentrations.[6,12,76,77] In addition, patients enrolled in RESHAPE-HF2 may have been less sick compared with patients enrolled in COAPT and MITRA-FR, as shown by lower NT-proBNP concentrations.[31] From these data, a larger prognostic benefit from TVI can be expected in patients with less advanced HF. On the other hand, the lower risk of events in these patients may require a larger study group or a longer follow-up.

Advanced right-sided HF is characterized by irreversible organ damage and dysfunction. Diuretic resistance and kidney or hepatic dysfunction, gut malabsorption, and malnutrition are commonly encountered and denote a poor prognosis.[71,78,79] Therefore, careful clinical assessment, echocardiography, and, at least for T-TEER, right-sided heart catheterization are mandatory in the preprocedural evaluation of candidates for atrioventricular valve interventions not only to define valve anatomy but also to predict outcomes and patient management.[52]

RV dysfunction has a major role for both mitral and tricuspid valve interventions.[68,70,80] Myocardial deformation imaging and 3-dimensional echocardiography are preferred for the assessment of RV geometry and function and prognostic stratification of patients with TR before tricuspid TVI (TTVI). Patients with severely depressed RV function were excluded from the TRISCEND II trial (Edwards EVOQUE Transcatheter Tricuspid Valve Replacement: Pivotal Clinical Investigation of Safety and Clinical Efficacy Using a Novel Device).[81] The Tricuspid Valve Academic Research Consortium proposed possible echocardiographic cutoffs.[48] Although actual evidence is limited,[82,83] irreversible pulmonary vascular resistance exceeding 3 Wood units has been adopted as an exclusion criterion for most studies. Systolic pulmonary artery pressure >70 mm Hg and fixed precapillary pulmonary hypertension with uncontrolled precapillary

pulmonary hypertension (systolic pulmonary artery pressure >60 mm Hg) were among the exclusion criteria of the TRILUMINATE Pivotal trial (Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System Pivotal) and Tri.Fr (a multicenter, controlled, randomized, superior, open-label, and parallel-group study testing the value of TriClip implantation in patients with severe STR) trials, respectively.[84,85]

The cause of HF may also have an impact on TVI, although this has not been assessed thoroughly. Specific therapies now exist for cardiac amyloidosis, hypertrophic cardiomyopathy, and other cardiomyopathies and may affect the course of VHD.[13,16,74,86,87]

MEDICAL THERAPY

Secondary MR

For SMR associated with HFrEF, GDMT for HF is indicated.[16] Observational studies report considerable underuse of GDMT in patients with HF, including also those undergoing M-TEER.[88–90] However, GDMT may improve LV performance, favor LV reverse remodeling, and reduce SMR in ≈40% of patients, with most data suggesting a main role of angiotensin receptor neprilysin inhibitors (ARNIs)[10,91,92] and recently of sodium-glucose cotransporter-2 inhibitors.[93]

Thus, GDMT must be uptitrated at maximum tolerated doses before M-TEER is considered for the treatment of SMR, with a meaningful effect to be expected from ARNIs and sodium-glucose cotransporter-2 inhibitors among the medications introduced recently.[16] The optimization of HF medical therapy before M-TEER was a major difference between the COAPT and MITRA-FR trials. Although both trials enrolled symptomatic patients with HFrEF and SMR, the COAPT trial used strict inclusion criteria with a central committee of HF specialists evaluating and optimizing GDMT before M-TEER. This nevertheless resulted in the tolerance of 3, 2, and 1 GDMT class (any dose) in 38.8%, 39.4%, and 19.8% of patients, respectively.[94] β-Blockers were best tolerated (93.1%), followed by angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or ARNI (68.5%) and then mineralocorticoid receptor antagonist (55.0%). Only 1.9% did not tolerate any GDMT.[94] A higher proportion of patients were on HF GDMT in RESHAPE-HF2 than in the other 2 studies.[31]

Secondary TR

Medical therapy options for the management of severe TR are limited, with no Class I recommendations in guidelines except for diuretics. Recently, sodium-glucose cotransporter-2 inhibitors have been recommended for all patients with HF with preserved ejection fraction, regardless of VHD.[18,74,95,96] Loop diuretics relieve congestion, although many patients with severe STR experience progressive cardiorenal syndrome, diuretic resistance, and the need for periodic intravenous diuretics. Mineralocorticoid receptor antagonists may have additive benefit, especially in the setting of hepatic congestion, which may promote secondary hyperaldosteronism.[18,74] Pulmonary vasodilators may be helpful in reducing RV afterload and STR in selected patients with pulmonary hypertension.[95] GDMT for HF might be effective for STR attributable to HFrEF.[16] Small observational studies reported the possible beneficial effect of ARNI and sodium-glucose cotransporter-2 inhibitors on RV function in patients with HF.[97,98] Further studies are needed to assess the impact of GDMT for HF on RV function and, namely, TR severity.[97,98]

In TRISCEND (Edwards EVOQUE Tricuspid Valve Replacement: Investigation of Safety and Clinical Efficacy After Replacement of Tricuspid Valve With Transcatheter Device), medical therapy was at investigator discretion and included diuretics in stable doses unless a patient had a history of intolerance.[99] In TRILUMINATE Pivotal, being a randomized controlled trial of T-TEER versus GDMT, the eligibility committee ensured that patients were on a background dose of diuretics, but no prespecified criteria for the dosing, drug type, or adjustment in follow-up were available.[84] In TRILUMINATE Pivotal, ≈90% of patients were on diuretics and <40% were on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or ARNI at baseline. These data likely due to the high rate of patients with preserved LVEF.

Increasing diuretics just before transcatheter procedure to improve fluid status and leaflet coaptation before T-TEER was described in the TRILUMINATE Pivotal trial.[84] No improvement of TR severity was observed in the control group of the TRILUMINATE Pivotal trial, suggesting the limited role of medical therapy on RV remodeling in patients with TR and preserved LVEF or its low prescription rate in this trial. On the other hand, in the control group of TRISCEND II trial, regression of TR to less than severe at 1 year was reported in 16.1% of the patients.[81] Further data are warranted to assess the impact of medical therapy on the severity of TR.

Limitations of GDMT in Patients With VHD

Limitations remain in the uptitration of GDMT in patients with severe SMR, mainly because of poor tolerance. Only a very low percentage of the patients in COAPT were able to tolerate therapeutic GDMT doses despite considerable efforts by a screening committee including HF specialists. Furthermore, the optimization of GDMT has been associated with an improvement by at least 1 grade of MR in less than half of patients. There is an important gap in evidence on GDMT for the treatment of patients with severe functional TR.

Postprocedural Enabling of Medical Therapy

Successful TVI facilitates the implementation of GDMT and affects the subsequent outcome as a consequence of hemodynamic improvement with improved stroke volume and blood pressure and reduced systemic, kidney, and hepatic congestion,[14,52,90,100] countering hypotension and deterioration in kidney function, which are the main causes of underuse of GDMT in HF.[94,101–103] An analysis of Euro-SMR registry showed GDMT uptitration in 307 patients (38%) after M-TEER and a lower risk of all-cause death (adjusted hazard ratio, 0.62 [95% CI, 0.41–0.93]; P=0.020) and of all-cause death or HF hospitalization (adjusted hazard ratio, 0.54 [95% CI, 0.38–0.76]; P<0.001) in patients who underwent GDMT uptitration compared with those who did not. Degree of MR reduction between baseline and the 6-month follow-up was an independent predictor of GDMT uptitration after M-TEER (adjusted odd ratio, 1.71 [95% CI, 1.08–2.71]; P=0.022).[90] These data suggest that GDMT combined with M-TEER has a major impact on outcome and therefore GDMT use before and after intervention needs standardization in protocol design.

PATIENT SELECTION AND TIMING OF TRANSCATHETER TREATMENT OF MR AND TR

Proper patient selection for TVI remains a major challenge for clinical practice and for the design of clinical trials. This topic has been extensively considered in recent in-depth reviews[48,51,52,95,104] and, with respect to SMR, in guidelines for HF and VHD.[16,18] According to current guidelines, M-TEER can be considered only in patients not eligible for surgery and not needing coronary revascularization, should be considered to reduce HF hospitalizations only in patients who have the clinical characteristics of those included in the COAPT trial, and may be considered to improve symptoms in the non–COAPT-like patients. These indications are, however, likely to be broadened after the recently published results of MATTERHORN[42] and RESHAPE-HF2[31] trials showing the noninferiority of M-TEER compared with surgery for the treatment of SMR and the efficacy of M-TEER compared with medical therapy alone, respectively, for the reduction of HF events in patients with HFrEF and less severe SMR (mean effective regurgitant orifice area [0.25 cm^2] was smaller in patients enrolled in RESHAPE-HF2 than among those in the COAPT trial [0.40 cm^2] and the MITRA-FR trial [0.31 cm^2]).[31]

The decision process leading to the selection of patients for TVI for TR compared with other strategies (medical therapy or surgery) should include (1) the identification of the cause and mechanisms of TR by means of clinical evaluation, imaging, and hemodynamic assessment; (2) evaluation of the stage of disease (ie, RV function, type and severity of pulmonary hypertension, organ damage); (3) anatomic considerations, namely suitability for different TTVI devices; and (4) assessment of comorbidities and surgical risk.[52] There is no evidence on the right timing for TTVI from prospective clinical trials to date. However, observational studies suggest that an intervention at an early or intermediate stage of disease might be more beneficial than at a later stage.[70,105]

Multidisciplinary Team

The central role of a multidisciplinary team for the management of VHD is highlighted by guidelines.[16,18,52,106] Decisions concerning treatment and intervention for atrioventricular valve disease should be made by a heart team with expertise in VHD comprising clinical and interventional cardiologists, HF specialists, cardiac surgeons, imaging specialists with experience in interventional imaging, cardiovascular anesthesiologists, and other specialists as needed (eg, electrophysiologists). GDMT management must be clearly specified. This has been implemented in recent major trials, including the COAPT, MATTERHORN, TRILUMINATE Pivotal, and TRISCEND II trials, and should be reinforced in the future.[73,81,84] The benefit of M-TEER observed in the COAPT trial resulted in part from the multidisciplinary effort to optimize preprocedural treatment and patient selection; this should be reproduced in clinical practice.

CLINICAL TRIAL DESIGN

In addition to peculiarities related to patient characteristics, other aspects of trial design in patients with atrioventricular VHD and HF undergoing TVI deserve consideration (Figure 2).

Sample Size

Key considerations for sample size determination include the expected event rate of the primary end point in the control group and the expected magnitude of treatment effect.[107] Most of the trials leading to current indications for HF medical therapy were clinical outcome trials[16,74] and have enrolled thousands of patients, which is not achievable in device intervention trials. COAPT, MITRA-FR, and RESHAPE-HF2 randomized 614, 304, and 505 patients, respectively (Table 2).[25,32,73] Similarly, the TRILUMINATE Pivotal randomized a total of 572 patients[84,108]; 176 patients were enrolled in the multicenter, prospective, single-arm TRISCEND study[109]; and a total of 400 and 300 patients were randomized in the TRISCEND II and Tri.Fr trials, respectively.[81]

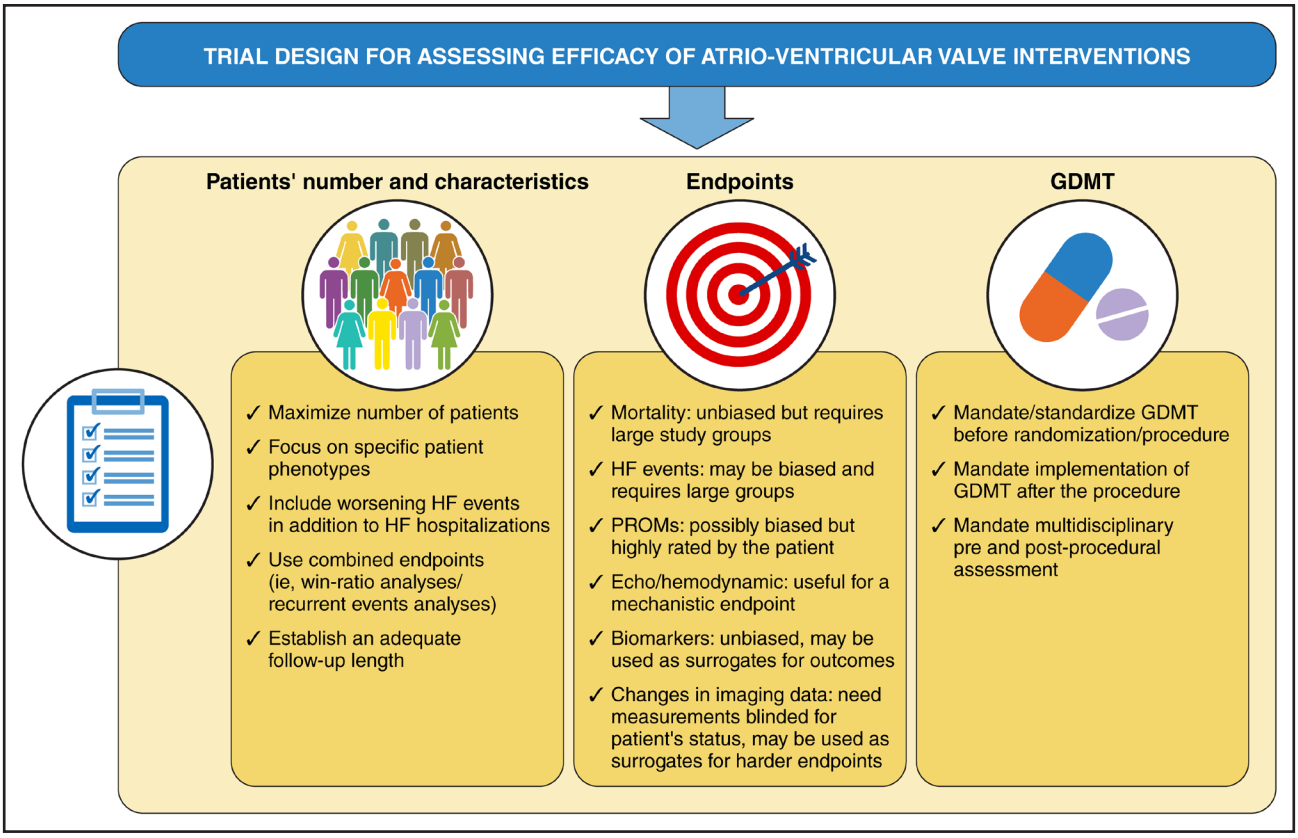

Figure 2. Trials design to assess efficacy and safety of transcatheter atrioventricular valve interventions.
GDMT indicates guideline-directed medical therapy; HF, heart failure; and PROM, patient-reported outcome measure.

Table 3 provides strategies that may help with statistical power calculations to get an affordable sample size while preserving scientific integrity. The inclusion of patients at higher risk for the primary end point and the use of a composite end point including patient-reported outcome measures (PROMs) in addition to mortality and hospitalizations, outpatient HF events, and exercise capacity assessment may boost the numbers of events and the power to detect differences, provide comprehensive assessment of the intervention, and reduce the required sample size (Table 3). However, except for mortality, all other components are influenced by knowledge of the procedure and treatment group assignment, and this may affect the results and their interpretation.[107] Laboratory examinations, including biomarkers of congestion and kidney and hepatic function, are objective, and although they are surrogates of outcomes, they may be useful for smaller studies.

EFFICACY END POINTS

Major Outcomes: Mortality and HF Hospitalizations

Recommendations in current HF guidelines are based mainly on randomized trials and strong end points.[16] This approach has also been used in the 2 major trials of M-TEER in patients with SMR.[27,28] No reduction in the primary end point of all-cause mortality or HF hospitalizations at 1 year was shown in MITRA-FR, whereas a significant reduction in HF hospitalizations (primary end point) and in mortality alone (secondary end point) at 2 years was shown in COAPT.[25,73] In RESHAPE-HF2, the rate of first or recurrent HF hospitalization or cardiovascular death at 24 months was 37.0 events per 100 patient-years in the device group and 58.9 events per 100 patient-years in the control group (relative risk, 0.64 [95% CI, 0.48–0.85]), and the rate of first or recurrent hospitalization for HF was significantly reduced by 41%.[32] A meta-analysis of the 3 trials reported better outcomes for the M-TEER group compared with the control group in terms of total unplanned HF hospitalizations within 24 months, recurrent events of hospitalization for HF, or all-cause mortality within 24 months, whereas statistical significance was not reached for all-cause mortality and cardiovascular mortality alone at 24 months.[110]

Transcatheter TR treatment was associated with greater survival and lower risk of HF rehospitalizations compared with medical therapy alone in a propensity-matched case-control study.[111] The TRILUMINATE Pivotal trial demonstrated an improvement in the composite hierarchical end point (death resulting from any cause

Table 2. Major Randomized Controlled Interventional Trials for Treatment of Mitral or Tricuspid Regurgitation

Study		Design, patients, N	Main enrolment criteria	Primary end point	Main results
Mitral valve					
EVEREST II[19,20]	Description	Multicenter, randomized, open-label, 2:1 randomized comparison of M-TEER and surgical therapy. N=279	Moderately severe or severe MR candidates for surgery. If symptomatic: LVEF >25%, LVESD ≤55 mm; if asymptomatic with ≥1 of LVEF 25%–60% or LVESD 40–55 mm and/or new atrial fibrillation and/or pulmonary hypertension.	Primary composite for efficacy: freedom from death, surgery for mitral valve dysfunction and from grade 3+ or 4+ MR at 12 mo. Primary for safety major adverse events at 30 d.	Efficacy: 55% with M-TEER vs 73% with surgery (P=0.007) driven by higher need of surgery mitral valve dysfunction. Similar mortality, LV size reduction, NYHA class and quality of life improvement. Lower rate of adverse events with M-TEER, 15% vs 48% in the surgery group at 30 d (P<0.001). 27% with SMR vs 73% with degenerative MR with significant heterogeneity: similar efficacy in SMR vs better efficacy in degenerative MR (P=0.02)
	Evidence for HF treatment	Strong	Moderate (no specific criteria for HF)	Moderate (end points on MR reduction)	Moderate (end points on MR reduction)
MITRA-FR[25]	Description	Multicenter, randomized, open-label, comparison of M-TEER and medical therapy. N=304	Severe SMR with regurgitant volume of >30 mL/beat or EROA >20 mm^2 LVEF 15%–40% NYHA class II to IV.	A composite of death resulting from any cause or unplanned hospitalization for HF at 12 mo after randomization.	HR for the primary end point, 1.16 (95% CI, 0.73–1.84). HR for all-cause death, 1.11 (95% CI, 0.69–1.77). HR for HFH, 1.13 (95% CI, 0.81–1.56).
	Evidence for HF treatment	Strong	Strong	Strong	Strong
COAPT[73]	Description	Multicenter, randomized, open-label comparison of M-TEER and medical therapy N= 614	Moderate to severe or greater SMR LVEF 20-50% NYHA II, III, or IVa despite GDMT and CRT (if appropriate)	HF hospitalizations at 24 mo. Freedom from device-related complications at 12 mo.	HR for HFH, 0.53 (95% CI, 0.40–0.70). HR for all-cause death at 24 months, 0.62 (95% CI, 0.46–0.82). Freedom from device-related complications at 12 mo was 96.6%.
	Evidence for HF treatment	Strong	Strong	Strong	Strong
RESHAPE-HF2[32]	Description	Multicenter, randomized, open-label, comparison of M-TEER and medical therapy. N=505	Moderate to severe or severe SMR LVEF 20%–50% (initially, LVEF was 15%–35% for patients with NYHA class II and 15%–45% for patients with NYHA class III or IV) NYHA class II to IV Either an HFH within 12 mo or elevated NPs (BNP ≥300 pg/mL or NT-proBNP ≥1000 pg/mL)	3 primary end points were: (1) Rate of the composite of first or recurrent HFH or cardiovascular death during 24 mo; (2) rate of first or recurrent HFH during 24 mo; and (3) change from baseline to 12 mo in KCCQ-OSS	(1) Rate ratio for first or recurrent HFH or cardiovascular death was 0.64 (95% CI, 0.48–0.85) at 24 mo; (2) rate ratio for first or recurrent HFH was 0.59 (95% CI, 0.4–0.82) at 24 mo; (3) KCCQ-OSS increased in the device group vs the control group (mean difference, 10.9 points [95% CI, 6.8–15.0]) at 12 mo.
	Evidence for HF treatment	Strong	Strong	Strong	Strong

(*Continued*)

Table 2. Continued

Study		Design, patients, N	Main enrolment criteria	Primary end point	Main results
MATTERHORN[42]	Description	A multicenter, prospective, randomized, controlled noninferiority trial with 2 parallel treatment groups (M-TEER, intervention group) or surgical mitral valve repair or replacement (surgery group). N=210	Clinically significant SMR (defined by at least 2 of the following criteria: EROA ≥20 mm², biplane VC width >8 mm, regurgitant volume ≥30 mL, regurgitant fraction of at least 50%, or at least 2 HFHs during the 12 mo before enrollment) LVEF ≥20% NYHA class II–IV despite GDMT Eligibility for both TEER or mitral valve surgery as determined by the local heart team	The primary efficacy end point was a composite of death, HFH, mitral valve reintervention, implantation of an assist device, or stroke within 1 y after the procedure.	Within 1 y, at least 1 of the components of the primary efficacy end point occurred in 16.7% of patients with available data in the intervention group and in 22.5% in the surgery group (estimated mean difference, −6 percentage points; [95% CI, −17 to 6]; $P<0.001$ for noninferiority).
	Evidence for HF treatment	Strong	Strong	Strong	Strong for noninferiority
REDUCE FMR Trial[159]	Description	Double-blinded, multicenter, randomized, proof-of-concept, sham-controlled comparison of coronary sinus–based mitral annular reduction (Carillon system) and sham procedure. N=120	NYHA class II–IV LVEF <50% LVEDD >55 mm, SMR grade 2-4+ despite ≥3 mo of GDMT 6MWT distance 150–450 m	Change in MR volume at 12 mo by quantitative echocardiography.	Significant reduction in MR volume vs control (decrease of 7.1 mL/beat [95% CI, −11.7 to −2.5] vs an increase of 3.3 mL/beat [95% CI, −6.0 to 12.6]; $P=0.049$). Significant reduction in LV volumes.
	Evidence for HF treatment	Strong	Strong	Mild (no outcome end point)	Moderate (surrogate end point)
Tricuspid valve					
TRILUMINATE Pivotal[84]	Description	Multicenter, randomized, open-label comparison of T-TEER and medical therapy. N=350	Severe TR (NYHA class II to IV, PASP <70 mm Hg, on stable GDMT for HF) At intermediate or greater surgical risk	Composite end point including all-cause death or TV surgery; HF hospitalization; and an improvement in quality of life (defined as an increase ≥15 points in the KCCQ score at the 1-y follow-up).	Efficacy at 1 y, win ratio, 1.48 (95% CI, 1.06–2.13). Rate: moderate or less TR at 30 d, 87.0% in the TEER group vs 4.8% in the control group.
	Evidence for HF treatment	Strong	Strong	Moderate to strong (outcomes only as components of the composite end point)	Strong (based on primary outcome)
Tri.Fr (multicenter, controlled, randomized, 1:1 ratio, superior, open-label, and parallel-group study sponsored by the French Ministry for Solidarity and Health)[112]	Description	Prospective, multicenter, controlled, randomized, 1:1 ratio, superior, open-label, and parallel-group study comparing Tri-Clip implantation and medical therapy only. N=300	Symptomatic secondary severe TR or greater stable for at least 30 d TR characterized by at least 1 of the following criteria: regurgitation volume >45 mL/beat; EROA >40 mm²; VC >7 mm; gap between leaflets ≤7 mm NYHA class II–IV without cirrhosis or ascites Signs of HF in the previous 12 mo with or without hospitalization Stable optimized medical and/or interventional treatment for at least 30 d Ineligible for corrective action on the valve by a surgical approach after a heart team consultation	Packer composite clinical end point (CCS), combining NYHA class, PGA, and major cardiovascular events (all-cause mortality, cardiovascular mortality, tricuspid valve surgery, HFH, cardiovascular and noncardiovascular hospitalizations) over a period of 12 mo after randomization.	At 1-y follow-up, 74.1% in the T-TEER group improved vs 40.6% in the medical therapy group (relative risk, 0.67 [95% CI, 0.61–0.72]).
	Evidence for HF treatment	Strong	Strong	Moderate to strong (outcomes only as components of the composite end point)	Strong (based on primary outcome)

(*Continued*)

Table 2. Continued

Study		Design, patients, N	Main enrolment criteria	Primary end point	Main results
TRISCEND II trial[81]	Description	Prospective, multicenter, randomized controlled pivotal clinical trial comparing the EVOQUE system with OMT (randomization in 2:1 ratio)	Severe or greater TR Signs or symptoms of TR or previous hospitalization for HF despite medical therapy Appropriate for TTVR	Hierarchical composite primary outcome of death resulting from any cause, implantation of an RV assist device or heart transplantation, postindex tricuspid valve intervention, HFH, an improvement of at least 10 points on the KCCQ-OSS, an improvement of at least 1 NYHA class, and an improvement of at least 30 m on the 6MWT.	Win ratio for the primary outcome favoring valve replacement was 2.02 (95% CI, 1.56–2.62) at 1 y.
	Evidence for HF treatment	Strong	Strong	Moderate to strong (outcomes only as components of the composite end point)	Strong

6MWT indicates 6-minute walking test; BNP, brain natriuretic peptide; CCS, Clinical Composite Score; COAPT, Cardiovascular Outcomes Assessment of MitraClip Percutaneous Therapy for HF With Functional Mitral Regurgitation; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; EVEREST II, Endovascular Valve Edge-to-Edge Repair Study; GDMT, guideline-directed medical therapy; HF, heart failure; HFH, hospitalization for heart failure; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; M-TEER, mitral-transcatheter edge-to-edge repair; MATTERHORN, Multicenter Mitral Valve Reconstruction for Advanced Insufficiency of Functional or Ischemic Origin; MITRA-FR, Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation; MR, mitral regurgitation; MV, mitral valve; NP, natriuretic peptide; NT-proBNP, N-terminal probrain natriuretic peptide; NYHA, New York Heart Association; OMT, optimal medical therapy; OR, odds ratio; OSS, Overall Summary Score; PASP, pulmonary artery systolic pressure; PGA, patient global assessment; PVR, pulmonary vascular resistance; REDUCE FMR, A Randomized Sham-Controlled Study of Percutaneous Mitral Annuloplasty in Functional Mitral Regurgitation; RESHAPE-HF2, Randomized Investigation of the MitraClip Device in Heart Failure: Second Trial in Patients With Clinically Significant Functional Mitral Regurgitation; RV, right ventricular; SMR, secondary mitral regurgitation; T-TEER, tricuspid-transcatheter edge-to-edge repair; TR, tricuspid regurgitation; TRILUMINATE, Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System Pivotal; TRISEND II, Edwards EVOQUE Transcatheter Tricuspid Valve Replacement: Pivotal Clinical Investigation of Safety and Clinical Efficacy Using a Novel Device; TTVR, transcatheter tricuspid valve replacement; TV, tricuspid valve; and VC, vena contracta.

*The prespecified analysis on the first 350 randomized patients was published.

or tricuspid valve surgery; hospitalization for HF; and an improvement in quality of life defined as an increase of at least 15 points in the Kansas City Cardiomyopathy Questionnaire [KCCQ] score at 1 year after T-TEER; win ratio, 1.48 [95% CI, 1.06–2.13]; *P*=0.02). The results were, however, driven by the improvement in quality of life, whereas the study failed to show a benefit in mortality and HF hospitalizations alone.[84]

The Tri.Fr trial adopted the so-called Packer composite clinical end point evaluated at 12 months after randomization, combining the occurrence of major cardiovascular events (cardiovascular hospitalization or death) and changes in New York Heart Association (NYHA) class or patient global assessment.[85] Despite a significant improvement in the composite clinical end point with T-TEER, statistical significance was not reached for major cardiovascular events or for cardiovascular death considered alone.[112] In the TRISCEND II trial, the primary end point was a hierarchical composite of death resulting from any cause, implantation of an RV assist device or heart transplantation, postindex tricuspid valve intervention, hospitalization for HF, an improvement of at least 10

Table 3. Strategies to Achieve Statistical Power in Atrioventricular TVI Trials

Control group event rate	A high-risk population is associated with a higher event rate and potentially allows a reduction in the sample size. The inclusion of patients with a previous HFH might increase the event rate in the control group. However, uncertainty about the clinical benefit of TEER for high-risk patients with advanced HF features (eg, advanced right-sided HF, irreversible end-organ damage) should be considered. Heterogeneity of MR and TR causes should also be considered.
Power	The greater the power is, the larger the required patient numbers are (but the smaller the likelihood of failing to detect a difference that is truly present). The TRILUMINATE and MITRA-FR trials reduced the power to 84% and 80%, respectively. A power <80% is generally not recommended.
Choice of primary end point	Composite primary end points comprising mortality and several nonfatal events have the potential to enhance statistical power by the greater frequency of patients experiencing at least 1 component of the composite during follow-up. In chronic HF, the standard composite primary end point is cardiovascular death and hospitalization for heart failure. Adding extra components, for example, including worsening HF events or worsening in quality of life or functional capacity, boosts the numbers of events, although diluting the effect and meaning of the composite. Because the least serious component may tend to occur earlier (and more frequently), the Finkelstein-Schoenfeld method or the win ratio approach, which invert the priorities to match with clinical severity, should be preferred.
Length of follow-up	Longer follow-up increases the rate of events.

HF indicates heart failure; HFH, heart failure hospitalization; MITRA-FR, Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation; MR, mitral regurgitation; TEER, transcatheter edge-to-edge-repair; TR, tricuspid regurgitation; TRILUMINATE, Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System Pivotal; and TVI, transcatheter valve intervention.

points in the score on the KCCQ Overall Summary Score, an improvement of at least 1 NYHA functional class, and an improvement of at least 30 m on the 6-minute walking test distance (6MWTD). The win ratio for the primary outcome at 1 year favoring valve replacement was 2.02 (95% CI, 1.56–2.62).[81] In the comparison of patient pairs, those in the valve replacement group had more wins than the individuals in the control group with respect to death resulting from any cause (14.8% versus 12.5%) and postprocedural tricuspid valve intervention (3.2% versus 0.6%) but not with respect to the annualized rate of hospitalization for HF (9.7% versus 10.0%).[81]

After the publication of the preliminary results of the predefined Breakthrough Pathway Cohort, including the first 150 randomized patients from the TRISCEND II trial, the EVOQUE device recently received its CE mark and US Food and Drug Administration approval.[113]

Patient-Reported Outcome Measures

Changes in symptoms and quality of life are increasingly used as primary/coprimary end points in trials and are meaningful for patients, maybe even more than mortality for some individuals.[114] The KCCQ and the Minnesota Living with Heart Failure Questionnaire are the most commonly used PROMs in HF.[114,115] In placebo controlled trials, a difference of 5 points in KCCQ may indicate a minimally significant difference, and an increase of at least 10 to 15 points is considered a moderate or large improvement that is less likely explained by placebo effect.[116,117] When looking at mean improvements in KCCQ, drug trials generally result in much lower effect size compared with interventional treatment that can only partly be explained by the lack of a placebo/sham control (Figure 3).

Multiple studies have shown an improvement in symptoms, often assessed by the NYHA class, quality of life, and exercise capacity after percutaneous treatment of MR and TR.[32,81,83,84,99,109,111,113,118–121] At 1 year in the TRILUMINATE Pivotal trial, the KCCQ score changed by a mean±SD of 12.3±1.8 points in the T-TEER group compared with 0.6±1.8 points in the control group.[84] Substantial improvements in 6MWTD, NYHA class, and KCCQ score were sustained from 30 days to 2 years.[119]

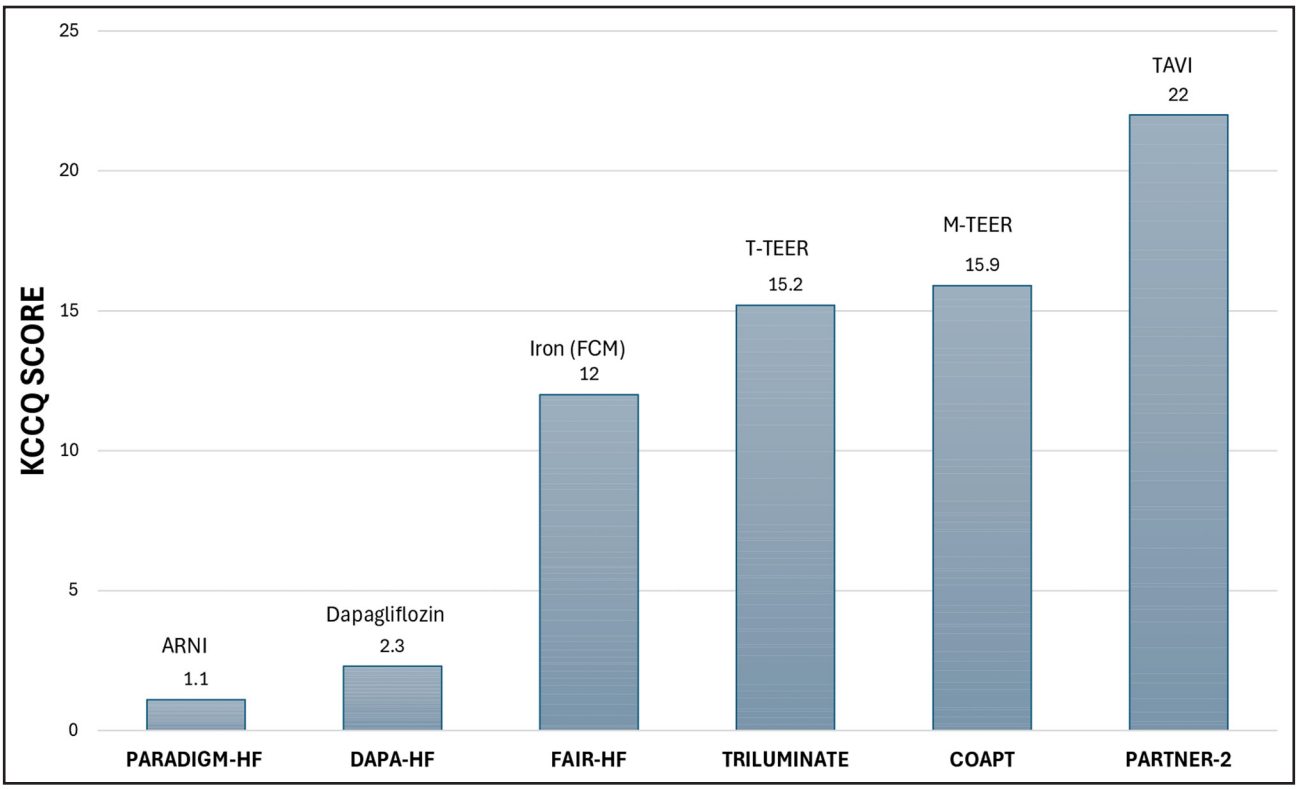

Figure 3. Changes in quality of life, measured by KCCQ Overall Summary Score, after medical or device interventions in major trials in patients with heart failure.

Reported differences were assessed at different time points (angiotensin-neprilysin inhibition and dapagliflozin at 8 months, ferric carboxymaltose at 12 weeks, tricuspid transcatheter edge-to-edge-repair at 1 year, mitral transcatheter edge-to-edge-repair at 1 month, transcatheter aortic valve implantation at 1 year). COAPT indicates Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; FAIR-HF, Ferinject Assessment in Patients With Iron Deficiency and Chronic Heart Failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; PARADIGM-HF, Angiotensin-Neprilysin Inhibition Versus Enalapril in Heart Failure; PARTNER-2, Placement of Aortic Transcatheter Valve; and TRILUMINATE, Trial to Evaluate Treatment With Abbott Transcatheter Clip Repair System in Patients With Moderate or Greater Tricuspid Regurgitation.

In TRISCEND II, a significantly higher proportion of patients experienced an increase of at least 10 points in the KCCQ Overall Summary Score, a decrease of at least 1 NYHA class, and an increase in 6MWTD by at least 30 m in the valve replacement group compared with controls.[81]

There are limitations, however, in the use of improvement in quality of life as an end point. First, some trials of devices and invasive treatment strategies cannot be double-blinded. Blinding and sham-controlled randomized trials become particularly important when the primary end point is based on end points such as quality of life. Second, an improvement in quality of life was also observed in the control arms of both unblinded and sham-control HF trials as a result of the placebo effect.[122] Third, to attribute a change in patient symptoms to TR reduction, patients should be on a stable medical regimen before and after device therapy. However, changes in the clinical conditions may mandate a change in medical therapy. In the TRILUMINATE Pivotal trial, increasing diuretics just before transcatheter procedure and increasing diuretics in the control group during follow-up were described, resulting in differences in "treatment" between the groups that might have confounded the results of device therapy.[48] Fourth, the current clinical assessment tools such as NYHA classification, KCCQ, and 6MWTD were developed to assess patients with HF caused by LV dysfunction but not patients with right-sided HF. The clinical course of right-sided HF, even in presence of severe TR, may be initially subclinical and then lead to signs of peripheral congestion with liver and kidney dysfunction, gut malabsorption, and peripheral oedema. These signs may have a major impact on patient's quality of life and exercise tolerance, similar to if not larger than what can be found in patients with LV dysfunction. However, abdominal distension, dyspepsia, anorexia, and early satiety due to systemic congestion involving splanchnic organs often dominate the clinical picture in patients with right-sided HF but are seldom present, except in the late phases, in the patients with LV dysfunction. Last, RV dilatation may cause also LV diastolic dysfunction through ventricular interdependence, leading to pulmonary congestion and dyspnoea.[123] Thus, multiple symptoms, some superimposable to those of the patients with LV dysfunction and some relatively specific for right-sided HF and systemic congestion, characterize patients with right-sided HF. Development of proper, more specific criteria to assess patients with right-sided HF seems warranted, although no such instruments are currently available. However, current assessments, mainly KCCQ, which has been recently validated in patients with severe TR,[124] seem rather sensitive to the effects of T-TEER, although with the limitations of unblinded studies.[117,125] Changes in the KCCQ score were associated with the degree of residual TR and magnitude of TR reduction at the 1-year follow-up, which supports a pathophysiological dose-response mechanism.[84] A prespecified analysis of the TRILUMINATE Pivotal trial showed that the health status benefit of T-TEER was sustained without attenuation through 1 year of follow-up, and short-term improvement in health status after T-TEER was strongly correlated with reduced 1-year mortality and HF hospitalization, suggesting a true biological effect of T-TEER and supporting the reliability of this end point.[126]

Composite End Points

Use of a composite end point comprising mortality and several nonfatal events may enhance statistical power. Most of the trials in patients with HF have been based on the composite primary end point of cardiovascular death and hospitalization for HF, which are assessed during the entire follow-up of the study.[107] This end point is now expanded to include outpatient worsening HF events or with the analysis of recurrent HF events.[127–129]

Other end points targeting important aspects of the disease or the efficacy of the intervention are often added in TVI trials, including quality of life, exercise capacity, or degree of residual MR or TR.

There are concerns related to the impact of a placebo effect on these measurements in the absence of blinding. However, having a larger threshold to define a significant improvement in PROMs such as quality of life, that is, an increase of at least 15 points on the KCCQ from baseline at 1 year, might reduce the possible placebo effect. In addition, the use of multiple measurements during a long follow-up may reduce the placebo effect because this is more likely to occur immediately after the procedure. Last, wearable technologies could provide less-biased, because not self-reported, assessment of functional capacity and quality of life. To date, they have been used in a relatively small study and were successful in showing an improvement in activity after T-TEER.[130–132]

When the Finkelstein-Schoenfeld method or the win ratio approach is used to assess composite end points, the outcomes of interest are evaluated according to a prespecified hierarchy, which allows the assignment of priority to the harder components of the primary outcome, that is, death and hospitalizations, and avoids issues related to different components of a nonhierarchical composite outcome being influenced in opposite directions by the active intervention such as what could happen with a traditional approach.[133,134] However, the drawback of the win ratio method is that most of the efficacy of the intervention could be explained by a reduction of those measurements that are less important from a clinical, regulatory, and guidelines standpoint, limiting the impact of the results of the trial. Therefore, the utility of the win ratio method depends on the proper definition

and ranking of clinically meaningful components of the primary outcome and the consistency of the active treatment effects across the different components of the end point.

In TTVI trials, the primary end points were mainly a hierarchical composite that included death resulting from any cause or tricuspid valve surgery, hospitalization for HF, and an improvement in symptoms (NYHA class), health status (as measured with KCCQ), or functional capacity (6MWTD).[81,84,85] The addition of PROMs and of worsening HF events is particular importance in trials investigating patients with severe TR because, unlike in SMR, right-sided HF does not necessarily result in hospitalization and is frequently managed in the ambulatory setting. Although currently not implemented in randomized controlled trials testing interventions in the field of valve heart disease and HF, wearable technologies could provide less-biased, because not self-reported, assessment of functional capacity, a key component of quality of life assessment.

Hemodynamics and Cardiac Function

Hemodynamic changes and the reduction in MR or TR grade have seldom been included as composite end points although they may be useful for the assessment of the efficacy of valve interventions. Improvements in hemodynamic parameters and reverse LV remodeling were repeatedly observed after M-TEER.[21,25,73,135,136] Reduced MR severity and decreased pulmonary pressure were associated with better short- and long-term outcomes after M-TEER.[100,137–139] Improvements in hemodynamic (ie, cardiac output), blood pressure, congestion, and RV and renal function may enable optimization of GDMT.[90,100,123,138,140]

Whether TTVI may determine short- or long-term changes in RV function is not settled. An observational study showed that T-TEER led to an increase in RV stroke volume and cardiac output with a decrease in RV end-diastolic volume. LV filling also improved with an increase in LV end-diastolic volume and LV stroke volume, likely through ventricular interdependence.[141] In the TRILUMINATE trial (Trial to Evaluate Treatment With Abbott Transcatheter Clip Repair System in Patients With Moderate or Greater Tricuspid Regurgitation; n=85) both RV end-diastolic diameter and tricuspid annular plane systolic excursion showed long-term favorable remodeling through 2 years.[119] Positive RV remodeling was also observed with other devices, including the PASCAL transcatheter valve repair system,[109] EVOQUE system for valve replacement,[81] Cardioband Tricuspid Valve Reconstruction System,[120] and TricValve transcatheter bicaval valves for the superior and inferior vena cavae.[142]

Among patients with severe TR enrolled in the TRISCEND study, TR was reduced to mild or less in 97.6% after transcatheter TV replacement, with consequent increases in stroke volume (10.5±16.8 mL) and cardiac output (0.6±1.2 L/min) and improvement in NYHA class, KCCQ score, and 6MWTD.[99] Increasing doses of diuretics was reported in the control arm of the TRILUMINATE Pivotal trial compared with the device arm.[84]

Biomarkers

Natriuretic peptides and, less frequently, cancer antigen 125 are used as makers of congestion.[143–145] Plasma concentrations of natriuretic peptides are related to LV dysfunction, whereas cancer antigen 125 may better reflect systemic congestion. Thus, NT-proBNP/BNP may be more appropriate for assessing MR, whereas cancer antigen 125 might be an important additional tool in the patients with TR. Biomarkers have seldom been used as surrogate end points for atrioventricular valve interventions in HF, although they have the advantage of being unbiased by knowledge of treatment allocation. To progress toward precision medicine and to gain deeper insights into the molecular characteristics of various stages of MR and TR, it is advisable to biobank blood in prospective trials for future omics studies. Conducting serial evaluations of biomarkers could offer insights into disease progression and prove valuable for guiding management.[143,146] However, procedures conducted on the right side for TR treatment may lead to acute variations of biomarker values that may be interpreted negatively but may reflect only the afterload mismatch, not long-term consequences, complicating interpretation during the acute phase.

Postprocedural Regurgitation Grade

The assessment of postintervention MR and TR grade relies on echocardiography.[48,63,95,147] Assessment of transcatheter intervention results may be complicated by the anatomy and functional effects of the MR and, to a larger extent, TR. Residual regurgitant jets after TEER may be multiple, in different planes, and of different severity and may merge, adding to the complexity of the assessment of residual MR and TR severity.[147] Guidelines for the evaluation of valvular regurgitation after transcatheter valve repair or replacement were developed by international societies.[147] A higher degree of residual MR and TR after intervention was associated with worse outcomes.[53,137,139,148–151]

A key difference between transcatheter valve replacement and TEER repair devices is the almost complete elimination of atrioventricular valve regurgitation with valve replacement.[81] The required degree of TR reduction for sufficient volume unloading or structural RV reverse remodeling, leading to favorable outcomes, remains unknown. However, data from the EuroTR Registry reported worse survival in patients with residual

TR 3+ after T-TEER, without significant differences between residual TR 1+ and 2+.[125] The complete elimination of TR with transcatheter tricuspid valve replacement (TTVR) may enhance the afterload mismatch after the procedure. Moreover, TTVR is burdened by a higher rate of procedural complications (ie, major bleeding and conduction disturbance) compared with T-TEER. Thus, to date, TTVR is indicated mainly in patients considered ineligible for T-TEER. However, a direct comparison between T-TEER and TTVR may be needed with better evidence and advances in TTVR.

SAFETY

From prior MitraClip studies, the COAPT trial investigators anticipated an ≈6% rate of adverse events, including single-leaflet device attachment, embolization, endocarditis, mitral stenosis, and need for surgery, LV assist device implantation, or heart transplantation, as well as other device-related complications that require nonelective cardiovascular surgery. The performance goal of an acceptable device-related complication rate of 12% was developed in concert with the US Food and Drug Administration after consideration of what composite risk of device-related complications was acceptable compared with the expected effectiveness.[26] The primary safety end-point rate was, however, much lower than expected and confirmed the high safety of M-TEER even in this high-risk population.[73] Adverse events in major mitral valve interventions trials are summarized in Table S1. The most frequent complications reported in observational studies include procedure-related complications, namely bleeding (0%–17%) and major vascular complications (ranging from 1.4% to 4.0%). Pericardial effusion or tamponade occurred in <0.5% of patients.[152] Rates of other complications were previously reported.[136,152] Device-related complications due to structural failure (ie, single-leaflet device attachment, leaflet injury) are rare. On the other hand, rates of functional impairment with residual MR >2+ and transmitral gradient >5 mm Hg are higher (up to ≈15%). Procedural experience and center procedural volume may affect procedural success.[153–155]

The safety of T-TEER was demonstrated in the TRILUMINATE studies.[84,156] Overall, 98.3% of the patients in the device arm of the TRILUMINATE Pivotal trial were free from major adverse events at 30 days. No death occurred during the hospital stay; the median length of stay was 1.0 days (1.0–2.0 days). One patient (0.6%) in the TEER group died within 30 days; that death was adjudicated as not related to the device or procedure.[84] Among the 172 patients in the attempted-procedure population, the device was successfully implanted in 170 (98.8%). Device success and procedural success at 30 days after the procedure were reported in 88.9% and 87% of patients, respectively (Table S2).[84]

The 1-year outcomes of the 176 patients enrolled in the TRISCEND study of transcatheter TV replacement in patients with moderate or greater symptomatic TR were recently published.[99] At 30 days, the composite major adverse events rate was 18.6%, driven primarily by severe bleeding events. Of note, anticoagulation was recommended for up to 6 months after the procedure. Cardiovascular mortality was reported in 1.7% of patients, and nonelective reinterventions on the tricuspid valve occurred in 2.3% (Table S3).[157] New permanent pacemakers were implanted in 15 patients (13.3%), all within 9 days after the procedure. The median length of hospital stay was 3.0 days (2.0–7.0 days). Device success was 94.4%; procedural success 93.0%; and clinical success 77.1%.[49,80] In TRISCEND II, severe bleeding occurred in 15.4% of the valve replacement group compared with in 5.3% of the control group (P=0.003), and new permanent pacemakers were implanted in 17.4% and 2.3%, respectively (P<0.001).[81]

The bRIGHT (An Observational Real-World Study Evaluating Severe Tricuspid Regurgitation Patients Treated with the Abbott TriClip Device) postapproval study was a prospective, single-arm, open-label, multicenter postmarket registry conducted at 26 sites in Europe. Successful TriClip device implantation occurred in 99% of subjects, and TR was reduced to moderate or less at 30 days in 77%.[83]

OTHER VARIABLES

Follow-Up Duration

In the COAPT trial, follow-up was performed at 1 week and at 1, 6, 12, 18, and 24 months in the device group; after a visit with the site HF specialist in the control group (either of which would occur within 14 days after randomization); and then annually through 5 years. Outcomes were assessed at 12 months in the MITRA-FR trial. Clinical follow-up was conducted at 1, 6, and 12 months in the TRILUMINATE trial. The timing of end-point assessment must be considered when interpreting the periprocedural early and late risks and benefits. Length of follow-up could also influence the rate of events. At a minimum, the occurrence of outcomes should be reported in hospital, at 30 days, and at 1 year. Common safety end points should be reported in hospital and at 30 days; less common ones may be identified during longer follow-up. Long-term outcomes should be reported for devices to ascertain whether device durability is acceptable. Imaging end points should be reported at postprocedure or predischarge, 30 days, and 1 year at minimum and during longer follow-up to provide data on durability. The experience from randomized trials shows that a 1-year follow-up may not be sufficient to assess the magnitude of the treatment effect that emerged beyond 1 year in COAPT.

Intention-to-Treat Compared With Per-Protocol Analysis

Analysis by intention-to-treat should be prioritized because it provides an unbiased comparison of treatment strategies.[158] In the TRILUMINATE trial, the analysis of primary end point was conducted in the intention-to-treat population, which included all patients who underwent randomization. The authors also conducted analyses in a per-protocol population (patients who underwent randomization and had no major protocol deviations), an as-treated population (patients who underwent randomization, grouped according to the treatment received), and an attempted-procedure population (patients who had been randomly assigned to the TEER group, except for those who withdrew consent before the index procedure). All analyses were performed according to the intention-to-treat principle in COAPT and MITRA-FR trials. An important consideration is allowance of crossovers that occurred after 2 years in COAPT, whereas T-TEER was possible at 1 year in TRILUMINATE. A policy should be observed to avoid crossovers, especially when using therapies for which a clear prognostic benefit is not yet established.

Table 4. Future Directions to Support Evidence for Transcatheter Interventions for MR and TR in Patients With HF

Size of the study group Maximize number of patients as much as possible Focus on specific well-characterized phenotypes Include all (ambulatory) worsening HF events in addition to HFHs Use combined end points/recurrent events analysis
Better assessment of patient-reported outcomes Blinded evaluation of NYHA class and quality-of-life questionnaires by study personnel Consider ≥15-point KCCQ difference in nonsham interventions Multiple evaluations in the long term to show reproducibility and stability of the results Use sham-controlled procedures if possible
Use objective measurements to support subjective data Serial biomarker measures related with congestion and cardiac function (natriuretic peptides, CA125, etc) and end-organ damage (troponin, kidney and liver function, gut microbiota) Imaging with core laboratory assessment for cardiac function and pulmonary circulation
Multidisciplinary screening and management, including specialists in HF and imaging
Standardization of medical treatment before and after procedures
Implement postapproval registries

CA125 indicates cancer antigen 125; HF, heart failure; HFH, heart failure hospitalization; KCCQ, Kansas City Cardiomyopathy Questionnaire; MR, mitral regurgitation; NYHA, New York Heart Association; and TR, TR, tricuspid regurgitation.

CONSIDERATIONS FOR FUTURE TRIALS

Design of clinical trials and hence building of evidence for TVI in patients with MR or TR and HF remain major unmet needs, only partially overcome by most recent trials. Major issues, compared with the trials of medical treatment, include the impossibility of enrolling a large number of patients and hence testing hard clinical end points such as mortality, as well as difficulties in having a double-blind sham-control design with inherent biases when subjective end points such as quality of life and PROMs are evaluated.

Table 4, Figure 2, and Figure S1 outline possible changes that may improve the next trial design. Multiple strategies may help to compensate for the need to randomize a relatively small number of patients. First, trials may become focused on specific, well-characterized phenotypes so that dilution of the effects due to heterogeneity of the studied population is reduced. An accurate characterization of clinical phenotypes, as outlined also here, and standardization of medical therapy both before and after the procedure are examples of this strategy. Second, a longer length of the follow-up may increase the number of events. Third, different definitions of outcomes such as the inclusion of worsening HF events occurring without a hospitalization and/or recurrent events analysis, rather than time to fist event, or the addition of days alive outside the hospital, considering also the length of the hospital stays, may also increase the power of the study. Fourth, trials may have composite end points, including variables not directly related with outcomes. As in recent trials,[84] such a composite end point may include both mortality (that is unbiased), all events of worsening HF (ie, both in hospital and ambulatory),[129] and PROMs.

PROMs such as quality-of-life questionnaires may be biased by knowledge of the procedure, if not its results, in an open-label trial. However, also in this case, specific strategies, as listed in Figure S1, may overcome, at least partially, the lack of a blinded, sham-controlled, protocol design. They include a blinded evaluation of NYHA class and quality-of-life questionnaires by the investigators without knowledge of patient's assignment at the time of randomization; use of higher thresholds to define clinically significant differences in KCCQ evaluation (ie, >15 points); and adoption of multiple evaluations in the long term to show the reproducibility and stability of the results because placebo effects are typically short-lived. The use of objective measurements and surrogate end points, namely biomarkers related to congestion, cardiac function (ie, natriuretic peptides, cancer antigen 125), and end-organ damage (i.e. troponin and markers of kidney and liver function), and activity monitors to support subjective data is also strongly advised. Activity monitors were adopted in a recent, relatively small study.[132]

Last, the implementation of postapproval registries may provide further evidence for patient selection, untoward side effects, and the safety of the procedures.

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Supplemental Material

Tables S1–S3

Figure S1

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