Transcatheter Mitral Valve Repair for Functional Mitral Regurgitation: Evaluating the Evidence

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Abstract

Objectives: Two trials (COAPT and MITRA-FR) were published in 2018 evaluating the effectiveness and safety of transcatheter repair for heart failure patients with significant functional MR, which yielded different results. This paper reviews the strength of the evidence, differences in trial designs, ethical and implementation implications, and delineates future research needs to help guide the appropriate dissemination of transcatheter repair for functional MR patients.

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Conflict of Interest: All authors report disclosures online via JTCVS editorial manager.
**Methods:** The National Heart, Lung and Blood Institute convened a workshop of interdisciplinary experts to address these objectives.

**Results:** Transcatheter repair of functional MR can provide significant benefits in terms of heart failure hospitalizations, survival and quality-of-life, when appropriate heart failure candidates, with moderate to severe or severe MR while on optimal guideline-directed medical therapy, can be identified. Key ingredients for success are pre-operative evaluation and management and post-operative care by an interdisciplinary heart team.

**Conclusions:** Given the discordance observed between trials, ongoing innovation in patient management and potential expansion of indications for use, the evidence base must be expanded to optimize appropriate implementation of this complex therapy. This will require more complete capture of outcome data in real-world settings for all eligible candidates, whether or not they receive this therapy. Inevitably, the indications for use of this therapy will expand, as will the devices and therapeutic approaches for this population, necessitating the study of comparative effectiveness through randomized trials or observational studies. Moreover, given the substantial variations in care delivery, conducting implementation research to delineate characteristics of the optimal care model would be of benefit.

A sizable proportion of the growing population of patients with heart failure (HF) develop secondary or functional mitral regurgitation (MR), most commonly as a consequence of progressive left ventricular (LV) dilatation and displacement of the papillary muscles causing traction and tethering with incomplete coaptation of the mitral valve (MV) leaflets (1–4). A major gap in our understanding of this disease is whether the MR itself causes the poor prognosis due to progressive volume overload or whether it is just a marker of more advanced myocardial disease (5). As such, considerable uncertainty exists as to whether correcting functional MR by surgical or transcatheter means would improve clinical outcomes. This uncertainty was recently explored in two randomized trials targeting patients with symptomatic HF, reduced left ventricular ejection fraction (LVEF) and moderate to severe MR: the MITRA-FR (1) and COAPT (6) trials.

These two trials, while apparently similar in overall study design, patient population and treatment interventions, yielded very different results. In the COAPT trial, transcatheter MV repair (TMVr) with Abbott’s MitraClip device (Santa Clara CA) in addition to guideline-directed medical therapy (GDMT) significantly reduced all HF hospitalizations within 2 years versus GDMT alone (1). In the MITRA-FR trial, rates of death or HF hospitalizations at 12 and 24 months did not differ between Mitraclip and GDMT versus GDMT alone (6, 7). The reasons underlying the discordant results between these trials are multifactorial and have been a matter of intense debate. Understanding the relative contribution of these factors has important implications for setting regulatory and reimbursement policies that will shape the subsequent adoption of this therapy, now approved by the Food and Drug Administration (FDA) but for which the Center for Medicare and Medicaid Services (CMS) has not issued a National Coverage Determination as of this writing. In April 2019, the National Heart, Lung and Blood Institute (NHLBI) through its collaborative clinical trials enterprise, the Cardiothoracic Surgical Trials Network (CTSN), convened a panel of experts to review the current evidence, identify implementation and ethical issues, and delineate future research.
needs that would help guide the appropriate dissemination of MitraClip® for functional MR patients.

DIFFERENCES IN TRIAL DESIGN

While the COAPT and MITRA-FR trials targeted similar patients and compared similar treatment strategies, there were significant differences in trial design, eligibility, concomitant medical therapy, study organization and outcome definitions.

Endpoints

The primary efficacy endpoint of COAPT was all HF rehospitalizations within 24 months of follow-up, and the primary safety endpoint was freedom from device-related complications with a pre-specified objective performance goal of 88%. By comparison, the primary efficacy endpoint of MITRA-FR was the composite of death or unplanned HF hospitalizations at 12 months after randomization; the trial had no primary safety endpoint. COAPT was originally designed to enroll 350 patients, and subsequently expanded to 614 patients, to detect an 18% absolute reduction in 2-year incidence rate of hospitalizations for HF with 80% power and 2-sided alpha of 0.05. MITRA-FR’s sample size was 304 patients to detect a 17% absolute reduction in the primary endpoint with 80% power and 2-sided alpha of 0.05. The efficacy implications of these differences in follow-up time and sample size are addressed below.

Echocardiographic Criteria

COAPT and MITRA-FR used different echocardiographic eligibility criteria and definitions of functional MR severity. COAPT included patients with moderate-to-severe (grade 3+) or severe (grade 4+) functional MR based on a pre-specified algorithm (Table 1). These criteria are based on the American Society of Echocardiography definitions in which moderate-to-severe functional MR is defined as an effective regurgitant orifice area (EROA) of at least 0.30 cm² (8). In MITRA-FR, severe functional MR was defined as an EROA >0.20 cm² or a regurgitant volume (RVol) >30 ml/beat per the 2012 European Society of Cardiology guidelines (9). Consequently, a number of patients with less severe degrees of MR were treated in MITRA-FR. In addition, COAPT included only patients with a LVEF ≥20% and ≤50% and a left ventricular end-systolic dimension ≤70 mm. By comparison, MITRA-FR included patients with a LVEF ≥5% and ≤40%, without restrictions in LV dimensions. Consequently, trial participants had markedly different baseline echocardiographic LV characteristics (Table 2), with patients in COAPT having functional MR with larger EROA (and regurgitant volumes) and smaller LV volumes, differences that may affect outcomes.

Medical Management and Optimizing Candidacy

Medical management of HF differed significantly between the two trials. COAPT required all patients to be on maximally-tolerated GDMT for HF for at least 3 months and receive cardiac resynchronization therapy (CRT) or coronary revascularization, as indicated, before randomization, as determined by a central eligibility committee (CEC). The CEC continued monitoring the regimens of GDMT during the trial in both arms, and required documentation of any change in medical therapy after MitraClip, along with its reasons (10).
By comparison, in MITRA-FR the appropriateness of GDMT at study entry was determined by site investigators and left to the treating physician’s discretion during follow-up. Unlike COAPT, neither doses of medications nor changes in medical therapy were documented in MITRA-FR, wherein medical management may have more closely mirrored real-world clinical practice.

**Implanting Investigator Experience**

COAPT was more explicit on required surgical and interventional competence than MITRA-FR, but detailed comparative information is lacking. One distinction is that in COAPT investigators could perform 3 roll-in procedures to augment their prior experience (1).

**DIFFERENCES IN PROCEDURAL AND CLINICAL OUTCOMES**

It is unclear to what extent operator and institutional experience in patient selection and procedure performance, and patient characteristics, may have affected the degree of variation in procedural outcomes. Overall, procedural success was higher in COAPT, as was the number of clips implanted per patient. Procedural complication rates, including device implant failure, cardiogenic shock and tamponade, were lower in COAPT, 8.5% vs. 14.6% in MITRA-FR. Proportionately fewer patients had residual 3–4+ MR post-procedure in COAPT compared with MITRA-FR (5% vs. 9%). In addition, the prevalence of 3–4+ MR among survivors at 1 year was higher among MITRA-FR patients compared with COAPT patients (17% vs. 5%). These findings suggest that COAPT patients experienced more effective and durable MR reduction compared with MITRA-FR patients.

In COAPT, the annualized rate of all HF hospitalizations within 24 months was significantly lower in patients randomized to MitraClip+GDMT vs. GDMT alone (35.8% vs. 67.9% per patient-year; hazard ratio [HR]: 0.53; 95% confidence interval [CI]: 0.40–0.70; p<0.0001). Freedom from device-related complications at 12 months with MitraClip+GDMT was 96.6% (lower 95% CI, 94.8%) and met the pre-specified objective performance goal. Moreover, 2-year all-cause mortality was lower in the MitraClip+GDMT group, as was the 2-year rate of mortality or HF hospitalizations. HF-related quality of life (QoL), as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) and New York Heart Association [NYHA] class, and functional status, as measured by the 6-minute walk test (6MWT), were significantly better in the MitraClip+GDMT group. Additionally, LV reverse remodeling was significantly better in the MitraClip+GDMT arm.

By comparison, in MITRA-FR (6), rates of death or HF hospitalizations at 12 months did not differ between MitraClip+GDMT vs. GDMT alone (54.6% vs. 51.3%; HR: 1.16; 95% CI: 0.73–1.84; p=0.53). At 24-months, all-cause death and unplanned HF hospitalizations remained similar between treatment groups (63.8% vs. 67.1% for Mitraclip+GDMT vs. GDMT alone; HR 1.01; 95% CI 0.77–1.34) (7). Furthermore, all-cause mortality, cardiovascular mortality, rehospitalizations for HF or major adverse cardiovascular events did not differ between groups either at 12 or 24 months.

In contrast, recently presented 36-month COAPT outcomes still show a beneficial HR for all HF hospitalizations (HR 0.49, 95% CI: 0.37–0.63) in favor of MitraClip+GDMT.
Moreover, mortality was significantly lower in MitraClip (HR: 0.67; 95% CI: 0.52–0.85), as was the composite endpoint of all-cause mortality or HF hospitalizations (HR: 0.48; 95% CI: 0.39–0.59). In terms of the safety profile, the risk of mitral intervention or surgery substantially favored MitraClip+GDMT (HR: 0.10; 95% CI: 0.05–0.20), while stroke or MI rates did not differ.

One question that was raised was whether differences in length of follow-up contributed to efficacy differences between trials. Looking at mortality alone, divergence of survival curves in COAPT, first seen at 6 months, was most prominent in the second year, and, as such, the shorter follow-up time for primary endpoint assessment (12 months) in MITRA-FR may have contributed to its lack of mortality benefit. However, as noted above, a mortality benefit was also not observed at 24 months in MITRA-FR, whereas the mortality benefit persisted in COAPT through 36 months. When analyzing COAPT using the same primary endpoint as MITRA-FR (a composite of mortality and HF hospitalizations at 12 months) a significant benefit was still seen for MitraClip recipients (Figure 1). At the same time, a post-hoc subgroup analysis of COAPT patients, with baseline echocardiographic characteristics similar to MITRA-FR patients (i.e., smaller EROAs (<0.30 cm²) and larger LV end-diastolic volume (LVEDV) index (>96 mL/m²), showed no treatment-related difference in the composite of 2-year mortality or HF hospitalizations (HR: 0.90; 95% CI: 0.33–2.43; p=0.83) (13). These findings suggest that different baseline characteristics may have played a role in the outcome differences seen in these two trials.

**STRENGTH OF EVIDENCE FOR USE IN REAL-WORLD CLINICAL PRACTICE**

COAPT was a tightly controlled efficacy and safety study, rather than a pragmatic trial in which the results would be generalizable to widespread clinical practice. For a variety of reasons, including the imaging expertise necessary to accurately quantify the severity of functional MR, the ability to optimize and sustain medical management, and the assurance of operator experience/expertise, it may be challenging to replicate the COAPT trial’s patient selection and management strategies, and, thus, to achieve the same beneficial outcomes in widespread clinical practice. Achieving the clinical benefits seen in COAPT with the MitraClip procedure in practice will require augmented multi-disciplinary heart teams (herein referred to as “Heart Team(s)”) with adoption of rigorous processes for patient evaluation, availability of technical and imaging expertise and specialized clinical management protocols (12). Successful patient selection requires expert echocardiographic assessment of functional MR severity and anatomic suitability for transcatheter intervention, as well as HF expertise in both selection and management. Indications for CRT in appropriate patients should be recognized. Importantly, in both Mitraclip trials, the surgeon member of the Heart Team determined that mitral surgery was not appropriate. Whether there are other indications to consider surgery in preference to transcatheter repair, such as the need to address multi-vessel CAD not amenable to PCI, significant TR and/or AF, must be adjudicated by the Heart Team in the patient’s best interest.

The importance of eligibility assessment is reflected in COAPT wherein 911 out of 1,576 patients, who were deemed eligible for randomization, were ultimately excluded by the CEC (1). A substantial number of these patients underwent a run-in period during which their
medical management was optimized, resulting in improvement in symptoms and/or severity of MR so that they were no longer trial candidates. Other exclusion factors included lesser degrees of MR or inadequate echo studies after core laboratory adjudication. The fact that each of these high-volume enrolling sites randomized, on average, only one patient per year is further evidence that the trial enrolled a very select population of patients and speaks to the potential challenge in generalizing these trial results.

Beyond patient selection, optimal patient management requires an experienced implanting physician as the use of this device in the functional MR population can be more challenging, especially in a population with poorer ventricular function than in those with primary MR. A study based on TVT registry data, which up to now has captured outcomes pertaining largely to patients with primary MR treated exclusively with MitraClip, has shown an inflection point for improved outcomes at 50 procedures, with continued improvement up to 200 procedures, reflecting in part better patient selection, better technical expertise and improved Heart Team coordination (13,14). The anticipated introduction of newer technologies for MV transcatheter intervention will require similar assessment as the learnings may be primarily device specific. Another element to ensuring optimal outcomes for patients is ongoing HF management, which is particularly critical in the functional MR population, where the majority have underlying LV systolic dysfunction. The COAPT trial investigators, in particular, continued to optimize patients’ HF therapy throughout the trial because the improvement in MR allowed for appropriate titration of GDMT. Whereas many of the centers that will be performing the MitraClip procedure have the relevant clinical specialties represented on their staff, selection and management of these patients requires a robust infrastructure in which decision-making and patient care are highly integrated.

NEED FOR FURTHER RESEARCH

There are important opportunities to conduct research that would help guide the appropriate use of TMVr.

Building on the TVT Registry to Study Real-World Outcomes

The TVT registry offers the opportunity to assess utilization patterns, understand patient characteristics, and assess clinical, functional, and patient-centered outcomes as TMVr evolves in clinical practice. Moreover, the registry can provide insights into clinical variables, such as severity of HF and type of MR, and institutional characteristics, such as institutional volume with TMVr, and their potential impact on outcomes. However, in addition to currently available data elements, some modifications to data collected in this registry may be useful to assess appropriate dissemination. In particular, the TVT MitraClip forms could be adapted to better capture whether patients are appropriate procedural candidates, for example, by including greater detail on frailty, the adequacy of GDMT received, and echocardiographic characteristics. The registry could also capture additional institutional characteristics, such as how the Heart Team is organized and operator experience, which facilitates examining the relationship between institutional and patient characteristics and outcomes. However, the lack of echocardiographic core lab assessment of baseline MR and adequacy of correction is a limitation.
In terms of outcomes, the registry collects 1-year data. Given that the long-term durability of this therapy is unknown, it is clear that long-term outcomes, such as death, repeat valve procedures and HF hospitalizations (which can be captured through linkage with Medicare and Truven Marketscan) are essential. Moreover, demonstrating improvement in patient-centered outcomes is key in a population, which is functionally impaired, and, as a result, has limited QoL (15). The registry collects 1-year KCCQ data; however, additional important endpoints that matter to patients are easy to collect, such as the timing of return to independent living at home or home status at the time of deterioration of their heart failure.

Finally, targeted observational studies are needed to delineate which patient subgroups are most likely to benefit. This is especially important as we can anticipate expansion of TMVr to a broader population, including those with lower surgical risk, lesser degrees of functional MR, and less symptomatic HF. For example, as mentioned above, it has been hypothesized that functional MR patients with larger EROAs relative to LVEDV (disproportionate MR) may derive a greater benefit from interventions directed to the MV (16). Patients with proportionate MR, on the other hand, have a degree of MR that is more commensurate to the degree of LV dilatation and, thus, would more often respond to interventions (such as GDMT, CRT or revascularization) directed at the LV that promote reverse remodeling and reduce LVEDV. These patients are unlikely to respond to correction of MR by transcatheter or surgical means. In contrast, patients with disproportionate MR have degrees of MR that are more severe than what would be predicted by LVEDV, and thus should benefit from interventions directed at the MV to reduce MR. However, this concept has not been prospectively validated, and, alone, may not be sufficient to explain the discrepant trial results (17). Although, data from both trials are currently being pooled to assess this hypothesis, larger-scale observational studies are important to validate this concept and other hypotheses that might allow better identification of optimal candidates for this device (18).

### Creating a Companion Registry to TVT

Creating a companion registry of patients, who are referred for, but do not receive, TMVr therapy would provide a fuller understanding of outcomes of the broader population of patients with symptomatic HF and functional MR. Patients with HF and functional MR would be evaluated by the Heart Team, and patients not on optimal GDMT, would then undergo further optimization of their medical therapy (Figure 2). If their functional MR improves, they would be followed for outcomes in the companion registry. If their functional MR does not improve sufficiently, candidacy for TMVr would be re-evaluated, and those who are not suitable for this intervention would be followed in the companion registry, while those receiving TMVr would flow into the TVT Registry. A companion registry would give insight into why patients do not undergo TMVr for clinical and socio-economic reasons. As such, this would allow exploration of sex-based and racial/ethnic-based disparities in those referred for and ultimately receiving TMVr. The registry would provide important insights into real-world outcomes of patients, who for a variety of reasons do not receive TMVr, to understand if there are reasons for expanding indications for this therapy, which would potentially lead to additional trials.
Randomized Comparative Effectiveness Trials and Implementation Research

Clinical practice is dynamic and incremental improvements in device design and use tend to expand the universe of eligible patients. It is likely that MitraClip therapy will disseminate across a spectrum of patients with varying degrees of functional and primary MR. In addition, other new transcatheter-based or surgical approaches for this population may be introduced into clinical practice. This evolution in treatment approaches and distinctly new indications of use will likely require the conduct of additional randomized trials to define comparative effectiveness and safety.

Questions regarding optimal implementation could be another focus of randomized trials. Such issues are particularly relevant to therapies that are complex in relation to patient selection and long-term management and that are resource-intensive like TMVr. One important area for such implementation trials, for example, centers on the structure of the Heart Team, its role in multi-disciplinary decision-making, and the infrastructure available to ensure optimal GDMT. Another high-priority area concerns evaluation of novel care models that could constitute cost-effective pathways of care.

ETHICAL CONSIDERATIONS

As this therapy expands into broader use, given the discordant trial findings, there is an ethical imperative to provide physicians and patients with the most accurate and up-to-date information needed to make optimal choices regarding the use of this therapy. Beyond survival, patient-centered outcomes, such as QoL and functional status, are critical to facilitate such decision-making. Toward that end we need a better understanding of the discrepancy in QoL and functional status outcomes. For example, whereas COAPT found that QoL improved over time, functional status (as measured by the 6MWT) continued to deteriorate over time, albeit less so in patients who received MitraClip therapy. Further research could help understand the drivers of QoL and functional status in TMVr recipients, and should include populations diverse in socio-economic characteristics, race, ethnicity and gender. Capturing such heterogeneity will allow us to more fully appreciate variations in clinical outcomes to provide tailored prognostic information to patients.

CONCLUSIONS

Transcatheter repair of functional MR can provide significant benefits in terms of HF hospitalizations, survival and QoL, when the appropriate candidates, those with symptomatic moderate to severe MR and reduced LV systolic function while on optimal GDMT, can be identified. If the benefits of this new therapy are to be achieved in routine practice for patients with HF and functional MR, the adoption process should more closely replicate the patient selection, management strategies and operator experience that were part of COAPT rather than MITRA-FR. Given the discrepancies observed between these trials, ongoing innovation in patient management and potential expansion of indications for use, this paper argues that the evidence-base be expanded to optimize dissemination of this complex therapy.
Specifically, information is needed about which patients are receiving TMVr, their pre- and post-procedure management, and outcomes in real-world clinical practice. The TVT registry has been designed to capture baseline characteristics and outcome data on all patients undergoing transcatheter valve interventions. Lacking from the registry and critical to understanding outcomes is greater detail on patient management, such as adequacy of GDMT both before and after delivery of the MitraClip; patient characteristics such as frailty and echocardiographic measurements; and site and institutional descriptors such as experience and composition of the Heart Team. These data elements could be incorporated into the registry or collected by selected sites as a supplement. From the perspective of managing the overall HF population with functional MR, more data are needed regarding the characteristics and outcomes of patients eligible for, but not receiving, TMVr, which would require establishing a companion registry. Inevitably, TMVr indications will expand, as will the devices and therapeutic approaches for this population, necessitating the study of comparative effectiveness, optimally through randomized trials or observational studies. Moreover, given substantial variations in care delivery, conducting implementation research to delineate characteristics of the optimal care model and factors influencing clinical uptake would be beneficial.

Expanding our evidence base to help guide appropriate dissemination of this potentially impactful therapy requires the collaboration and support of numerous stakeholders, including federal research funding agencies, regulators, device industry, insurers and the health systems that provide these services. Whereas industry traditionally has an incentive to invest in trials of new devices or new indications, and federal funding agencies have a greater mandate to study comparative effectiveness and implementation science, the field would benefit from more public-private partnerships. Addressing population health and implementation science issues, including economics of care delivery, will require these partnerships to include insurers and health systems.

Transcatheter repair of the MV can offer important survival and QoL benefits to a sub-set of patients with HF and significant functional MR. However, the experience of the two trials discussed here, indicates that achieving such benefits requires a tightly integrated team-based approach to accurately identify and manage appropriate patients, where the ingredients to ensure success have not been fully delineated. Optimal dissemination will, therefore, require research that provides insight into how to choose the right patients and how best to deliver their care. Moreover, innovation in patient management is required to further reduce the substantial mortality and morbidity that continues to be associated with this disease, which, in turn, will require ongoing investment in clinical research to evaluate the value of these innovations.

Sources of Funding:

The CTSN is supported by a cooperative agreement (U01 HL088942) funded by the National Heart, Lung, and Blood Institute. The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung and Blood Institute, the National Institutes of Health, or the US Department of Health and Human Services.
### Glossary of Abbreviations:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>6MWT</td>
<td>6-minute walk test</td>
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<tr>
<td>AF</td>
<td>atrial fibrillation</td>
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<td>CABG</td>
<td>coronary artery bypass graft</td>
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<td>CEC</td>
<td>central eligibility committee</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<td>COAPT</td>
<td>Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation Trial</td>
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<tr>
<td>CRT</td>
<td>cardiac resynchronization therapy</td>
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<td>CTSN</td>
<td>Cardiothoracic Surgical Trials Network</td>
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<tr>
<td>EROA</td>
<td>effective regurgitant orifice area</td>
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<tr>
<td>GDMT</td>
<td>guideline-directed medical therapy</td>
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<td>HF</td>
<td>heart failure</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>KCCQ</td>
<td>Kansas City Cardiomyopathy Questionnaire</td>
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<tr>
<td>LV</td>
<td>left ventricular</td>
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<tr>
<td>LVEDV</td>
<td>left ventricular end-diastolic volume</td>
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<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<tr>
<td>MITRA-FR</td>
<td>Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation Trial</td>
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<tr>
<td>MR</td>
<td>mitral regurgitation</td>
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<td>MV</td>
<td>mitral valve</td>
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<tr>
<td>NHLBI</td>
<td>National Heart, Lung, and Blood Institute</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>QoL</td>
<td>quality of life</td>
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<tr>
<td>RVol</td>
<td>regurgitant volume</td>
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<tr>
<td>TMVr</td>
<td>transcatheter mitral valve repair</td>
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<tr>
<td>TV</td>
<td>tricuspid valve</td>
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</table>
REFERENCES


Central Message:

Discordant clinical trial outcomes of transcatheter repair of functional MR argue for additional research to identify optimal candidacy and measure long-term effectiveness.
Perspective Statement:

Evidence-based diffusion of transcatheter MV repair requires more complete capture of patient characteristics and outcomes in real-world clinical practice. Indications for use will expand, as will devices and therapeutic approaches, necessitating comparative effectiveness studies. Moreover, given substantial variations in patient selection and care delivery, implementation research is beneficial.
Central Figure:
Death or HF Hospitalization at 12m in COAPT and MITRA-FR (Obadia et al, NEJM 380;20:p1977)
FIGURE 1:
FIGURE 2:
An Expanded Registry Infrastructure for Patients with Symptomatic HF and Functional MR
Table 1.

Echocardiographic criteria for enrollment in the COAPT trial.

<table>
<thead>
<tr>
<th>Tier 1 (N=570; 85.7%)</th>
<th>Tier 2 (N=70; 10.5%)</th>
<th>Tier 3 (N=25; 3.8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EROA ≥0.3 cm² or PV systolic flow reversal</td>
<td>EROA 0.2 cm² to &lt;0.3 cm² with one of the following:</td>
<td>EROA not measured or &lt;0.2 cm², with at least 2 of the following:</td>
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<tr>
<td></td>
<td>- RVol ≥45 ml/beat</td>
<td>- RVol ≥45 ml/beat</td>
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<td>- RF ≥40%</td>
<td>- RF ≥40%</td>
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<td>- VC width ≥0.5 cm</td>
<td>- VC width ≥0.5 cm</td>
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<td></td>
<td>- PISA radius &gt; 0.9 cm</td>
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<td></td>
<td></td>
<td>- Large (≥6.0 cm) holosystolic jet wrapping around LA</td>
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<td></td>
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<td>- Peak E velocity ≥150 cm/s</td>
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</table>

EROA = Effective Regurgitant Orifice Area; LA = Left Atrium; PISA = Proximal Isovelocity Surface Area; PV = Pulmonary Valve; RVol = Regurgitant Volume; RF = Regurgitant Fraction; VC = Vena Contracta
Table 2.
Differences in mitral regurgitation severity, left ventricular function and dimension in the COAPT and MITRA-FR trials.

<table>
<thead>
<tr>
<th>Category</th>
<th>COAPT (N=614)</th>
<th>MITRA-FR (N=304)</th>
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<tbody>
<tr>
<td>EROA, cm²</td>
<td>0.41±0.15</td>
<td>0.31±0.10</td>
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<tr>
<td>&lt;0.30 cm²</td>
<td>80/591 (14%)</td>
<td>157/301 (52%)</td>
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<tr>
<td>0.30–0.40 cm²</td>
<td>270/591 (46%)</td>
<td>95/301 (32%)</td>
</tr>
<tr>
<td>&gt;0.40 cm²</td>
<td>241/591 (41%)</td>
<td>49/301 (16%)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>31±9</td>
<td>33±7</td>
</tr>
<tr>
<td>LVEDV, mL/m²</td>
<td>101±34</td>
<td>135±35</td>
</tr>
</tbody>
</table>

EROA = Effective Regurgitant Orifice Area; LVEDV = Left Ventricular End-Diastolic Volume; LVEF = Left Ventricular Efficiency.