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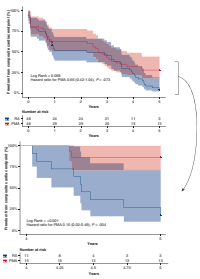

SUBANNULAR REPAIR OR TRANSCATHETER EDGE-TO-EDGE REPAIR FOR SECONDARY MITRAL REGURGITATION? MORE DATA FOR INTERNATIONAL GUIDELINES

To the Editor:

Okuno and colleagues[1] reported 2-year outcomes comparing surgical repair with restrictive mitral annuloplasty (RMA) versus transcatheter edge-to-edge repair (TEER) for secondary mitral regurgitation (SMR). It highlights contradictions in the 2020 American Heart Association/American College of Cardiology (AHA/ACC) guidelines for the indication for TEER in SMR was Class IIb with level of evidence B-R.[2] In that study of 202 patients, the investigators compared propensity-matched surgical versus transcatheter repair for SMR with a report published immediately after the presentation of new AHA/ACC guidelines. After 2 years' follow-up, although the investigators found no significant difference in survival ($P = .909$), they recorded superiority in RMA with coronary revascularization versus TEER for decreasing mitral regurgitation (MR), improving ventricular ejection fraction, and reducing New York Heart Association functional class III or IV.[1]

Left ventricular remodeling predicts poor prognosis in ischemic myocardial disease and is reversible with recovery of viable myocardium.[3,4] Cardiothoracic Surgical Trials Network trial subanalyses included 75% of patients receiving concomitant coronary artery bypass grafting surgery, eliminating the possibility of improvement in regional wall motion for 25% of patients.[4,5] Subannular procedure combined with RMA have been superior to RMA alone in both ischemic and nonischemic cardiomyopathy in other studies.[3,6,7] In a papillary muscle approximation (PMA) randomized trial, 96 patients with severe chronic ischemic mitral regurgitation underwent complete surgical myocardial revascularization associated with either isolated RMA or PMA + RMA over a 5-year follow-up. Left ventricular end-diastolic diameter improved at 5-year follow-up (5.8 ± 4.1 mm and −0.2 ± 2.3 mm, respectively; $P < .001$), maintaining the benefit achieved immediately postoperatively with freedom from major adverse cardiac and cerebrovascular events ($P = .004$)[3] (Figure 1). TEER use in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) study did not reveal an improvement of left ventricular remodeling (left ventricular end-diastolic volume/mL, 194.4 ± 69.2 mL vs 192.2 ± 76.5 mL),[8,9] although patients who underwent TEER had sustained 3-year improvements in MR severity, quality-of-life measures, and functional capacity compared with those who received guideline-directed medical therapy (GDMT) at 3 years' follow-up.[10] The benefit of TEER over GDMT was confirmed among 58 patients primarily managed with alone who crossed-over receiving TEER. For the subsequent composite rate of mortality or hospitalization for cardiac failure, hospitalization for cardiac failure was reduced compared with GDMT alone ($P = .006$).[10]

Okuno and colleagues[1] revealed that restrictive mitral annuloplasty was superior to TEER at 2 years as a secondary end point. Evidence from randomized controlled trials (RCTs) proved that RMA had higher MR recurrence rates at 2 and 5 years' follow-up (58.8% and 55.9%, respectively).[3,5] Suitability for RMA should include smaller preoperative left ventricular end systolic diameter and reduced apical tethering of the leaflets. Seventy-four patients from the Cardiothoracic Surgical Trials Network trial with severe ischemic mitral regurgitation with no persistent or recurrent MR after RMA recorded significantly smaller left ventricles at 2 years' follow-up compared with patients with recurrent MR post-RMA alone (43 ± 26 mL/m^2 vs 63 ± 27 mL/m^2). Left ventricular end systolic volume was significantly lower compared with patients managed with mitral valve replacement (61 ± 39 mL/m^2).[5]

In the PMA trial, double-level repair achieved geometric restitution by normalization of 3 measures: anteroposterior annular dilation, tenting area, and interpapillary muscle distance. The goal is to address both the valvular and ventricular features of secondary MR (Carpentier class IIIb).[3,4,6,7] The fundamental role of papillary muscles is also focused on by Kainuma and colleagues.[11] Kainuma and colleagues[11] recorded that the use of restrictive mitral annuloplasty alone only partially alleviated the tethering of leaflet, which instead significantly favored a reduction in tethering and interpapillary muscles distance. The latter was the main determinant of MR recurrence. These beneficial effects could be mainly attributed to post-RMA reverse left ventricular remodeling leading to a reduction in interpapillary muscle distance (31 ± 6 mm to 25 ± 5 mm),

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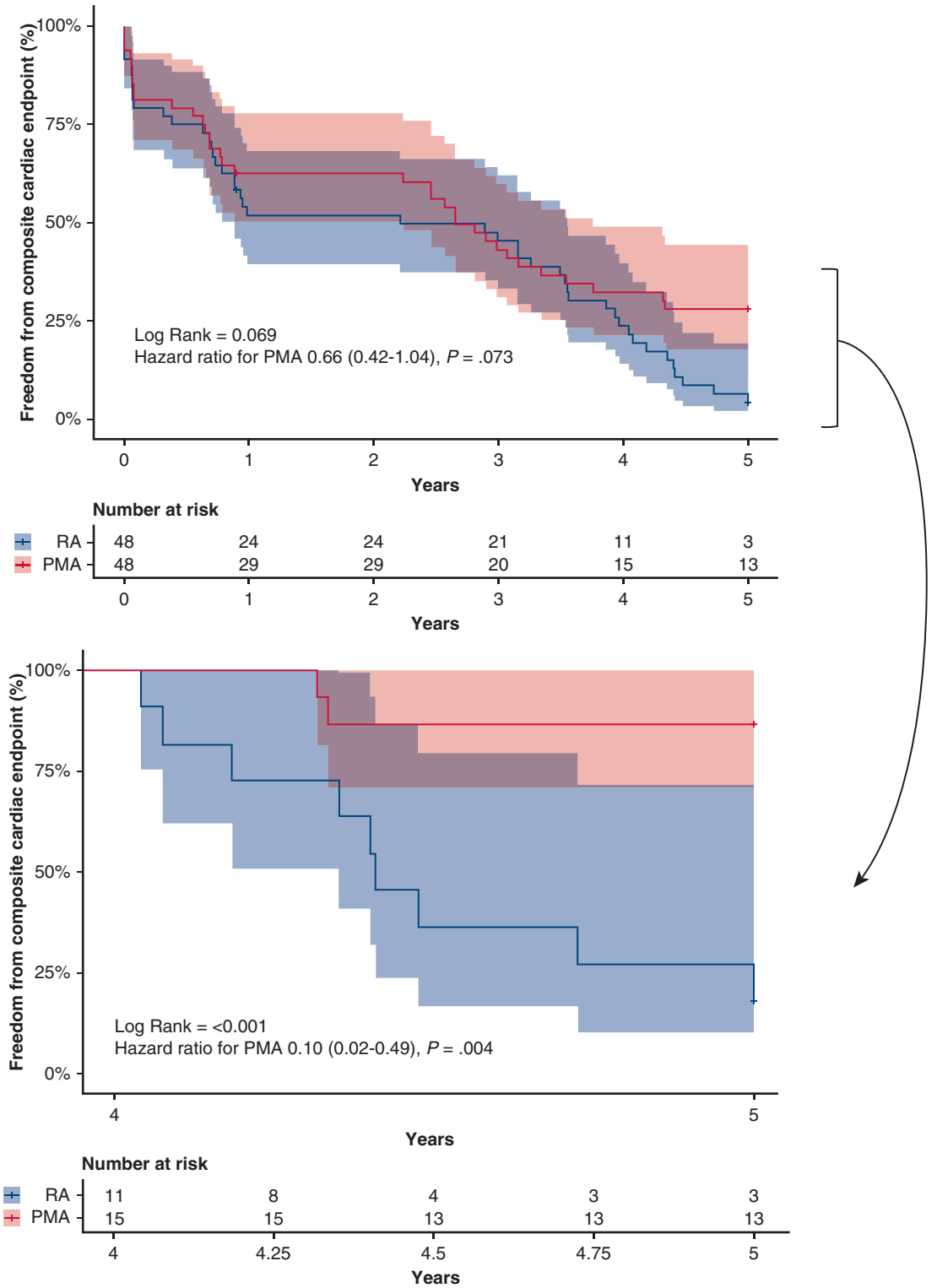

FIGURE 1. Composite cardiac end point. The composite end point of the rate of major adverse cardiac or cerebrovascular events (MACCEs) included cardiac death, stroke, subsequent mitral valve surgery, rehospitalization, and an increase in New York Heart Association functional class of 1 or more. Vertical marks indicate that a patient's data were censored at that point. At 5 years, there were no significant between = group differences with respect to the composite end point of MACCE, with 45 events in the restrictive annuloplasty (*RA*) group and 34 events in the papillary muscle approximation (*PMA*) group (*left*). However, the incidence of MACCE was significantly reduced in the PMA group during the last year of follow-up (*right*).

TABLE 1. Randomized clinical trial (RCT) reporting secondary mitral regurgitation (SMR)

First author or Study acronym	Type of study	No. of patients	Treatment	Mean follow-up (y)	Criteria for SMR	Findings
Harmel, 2019[7]	Prospective	101	RMA (50) RMA + PMR (51)	1	• Ischemic cardiomyopathy 100% • Average LVEDD >60 mm; LVEF <40% • EROA >0.2 cm^2	Better improvement of left ventricular remodeling in PMR group MR > 2+ more common among patients with RMA Better survival in RMA + PMR
Stone, 2018[9] COAPT	RCT	614	TEER (302) GDMT (312)	2	• Ischemic cardiomyopathy 62.5% • Average LVEDV 192 mL; LVEF 31% ± 9% (18% LVEF >40%) • MR grade 3 or 4 • EROA mean value 0.41 cm^2; 14% EROA <0.3 cm^2; 41% ≥ 0.4 cm^2	Lower rate of unplanned hospitalization in TEER with disproportionate SMR. Slight improvement of LVEDV/mL/min (from 194.4 ± 37.4-192.2 ± 76.5)
Iung, 2019[12] MITRA Fr	RCT	306	TEER (152) GDMT (154)	1	• Ischemic cardiomyopathy 62.5% • Average LVEDV 252 mL 33% ± 7% (all LVEF ≤40%) • EROA mean value 0.31 cm^2 • 50% EROA <0.3 cm^2; 16% ≥ 0.4 cm^2	No difference in unplanned hospitalization rate and death between TEER vs GDMT. Slight improvement of LVEDV/mL/min (from 136.2 ± 37.4-134.2 ± 37)
Nappi, 2016[8] PMA trial	RCT	96	RMA (48) RMA plus PMA (48)	5	• Ischemic cardiomyopathy 100% • Coronary artery disease with or without the need for coronary revascularization • Average value LVEDD 62 mm LVEF 42% • MR grade 3 or 4 • EROA> 0.2 cm^2 or regurgitant volume >30 mL* • EROA mean value 0.34 cm^2	Lower rate of unplanned hospitalization in PMA group. Better improvement of LVEDD in PMA (62.7 ± 3.4-56.5 ± 5.7) vs RMA (61.4 ± 3.7-60.6 ± 4.6). Lower incidence of recurrent MR in the PMA group (27% vs 55.9%)
Goldstein, 2016[5] CTSN	RCT	251	MVR (125) RMA (126)	2	• Ischemic cardiomyopathy 100% • Average value LVESV 63.4 mL; LVEF 40% • MR grade 4 • EROA ≥0.4 cm^2 with tethering • Eligible for surgical repair and replacement of mitral valve • Coronary artery disease with or without the need for coronary revascularization	Better improvement of LVESVI in MVR (52.6 ± 27.7 mL vs 60.6 ± 39.0 mL). Better improvement of LVESVI in RMA with smaller LV (43 ± 26 mL/m^2 vs 63 ± 27 mL/m^2). Higher incidence of recurrent MR in the RMA (58.8% vs 3.8%)

RMA, Restrictive mitral annuloplasty; *PMR*, papillary muscle relocation; *LVEDD*, left ventricular end-diastolic diameter *LVEF*, left ventricular ejection fraction; *EROA*, effective regurgitant orifice area; *MR*, mitral regurgitation; *COAPT*, Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; *TEER*, transcatheter edge-to-edge repair; *GDMT*, guide-direct medical therapy; *LVEDV*, left end-diastolic volume; *MITRA Fr*, Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation; *PMA trial*, papillary muscle approximation trial; *CTSN*, Cardiothoracic Surgical Trials Network; *MVR*, mitral valve replacement; *LVESI*, left end-systolic volume index. *European Society of Cardiology guidelines.

potentially offsetting the negative effect of increasing posterior leaflet angle.[11]

PMA is more suitable than TEER in patients with SMR due to nonischemic cardiomyopathy (Carpentier class I) where annular dilation, lateral displacement of anterior and posterior papillary muscle, symmetrical tethering with apical tenting of anterior leaflet, and central jet were prevalent. Patients with severe left ventricular dilation and moderate-to-severe MR had poorer outcomes both in the small group of patients in the COAPT[8] and in Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation[12] trials. These patients had similar features of proportionate MR and did not respond favorably to TEER (Table 1).[13]

All 5 AHA/ACC recommendations were classified as level of evidence B-R or B-NR, indicating moderate quality of studies. The available literature lacks RCTs designed with a large number of enrolled patients that include candidates receiving TEER, mitral valve replacement, or mitral valve repair with or without a subvalvular procedure. ACC/AHA guidelines reference 2 TEER-based RCTs with 3-year outcomes that are reported only for the COAPT trial,[9] and the analysis of the new pathophysiological framework of the pathomechanism for SMR.[10] None of these recommendations are based on reports with 5 years' follow-up.[2] For double-level repair, there currently is no solid evidence supported by more than 1 RCT, or meta-analysis of moderate-quality RCTs, that allows recommending this procedure.

Although the results of the Multicenter Randomized, Controlled Study to Assess Mitral Valve Reconstruction for Advanced Insufficiency of Functional or Ischemic Origin[14] randomized study are awaited, other RCTs have demonstrated the efficacy of using novel devices. None of these are directed toward manipulating the papillary muscles by either an approximation or a relocation procedure.

In the Edwards Pascal Transcatheter Mitral Valve Repair System Study RCT (N = 124), the Pascal system (Edwards Lifesciences) was implanted in patients enrolled for treatment of functional, degenerative, and mixed etiology. The Pascal transcatheter valve repair system and the MitraClip system (Abbott, Abbott Park, Ill) were compared in patients with both functional and degenerative MR. Evidence from the Edwards Pascal Transcatheter Mitral Valve Repair System Study recorded a high rate of survival, with a significant rate of reduction in heart failure-related hospitalization with reverse positive left ventricular remodeling at 1 and 2 years' follow-up.[15-18]

Additional multicenter RCTs designed with a minimum of 5-year follow-up enrolling patients to undergo either TEER or double-level repair should be encouraged.

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