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Progression of Tricuspid Regurgitation After Surgery for Ischemic Mitral Regurgitation

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ABSTRACT

BACKGROUND Whether to repair nonsevere tricuspid regurgitation (TR) during surgery for ischemic mitral valve regurgitation (IMR) remains uncertain.

OBJECTIVES The goal of this study was to investigate the incidence, predictors, and clinical significance of TR progression and presence of ≥moderate TR after IMR surgery.

METHODS Patients (n = 492) with untreated nonsevere TR within 2 prospectively randomized IMR trials were included. Key outcomes were TR progression (either progression by ≥2 grades, surgery for TR, or severe TR at 2 years) and presence of ≥moderate TR at 2 years.

RESULTS Patients' mean age was 66 ± 10 years (67% male), and TR distribution was 60% ≤trace, 31% mild, and 9% moderate. Among 2-year survivors, TR progression occurred in 20 (6%) of 325 patients. Baseline tricuspid annular diameter (TAD) was not predictive of TR progression. At 2 years, 37 (11%) of 323 patients had ≥moderate TR. Baseline TR grade, indexed TAD, and surgical ablation for atrial fibrillation were independent predictors of ≥moderate TR. However, TAD alone had poor discrimination (area under the curve, ≤0.65). Presence of ≥moderate TR at 2 years was higher in patients with MR recurrence (20% vs. 9%; p = 0.02) and a permanent pacemaker/defibrillator (19% vs. 9%; p = 0.01). Clinical event rates (composite of ≥1 New York Heart Association functional class increase, heart failure hospitalization, mitral valve surgery, and stroke) were higher in patients with TR progression (55% vs. 23%; p = 0.003) and ≥moderate TR at 2 years (38% vs. 22%; p = 0.04).

CONCLUSIONS After IMR surgery, progression of unrepaired nonsevere TR is uncommon. Baseline TAD is not predictive of TR progression and is poorly discriminative of ≥moderate TR at 2 years. TR progression and presence of ≥moderate TR are associated with clinical events. (Comparing the Effectiveness of a Mitral Valve Repair Procedure in Combination With Coronary Artery Bypass Grafting [CABG] Versus CABG Alone in People With Moderate Ischemic Mitral Regurgitation, NCT00806988; Comparing the Effectiveness of Repairing Versus Replacing the Heart's Mitral Valve in People With Severe Chronic Ischemic Mitral Regurgitation, NCT00807040) (J Am Coll Cardiol 2021;77:713–24)

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

ICD = implantable cardioverter-defibrillator

IMR = ischemic mitral valve regurgitation

MACE = major adverse clinical events

MR = mitral regurgitation

MV = mitral valve

ROC = receiver-operating characteristic

RV = right ventricular

TR = tricuspid regurgitation

Progression of tricuspid regurgitation (TR) after mitral valve (MV) surgery is associated with significant morbidity, yet the optimal indications for treating TR at time of MV surgery remain unclear (1–4). Current guidelines recommend concomitant tricuspid valve repair in cases of moderate or more pre-operative TR, or in cases of pre-operative tricuspid annular dilation (>40 mm or 21 mm/m^2) in patients with only mild TR (Class IIa) (5,6). A prospectively randomized trial investigating this strategy in patients with primary mitral regurgitation (MR) is ongoing (NCT02675244). However, in patients with ischemic mitral valve regurgitation (IMR), data on TR progression after MV surgery are limited (7–9). The reported incidence of significant (≥moderate) TR after IMR surgery in a retrospective series is as high as 50% at 1 to 3 years (7). Prospective confirmation of this high incidence is lacking. Given the important pathophysiological differences, results from the ongoing trial in primary MR cannot be extrapolated to surgery for ischemic MR. Moreover, the value of the pre-operative tricuspid annular dimension to predict TR progression in an ischemic heart disease population is unclear.

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In 2 prospective National Heart, Lung, and Blood Institute-supported Cardiothoracic Surgical Trials Network (CTSN) trials investigating surgery for moderate or severe IMR, a selective approach toward concomitant tricuspid valve repair was adopted and left to the discretion of the surgeon (10,11). Tricuspid valve surgery was performed in <8% of the patients undergoing surgery for IMR, and 92% of patients had no concomitant intervention at the level of the tricuspid valve. Within these trials, serial echocardiography, including dedicated tricuspid valve and right ventricular (RV) assessment, was performed at baseline, 6 months, 1 year, and 2 years and analyzed by an independent central core laboratory.

The purpose of the current analysis was to assess the rate of TR progression from pre-operative baseline and the presence of ≥moderate TR at 2 years after IMR surgery in patients with untreated nonsevere secondary TR within the CTSN IMR trials. Clinical, echocardiographic, and procedural predictors of TR progression and ≥moderate TR were evaluated, as well as the clinical impact of TR progression and ≥moderate TR after IMR surgery.

METHODS

PATIENT POPULATION. The patient population originates from 2 randomized surgical trials in patients with IMR conducted by the CTSN, as previously described (10–13). Briefly, a total of 301 patients with moderate IMR were randomized to receive coronary artery bypass grafting (CABG) alone versus CABG + MV repair, and 251 patients with severe IMR were randomized to undergo MV repair ± CABG versus MV replacement ± CABG. The trials were conducted in 26 and 22 centers, respectively, with a coordinating center, an independent clinical events committee adjudicating mortality and adverse events, and a data and safety monitoring board that oversaw trial progress. Participating centers' Institutional Review Boards approved the protocol, and all patients signed a written informed consent. Complete inclusion and exclusion criteria have been previously reported.

In the current analysis, all patients who had moderate or less TR without concomitant tricuspid intervention at the time of IMR surgery within both trials were included for analysis. **Figure 1** shows the study population.

ECHOCARDIOGRAPHY. All echocardiographic examinations were reviewed and analyzed by an independent central core laboratory. Measures of left ventricular function and MR were assessed according to international recommendations (14–16). TR was graded as none/trace, mild, moderate, or severe by using an integrative approach (15,16). Parameters used to grade TR included: 1) the vena contracta width; 2) the radius of proximal flow conversion; and 3) qualitative assessment of the color flow TR jet, the density and shape of the continuous wave TR signal, and, when available, the hepatic vein flow signal.

The tricuspid annular diameter was measured in late diastole in a standard apical 4-chamber view, as recommended (17). Tricuspid annular dilation was defined as an annular dimension ≥40 mm or 21 mm/m^2. In addition, measures of RV size and function were obtained in a focused RV view (18).

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

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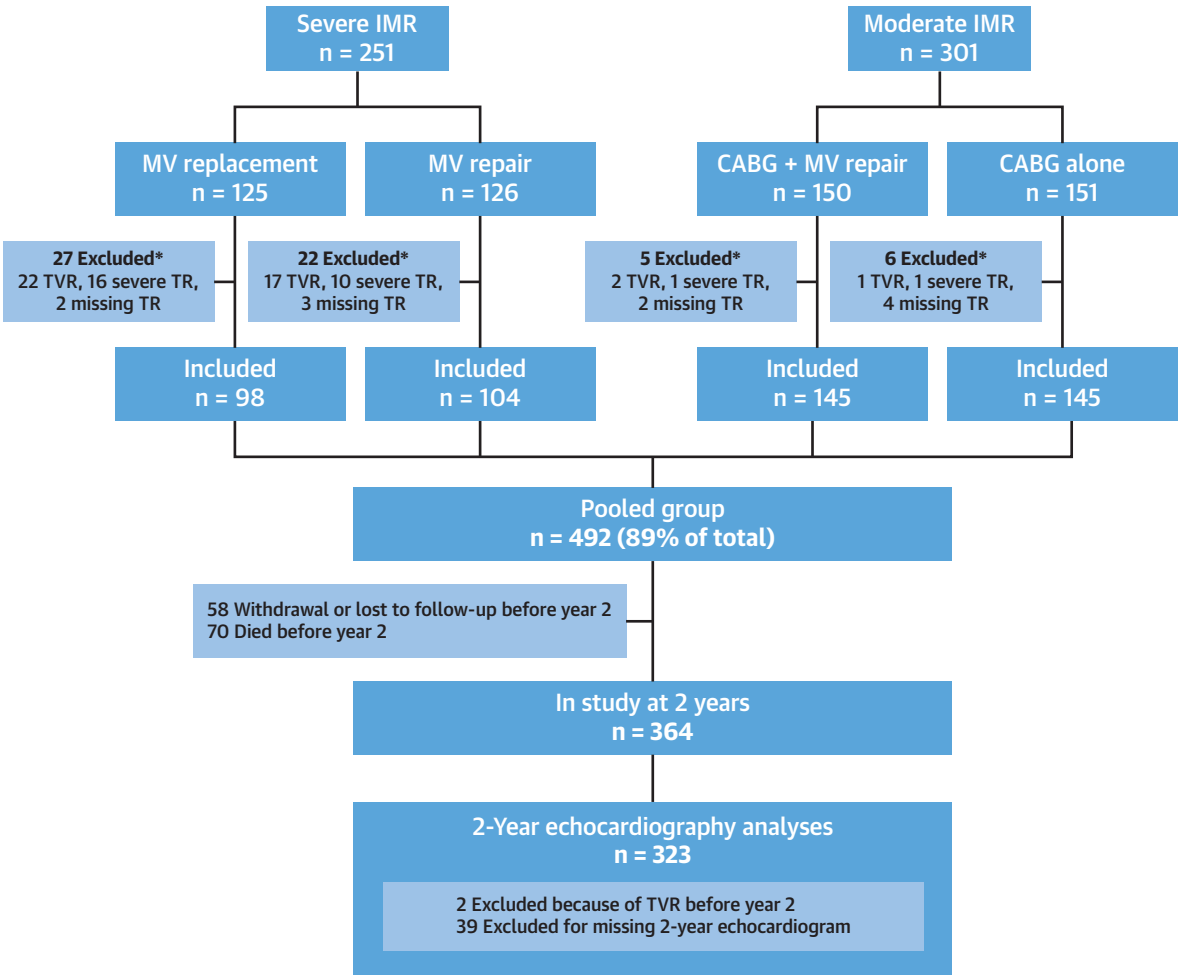
FIGURE 1 Study Flowchart



*Subcategories not mutually exclusive. CABG = coronary artery bypass graft; IMR = ischemic mitral regurgitation; MV = mitral valve; TR = tricuspid regurgitation; TVR = tricuspid valve repair.

DEFINITION OF TR PROGRESSION. Progression of TR was defined as the composite of the following: 1) presence of severe TR at 2 years' post-randomization; 2) re-operation for TR within 2 years' post-randomization; or 3) TR progression from baseline by 2 grades at 2 years' post-randomization, similar to the endpoint definition in the ongoing randomized trial in primary MV surgery (NCT02675244). In addition, presence of ≥moderate TR at 2 years was evaluated, irrespective of the TR grade at baseline.

Patients who died before the 2-year visit (n = 70) or were missing the 2-year echocardiogram endpoints (n = 97) were excluded from outcome analyses (**Figure 1**). Details on TR status at baseline and at last follow-up in the patients who died are provided in Supplemental Tables 1 and 2.

CLINICAL OUTCOME. Major adverse clinical events (MACE) were defined as the composite of: 1) increase of ≥1 New York Heart Association functional class; 2) hospitalization for heart failure; 3) redo MV surgery; and 4) stroke (10,11). The association between either TR progression or ≥moderate TR at 2 years' post-randomization with the incidence of MACE (or any of its components) within 2 years' post-randomization was assessed.

STATISTICAL ANALYSIS. Continuous data are expressed as mean ± SD and were compared by using Student's *t*-tests, Wilcoxon tests, or analysis of variance as appropriate. Categorical data are expressed as percentages and were compared by using chi-square or Fisher exact tests as appropriate. Univariable and multivariable logistic regression analyses were

TABLE 1 Baseline Characteristics of the Patient Cohort

	Total Cohort (N = 492)	Severe IMR Group (n = 202)	Moderate IMR Group (n = 290)	p Value
Age, yrs	66.3 ± 10.4	68.4 ± 9.8	64.8 ± 10.5	0.0001
Male	328 (66.7)	127 (62.9)	201 (69.3)	0.14
BSA, m^2	1.9 ± 0.3	1.9 ± 0.2	2.0 ± 0.3	0.03
Medical and surgical history				
Diabetes	205 (41.8)	71 (35.3)	134 (46.2)	0.02
Hypertension	405 (82.3)	162 (80.2)	243 (83.8)	0.30
Renal insufficiency	103 (21.0)	54 (26.7)	49 (17.0)	0.009
Myocardial infarction	343 (69.7)	150 (74.3)	193 (66.6)	0.07
Heart failure	293 (59.6)	141 (69.8)	152 (52.4)	0.0001
Atrial fibrillation	108 (22.0)	58 (28.7)	50 (17.4)	0.003
Permanent pacemaker or ICD	60 (12.2)	36 (17.8)	24 (8.3)	0.002
Echocardiography data				
LV ejection fraction, %	40.4 ± 11.3	40.8 ± 11.6	40.2 ± 11.2	0.53
LVESVI, ml/m^2	60.3 ± 26.0	64.2 ± 26.3	57.6 ± 25.5	0.006
MR effective regurgitant orifice area, cm^2	0.29 ± 0.14	0.39 ± 0.15	0.23 ± 0.09	<0.0001
Tricuspid regurgitation				<0.0001
None/trace	297 (60.4)	97 (48.0)	200 (69.0)	
Mild	153 (31.1)	79 (39.1)	74 (25.5)	
Moderate	42 (8.5)	26 (12.9)	16 (5.5)	
Tricuspid annular diameter, mm	38.3 ± 5.2	38.2 ± 5.5	38.3 ± 5.1	0.88
Tricuspid annular index, mm/m^2 BSA	20.3 ± 3	20.5 ± 3	20.1 ± 2.9	0.09
TAPSE, mm	16.8 ± 3.8	16.4 ± 3.7	17 ± 3.9	0.11
RV fractional area change, %	42.4 ± 8.5	42.2 ± 7.8	42.6 ± 9	0.63
Tricuspid regurgitation peak velocity, cm/s	293.1 ± 54.5	305 ± 49	283.7 ± 56.8	0.0002
Operative data				
Cardiopulmonary bypass time, min	136.5 ± 54.6	139.8 ± 47.3	134.3 ± 59.2	0.25
Aortic cross-clamp time, min	98.2 ± 40.8	101.2 ± 39.6	96.1 ± 41.6	0.17
MV repair	246 (50.0)	97 (48.0)	149 (51.4)	0.46
MV replacement	106 (21.5)	105 (52.0)	1 (0.3)	<0.0001
CABG	448 (91.1)	158 (78.2)	290 (100.0)	<0.0001
Surgical AF ablation	42 (8.5)	22 (10.9)	20 (6.9)	0.12

Values are mean ± SD or n (%).

AF = atrial fibrillation; BSA = body surface area; CABG = coronary artery bypass grafting; ICD = implantable cardioverter-defibrillator; IMR = ischemic mitral valve regurgitation; LV = left ventricular; LVESVI = left ventricular end-systolic volume index; MR = mitral regurgitation; MV = mitral valve; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.

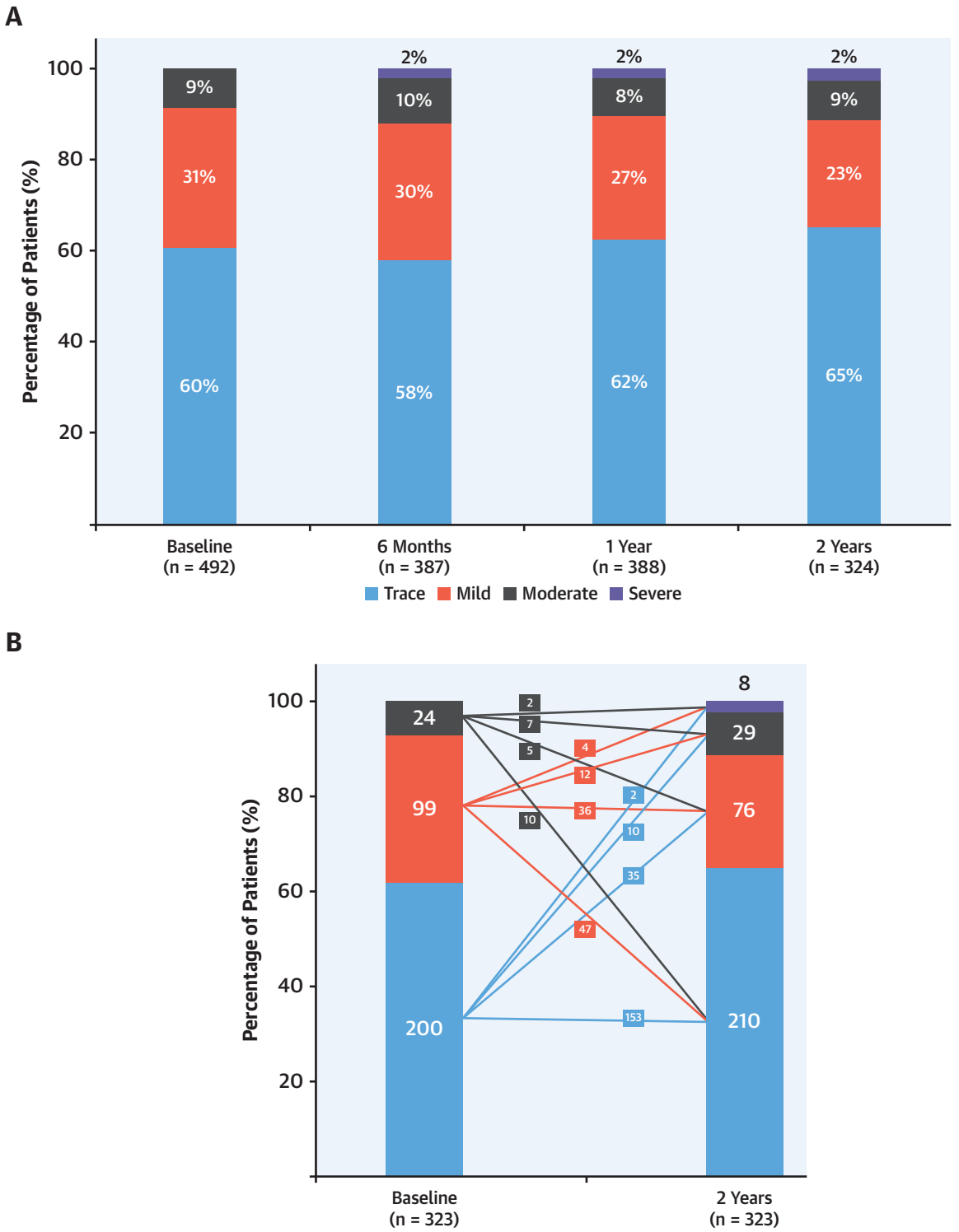
performed to determine whether any pre-specified clinically relevant baseline measures, including age, sex, history of atrial fibrillation, history of permanent pacemaker or implantable cardioverter-defibrillator (ICD), MR effective regurgitant orifice area, severity of TR, tricuspid annular dimension, tricuspid annular plane systolic excursion, RV fractional area change, tricuspid regurgitation peak velocity, type of MV intervention, and concomitant surgical ablation for atrial fibrillation, were associated with ≥moderate TR at 2 years' post-randomization. Variables with a p value <0.15 in univariable analyses were considered for inclusion in a multivariable logistic regression model. The final model was selected by using backwards selection. Results are reported as odds ratios with 95% confidence intervals. Receiver-operating characteristic (ROC) curve analysis was used to evaluate the discrimination of a baseline annular dimension for predicting TR progression and ≥moderate TR at 2 years. All analyses were conducted by using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

PATIENT CHARACTERISTICS. A total of 492 patients were included in the study; 202 patients were enrolled in the severe IMR trial and 290 were enrolled in the moderate IMR trial. Table 1 summarizes the baseline characteristics of the study population. TR at baseline was none or trace in 60.4%, mild in 31.1%, and moderate in 8.5%, with a higher proportion of moderate TR in the severe IMR group (26 of 202 [12.9%] vs. 16 of 290 [5.5%]).

Of the patients who were excluded from this analysis (Figure 1), a total of 50 patients had baseline

FIGURE 2 TR at Baseline and at Different Stages of Follow-Up



(A) Tricuspid regurgitation (TR) grade in the study cohort at baseline and 6 months, 1 year, and 2 years after the index surgery. **(B)** TR grade at baseline and at 2 years after the index surgery for the patients with 2-year follow-up available (n = 323, excluding 1 patient with 2-year echocardiogram follow-up who underwent interim tricuspid valve surgery). Changes in TR from baseline to 2 years (absolute numbers of patients) are presented.

TABLE 2 Baseline and Operative Characteristics in Patients With Versus Without ≥Moderate TR at 2-Year Follow-Up

	All (N = 323)	≥Moderate TR at 2 Years (n = 37)	<Moderate TR at 2 Years (n = 286)	p Value
Age, yrs	65.6 ± 10.1	68.5 ± 10.7	65.3 ± 10.0	0.07
Male	220 (68.1)	20 (54.1)	200 (69.9)	0.05
BSA, m^2	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.3	0.27
Medical and surgical history				
AF	66 (20.6)	17 (45.9)	49 (17.3)	<0.0001
Permanent pacemaker or ICD (at baseline)	31 (9.6)	6 (16.2)	25 (8.7)	0.15
Severe IMR trial	129 (39.9)	19 (51.4)	110 (38.5)	0.13
Echocardiography data				
LVESVI, ml/m^2	60.2 ± 24.6	53.0 ± 22.1	61.1 ± 24.8	0.06
MR effective regurgitant orifice area, cm^2	0.29 ± 0.15	0.30 ± 0.12	0.29 ± 0.15	0.81
TR				<0.0001
None/trace	200 (61.9)	12 (32.4)	188 (65.7)	
Mild	99 (30.7)	16 (43.2)	83 (29.0)	
Moderate	24 (7.4)	9 (24.3)	15 (5.2)	
Tricuspid annular diameter, mm	38 ± 5.2	39.6 ± 5.1	37.8 ± 5.1	0.04
Tricuspid annular index, mm/m^2 BSA	20.1 ± 2.9	21.6 ± 2.8	19.9 ± 2.9	0.0008
TAPSE, mm	16.8 ± 4	16.7 ± 3.8	16.9 ± 4	0.85
RV fractional area change, %	42.5 ± 8.4	43.1 ± 6.9	42.4 ± 8.5	0.67
TR peak velocity, cm/s	290 ± 51.4	301.8 ± 51.6	288 ± 51.2	0.15
Operative data				
Cardiopulmonary bypass time, min	136.5 ± 53	136.3 ± 46.7	136.5 ± 53.8	0.98
Aortic cross-clamp time, min	99.7 ± 37.9	101.5 ± 39.6	99.5 ± 37.8	0.76
MV repair	170 (52.6)	21 (56.8)	149 (52.1)	0.59
MV replacement	66 (20.4)	7 (18.9)	59 (20.6)	0.81
CABG	300 (92.9)	34 (91.9)	266 (93.0)	0.74
Surgical AF ablation	23 (7.1)	7 (18.9)	16 (5.6)	0.01

Values are mean ± SD or n (%).
TR = tricuspid regurgitation; other abbreviations as in Table 1.

severe TR and/or received concomitant tricuspid valve surgery at the discretion of the surgeon during the index IMR surgery. These patients were 68.1 ± 8.8 years old, 46% were female, and the baseline tricuspid annular dimension was 43.2 ± 6.4 mm (indexed value of 23.1 ± 3.9 mm/m^2). TR severity at baseline was severe in 20 (48%), moderate in 11 (26%), mild in 8 (19%), trace in 2 (5%), and unreported in 1 (2%) of the patients who received concomitant tricuspid valve surgery.

TR PROGRESSION AFTER IMR SURGERY. Postoperative TR at each study visit is shown in Figure 2A. At 2 years after surgery, there was evidence of TR progression in 6.2% of the evaluated patients (20 of 325). Of these, 8 patients had severe TR (baseline TR grade was none/trace in 2 patients, mild in 4 patients, and moderate in 2 patients, respectively), 2 patients had received tricuspid valve surgery during follow-up (baseline TR grade none/trace in 1 patient and mild in 1 patient), and 10 patients had progressed from none/trace to moderate TR.

Moderate or severe TR at 2 years was observed in 11.5% (37 of 323) of patients, of whom 8 had severe TR, and 29 had moderate TR. Figure 2B shows the difference between the baseline TR grade and the TR grade at 2 years in patients with available 2-year follow-up data. The 2 patients who underwent tricuspid valve surgery during follow-up were excluded from this analysis at 2 years. Of the 42 patients with moderate TR at baseline, 15 patients (36%) died during the 2-year follow-up, and 3 patients were missing the 2-year echocardiogram. Among the 24 patients with moderate TR at baseline and who had 2-year follow-up data, 5 had mild TR, and 10 only

TABLE 3 Independent Baseline Predictors of ≥Moderate TR at 2 Years

	OR (95% CI)	p Value
Baseline TR		0.002
Mild vs. none/trace	2.51 (1.11–5.66)	
Moderate vs. none/trace	6.66 (2.31–19.23)	
Tricuspid annular index, mm/m^2 BSA	1.17 (1.03–1.34)	0.02
Surgical AF ablation	3.44 (1.20–9.84)	0.02

CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 and 2.

TABLE 4 TR Progression and ≥Moderate TR at 2 Years by Recurrent MR and Presence of Pacemaker/ICD Lead at the 1-Year and 2-Year Follow-Up

	≥Moderate MR at 1 Year			≥Moderate MR at 2 Years*		
	Yes	No	p Value	Yes	No	p Value
TR progression	8/60 (13.3)	11/251 (4.4)	0.02	6/65 (9.2)*	12/258 (4.7)	0.22
≥Moderate TR	12/58 (20.7)	22/251 (8.8)	0.009	13/65 (20)	24/258 (9.3)	0.02
	Pacemaker or ICD by 1 Year			**Pacemaker or ICD by 2 Years**		
	Yes	No	p Value	Yes	No	p Value
TR progression	6/79 (7.6)	14/246 (5.7)	0.59	7/87 (8.0)	13/238 (5.5)	0.39
≥Moderate TR	15/78 (19.2)	22/245 (9.0)	0.01	16/85 (18.8)	21/238 (8.8)	0.01

Values are n/N observed (%). *2 patients who had MV surgery in between year 1 and 2 are excluded from the denominator.
Abbreviations as in Tables 1 and 2.

had none/trace TR at the 2-year follow-up visit. Post-operative TR in the subgroup of patients with full echocardiography follow-up at each study time point is presented in Supplemental Figure 1.

BASELINE PREDICTORS OF POST-OPERATIVE TR. In patients with versus those without TR progression, there were no significant differences in baseline TR grade, tricuspid annular dimension, or procedural characteristics; however, the number of patients with TR progression was low. In patients with versus those without ≥moderate TR at 2 years, the most relevant baseline and procedural characteristics are summarized in **Table 2**. In univariable analysis, the baseline TR grade, tricuspid annular dimension, atrial fibrillation, surgical ablation of atrial fibrillation, and male sex were different between these 2 patient groups. In multivariable analysis, baseline TR grade, concomitant surgical ablation of atrial fibrillation, and indexed tricuspid annular dimension were independently predictive of ≥moderate post-operative TR (**Table 3**).

MR RECURRENCE AND PACEMAKER/ICD LEADS. Among survivors at 2 years with known TR progression status, post-operative recurrence of ≥moderate MR was observed in 60 (19.3%) of 311 patients at 1 year and in 65 (20.1%) of 323 at 2 years. The rate of TR progression and ≥moderate TR at 2 years was 13.3% (8 of 60) and 20.7% (12 of 58), respectively, in patients who had MR recurrence at 1 year. This was lower in those patients without MR recurrence, in whom TR progression and ≥moderate TR at 2 years was observed in only 4.4% (11 of 251) and 8.8% (22 of 251) (**Table 4**).

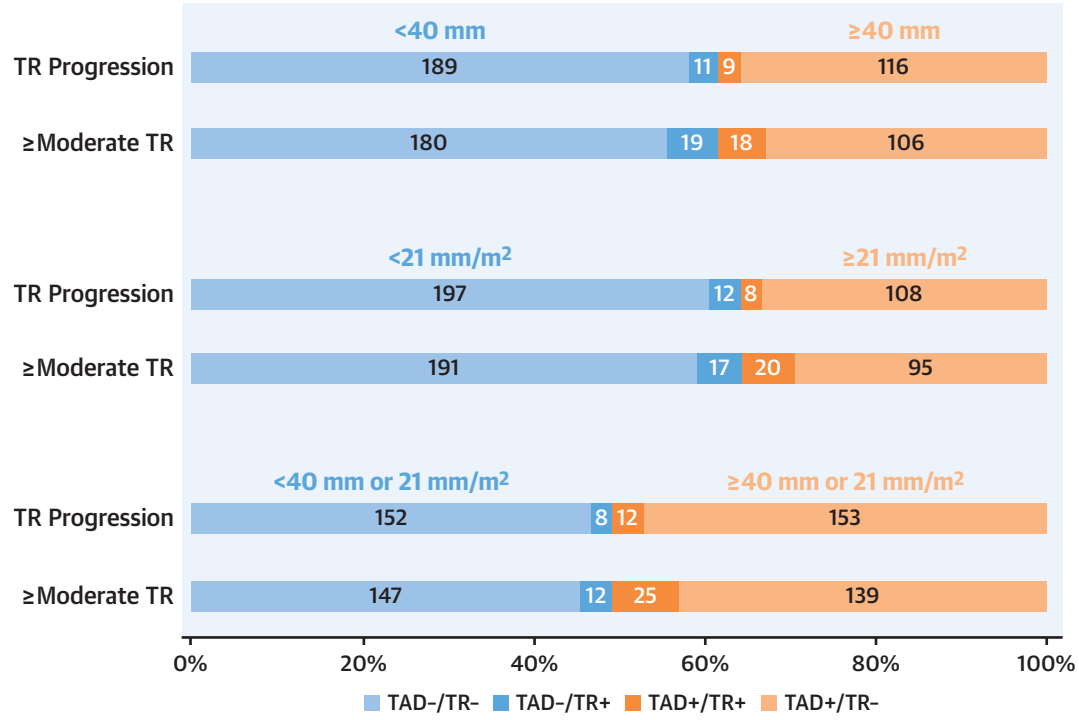
Across all 492 patients included in this study, during the 2-year follow-up period, a total of 69 patients underwent a permanent pacemaker or ICD implantation, in addition to the 60 patients with a history of a pacemaker or ICD lead at baseline. The proportion of patients with ≥moderate TR at 2 years was higher in patients with a permanent pacemaker or ICD lead by 2 years' post-randomization (**Table 4**).

TRICUSPID ANNULAR DILATION. At baseline, the tricuspid annulus in the study population measured 38.3 ± 5.2 mm (or 20.3 ± 3 mm/m^2 indexed for body surface area). A higher TR grade at baseline was associated with a larger annular size (37.6 ± 5.0 mm in none/trace TR, 39.0 ± 5.6 mm for mild TR, and 40 ± 5.2 mm in moderate TR patients, respectively; p = 0.003) (Supplemental Figure 2).

Tricuspid annular dilation according to the guideline definition (≥40 mm or 21 mm/m^2) was present in 269 (54.8%) of 491 patients. According to baseline TR grade, 145 of 296 patients with none/trace TR (49.0%), 91 of 153 patients with mild TR (59.5%), and 33 of 42 patients with moderate TR (78.6%) had annular dilation. The value of tricuspid annular dilation at baseline for predicting either TR progression or ≥moderate TR at 2 years is visually displayed in **Figure 3** (additional details are provided in Supplemental Table 3). ROC curve analysis to assess the value of nonindexed and indexed annular dimensions for TR progression at 2 years (area under the curve, 0.58 and 0.56, respectively), or for prediction of presence of ≥moderate TR at 2 years (area under the curve, 0.60 and 0.65), yielded no annular dimension cutoffs with sensitivity and specificity >60%.

IMPACT OF TRIAL AND RANDOMIZATION ARM ON THE TR PROGRESSION. In the severe IMR trial, TR progression was observed in 6 of 129 patients surviving at 2 years (4.7%), and ≥moderate TR was present in 19 (14.7%) of 129. In the moderate IMR trial, TR progression occurred in 14 of 196 patients surviving at 2 years (7.1 %), and ≥moderate TR was present in 18 (9.3%) of 194 patients. Differences between the trials were not significant (p = 0.36 for TR progression;

FIGURE 3 Discriminative Value of Baseline Tricuspid Annular Dilation for TR Progression and ≥Moderate TR After Surgery



Tricuspid regurgitation (TR) at 2 years according to tricuspid annular dilation (TAD) at baseline, applying the nonindexed, indexed, and combined dilation cutoff, respectively. Patients without annular dilation based on the cutoff are displayed in **blue**, and patients with annular dilation are displayed in **orange**. The number of patients who had either TR progression (n = 20) or ≥moderate TR (n = 37) are highlighted in **dark colors**, whereas the patients without TR progression or <moderate TR are displayed in **light colors**.

p = 0.13 for difference in ≥moderate TR). Moreover, baseline MR severity (effective regurgitant orifice area) was not predictive of TR progression or ≥moderate TR at 2 years (Table 2).

Differences across randomization arms are summarized in Supplemental Table 4. Briefly, in the severe IMR trial, there was a tendency for more ≥moderate TR at 2 years after MV repair versus MV replacement (13 of 68 [19%] vs. 6 of 61 [9.8%]; p = 0.14). In the moderate IMR trial, TR progression tended to be higher after isolated CABG versus after CABG + repair (TR progression in 9 of 94 [9.6%] vs. 5 of 102 [4.9%]; p = 0.20).

IMPACT OF RIGHT CORONARY ARTERY GRAFTING. The right coronary artery was revascularized in a total of 73 patients (14.9%), of whom 53 of 290 patients were included in the moderate IMR trial and 20 of 201 in the severe IMR trial. Right coronary artery grafting occurred in 3 of 20 patients with TR progression at 2 years (15%), versus 47 of 304 patients without TR progression (15.5%; p > 0.99). Right coronary artery grafting tended to be more common in patients with less than moderate TR at 2 years (47 of 285 patients [16.5%]) compared with patients with ≥moderate TR at 2 years (3 of 37 patients [8.1%]), although this finding was not statistically significant (p = 0.19).

CLINICAL OUTCOME. TR progression and ≥moderate TR at 2 years were associated with MACE during the 2-year follow-up period (Table 5). Specifically, a higher proportion of patients with post-operative TR had an increase of ≥1 New York Heart Association functional class during follow-up and/or a higher rate of hospitalizations for heart failure.

DISCUSSION

This analysis investigated the evolution of nonsevere TR that was not corrected during surgery for IMR in 2 prospective randomized trials. Key findings are that: 1) the incidence of TR progression (6%) and the incidence of ≥moderate TR (11%) at 2 years after IMR surgery is lower than expected based on retrospective data; 2) baseline tricuspid annular dilation (40 mm or 21 mm/m²) is not predictive of TR progression and is

TABLE 5 Clinical Events in Patients With Versus Without TR Progression or ≥Moderate TR

	No Progression (n = 305)	TR Progression (n = 20)	p Value	<Moderate TR at 2 Years (n = 286)	≥Moderate TR at 2 Years (n = 37)	p Value
MACE	69/305 (22.6)	11/20 (55.0)	0.003	64/286 (22.4)	14/37 (37.8)	0.04
Increase of ≥1 NYHA functional class	23/299 (7.7)	4/19 (21.1)	0.07	20/280 (7.1)	7/37 (18.9)	0.03
Rehospitalization for heart failure	44/305 (14.4)	9/20 (45.0)	0.002	41/286 (14.3)	10/37 (27.0)	0.05
MV surgery after index procedure	4/305 (1.3)	2/20 (10.0)	0.05	3/286 (1.0)	1/37 (2.7)	0.39
Stroke	7/305 (2.3)	0/20 (0.0)	>0.99	7/286 (2.4)	0/37 (0.0)	>0.99

Values are n/N observed (%).
MACE = major adverse clinical events; NYHA = New York Heart Association; other abbreviations as in Tables 1 and 2.

poorly discriminative of ≥moderate TR at 2 years; and 3) both TR progression and ≥moderate TR at 2 years are associated with post-operative MR recurrence and presence of a permanent pacemaker, as well as with a higher clinical event rate during follow-up (**Central Illustration**).

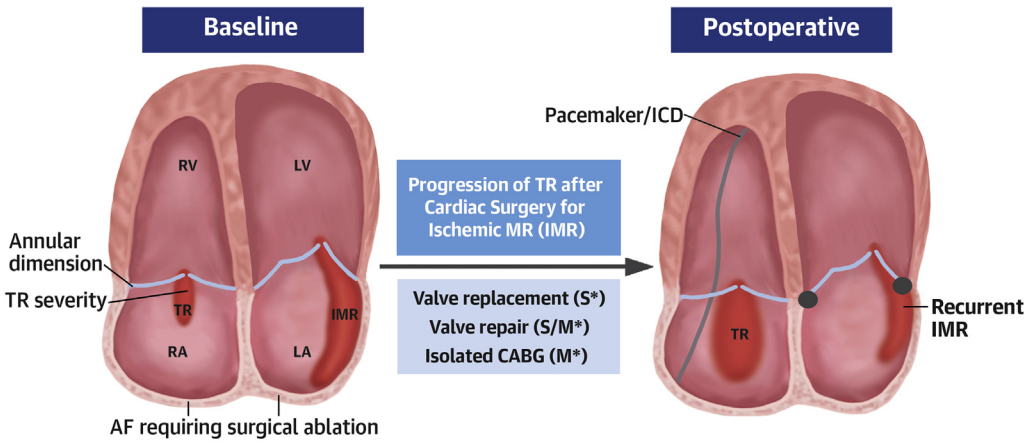
INCIDENCE OF TR PROGRESSION AFTER IMR SURGERY. In contrast to the multitude of reports and the ongoing debate on TR progression after surgery for primary MV disease, data on TR progression after IMR surgery are scarce and limited to retrospective observations. In patients with IMR, given the presence of clinical heart failure and ischemic heart disease (potentially even RV ischemia), the prevalence and significance of secondary TR are expected to be high, and the threshold to intervene on the tricuspid valve during IMR surgery might be lower than for primary MR (19). Matsunaga and Duran (7) observed ≥moderate TR in >50% of patients at 1 to 3 years after MV repair for IMR. Other groups report ≥moderate TR at 5 years after IMR surgery in 31% of patients with baseline trace or mild TR (8), or TR progression of at least 2 TR grades in 25% of patients ~7 years after surgery for secondary MR (66% ischemic etiology) (9).

TR severity, however, can be dynamic and load dependent (20), and retrospective database analyses predispose toward capturing sicker patients in a decompensated state, when seeking medical advice or at hospital admission. In the current study, echocardiography data were prospectively collected at predefined time points in patients receiving heart failure medication at the discretion of the investigators. This study adds important data to the current perception in that it shows a rate of TR progression and ≥moderate TR after IMR surgery that is several times smaller than previously reported.

TRICUSPID ANNULAR DILATION. In this study, the baseline tricuspid annular dimension correlated with baseline TR severity, corroborating the value of the tricuspid annular dimension as a surrogate marker of TR severity (1). Nonetheless, the performance of the parameter in predicting TR progression or ≥moderate TR was poor, even when assessing for alternative (i.e., higher) cutoffs in ROC analysis. Measurement of the tricuspid annulus in two-dimensional echocardiography has well-known limitations given the noncircular 3-dimensional annular shape (21,22). Although 3-dimensional annular sizing has been advocated, a strategy based on a 3-dimensional annular measurement could not improve the predictive value for TR progression after primary MR surgery (23). Reverse RV remodeling after CABG in patients with pre-operative RV ischemia and annular dilation might play a role specifically in an IMR population (35% of patients with moderate TR at baseline showed improvement in TR after surgery). In addition, the association between post-operative TR and time-dependent post-operative MR recurrence and implantation of pacemaker leads, both prevalent in the IMR population, likely interfere with the predictive value of baseline tricuspid annular size.

CLINICAL IMPLICATIONS. Despite the lower-than-anticipated incidence of TR progression and degree of ≥moderate TR at 2 years, the clinical impact of TR progression after IMR surgery is confirmed by the current study. Increasing epidemiological evidence suggests that both TR and the progression of TR are associated with clinical events and impaired long-term outcome (24–27). Efforts to reduce and/or avoid post-operative TR in patients with IMR remain warranted. The poor discriminative value of the tricuspid annular dimension in this analysis, however, does not support the routine application of concomitant tricuspid valve repair based on tricuspid annular dimension alone. Other predictors of ≥moderate TR were TR at baseline and concomitant surgical ablation of atrial fibrillation. Atrial fibrillation is a known predictor of TR progression in patients with left ventricular dysfunction (27) and post-MV repair (28), with ongoing biatrial remodeling and dilation causing progressive TR. Patients who underwent a surgical ablation of atrial fibrillation in the trials likely represented a subgroup of patients

CENTRAL ILLUSTRATION **Progression of Tricuspid Regurgitation After Cardiac Surgery for Ischemic Mitral Regurgitation**



	Rate	Associated with	
	At 2 years	Baseline	Postoperative
TR progression	6.2%		• Recurrent IMR
≥ Moderate TR	11.5%	• Baseline TR grade • Tricuspid annular dimension (indexed) • Surgical AF ablation	• Recurrent IMR • Permanent pacemaker/ICD

Bertrand, P.B. et al. J Am Coll Cardiol. 2021;77(6):713–24.

At 2 years after surgery for ischemic mitral regurgitation (IMR), progression of tricuspid regurgitation (TR) is not as common as generally expected. Post-operative TR depends not only on pre-operative risk factors (baseline TR, tricuspid annular size, or atrial fibrillation) but is associated with post-operative factors such as mitral regurgitation recurrence and permanent pacemaker/defibrillator as well. *M = moderate IMR trial; *S = severe IMR trial; AF = atrial fibrillation; CABG = coronary artery bypass graft; ICD = implantable cardioverter-defibrillator; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

with therapy-refractory or persistent atrial fibrillation who are at higher risk of developing ongoing atrial remodeling and TR. It remains to be determined whether nonsevere TR should be treated during IMR surgery in this subgroup.

STUDY LIMITATIONS. This study was a post hoc secondary analysis using data from 2 prospective randomized controlled trials. Follow-up duration was limited to 2 years. Further follow-up of this patient population will be important to determine further progression of TR, predictors of progression, and its clinical impact. There is a potential survival bias by this cross-sectional analysis at 2 years, as well as potential ascertainment bias due to patients who were lost to follow-up. However, when including the available echocardiogram data at last visit of the patients who died or were lost to follow-up, the overall rate of TR progression remains similar (Supplemental Tables 1 and 2). This study includes patients with both moderate IMR and severe IMR who were treated with either MV replacement, MV repair, or isolated CABG. This approach, however, did not interfere with the findings of the study, as shown in the comparison between trials and randomization arms (Supplemental Table 4). Finally, medical therapies during follow-up were not monitored, nor does this analysis account for the impact of post-operative occurrence of atrial fibrillation, pulmonary hypertension, or interim myocardial infarction on the post-operative progression of TR.

CONCLUSIONS

After IMR surgery, progression of unrepaired non-severe TR is uncommon. Baseline tricuspid annular dilation is not predictive of TR progression, and although associated, only poorly discriminative of ≥moderate TR at 2 years. Both TR progression and the presence of ≥moderate TR at 2 years after IMR surgery are associated with high clinical event rates.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

After surgery for ischemic MR, progression of post-operative TR depends not only on pre-operative risk factors such as annular size or atrial fibrillation but also on post-operative factors such as residual or recurrent MR and the use of a permanent pacemaker or defibrillator.

TRANSLATIONAL OUTLOOK:

Further studies are needed to examine the natural history of TR after surgery for ischemic MR and to identify patients who benefit from concomitant tricuspid valve intervention.

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KEY WORDS ischemic heart disease, mitral valve regurgitation, mitral valve surgery, tricuspid annular dilation, tricuspid valve regurgitation

APPENDIX For supplemental figures, tables, and a listing of the CTSN Investigators, please see the online version of this paper.