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Impact of Tricuspid Regurgitation on Clinical Outcomes

The COAPT Trial

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ABSTRACT

BACKGROUND The presence of tricuspid regurgitation (TR) may affect prognosis in patients with mitral regurgitation (MR).

OBJECTIVES This study sought to determine the impact of TR on outcomes in patients with heart failure and severe secondary MR randomized to guideline-directed medical therapy (GDMT) or edge-to-edge repair with the MitraClip in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial.

METHODS A total of 614 patients with symptomatic heart failure with moderate to severe (3+) or severe (4+) secondary MR were randomized to maximally tolerated GDMT plus MitraClip or GDMT alone; 599 had core laboratory evaluable echocardiograms. Patients were divided into 2 groups by baseline TR severity: none/trace/mild TR (≤Mild TR) (n = 501 [83.6%]) and moderate/severe TR (≥Mod TR) (n = 98 [16.4%]). Two-year composite endpoints of death or heart failure hospitalization (HFH) and the individual endpoints were analyzed.

RESULTS Patients with ≥Mod TR were more likely to be New York Heart Association functional class III/IV ($p < 0.0001$) and have a Society of Thoracic Surgeons score of ≥8 ($p < 0.0001$), anemia ($p = 0.02$), chronic kidney disease ($p = 0.003$), and higher N-terminal pro-B-type natriuretic peptide ($p = 0.02$) than those with ≤Mild TR. Patients with ≥Mod TR had more severe MR ($p = 0.0005$) despite smaller left ventricular volumes ($p = 0.005$) and higher right ventricular systolic pressure ($p < 0.0001$). At 2 years, the composite rate of death or HFH was higher in patients with ≥Mod TR compared with ≤Mild TR treated with GDMT alone (83.0% vs. 64.3%; hazard ratio: 1.74; 95% confidence interval: 1.24 to 2.45; $p = 0.001$) but not following MitraClip (48.2% vs. 44.0%; hazard ratio: 1.14; 95% confidence interval: 0.71 to 1.84; $p = 0.59$). Rates of death or HFH, as well as death and HFH alone, were reduced by MitraClip compared with GDMT, irrespective of baseline TR grade ($p_{interaction} = 0.16$, 0.29, and 0.21 respectively).

CONCLUSIONS Patients with severe secondary MR who also had ≥Mod TR had worse clinical and echocardiographic characteristics and worse clinical outcomes compared to those with ≤Mild TR. Within the COAPT trial, MitraClip improved outcomes in patients with and without ≥Mod TR severity compared with GDMT alone. (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation [COAPT]; NCT01626079) (J Am Coll Cardiol 2020;76:1305–14)

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

EF = ejection fraction

EROA = effective regurgitant orifice area

GDMT = guideline-directed medical therapy

HFH = heart failure related hospitalization

HR = hazard ratio

LV = left ventricular

MR = mitral regurgitation

MV = mitral valve

NYHA = New York Heart Association

RV = right ventricular

STS = Society of Thoracic Surgeons

TR = tricuspid regurgitation

TV = tricuspid valve

Tricuspid regurgitation (TR) commonly accompanies secondary mitral regurgitation (MR) and may be due to the development of secondary pulmonary hypertension, with or without right ventricular (RV) dilatation and/or dysfunction (1). Severe MR and TR may coexist in up to 30% of patients presenting with heart failure with reduced left ventricular (LV) ejection fraction (EF) and is associated with increased mortality (2). Significant TR has been reported in as many as 30% of patients before surgical treatment of ischemic MR, in 50% of patients following mitral valve (MV) repair, and in >70% of patients at long-term follow-up (3). Multiple studies have shown that baseline TR also has a substantial impact on outcomes following transcatheter edge-to-edge MV repair (4–7). Single-site and registry studies using site-reported grading of both MR and TR suggest that transcatheter treatment of MR is associated with a significant reduction in TR severity (5,8,9).

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The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial demonstrated that transcatheter treatment of MR with the MitraClip (Abbott Vascular, Santa Clara, California) improves quality of life and exercise capacity, reduces the rate of hospitalizations, and improves survival in selected patients with heart failure and secondary MR compared to maximally tolerated guideline-directed medical therapy (GDMT) alone (10). In COAPT, an echocardiographic core laboratory was used to evaluate cardiac chamber size and function as well as valvular function (11). We thus sought to examine the impact of baseline TR on outcomes after optimal medical therapy and transcatheter repair in patients with heart failure and secondary MR from the COAPT trial.

METHODS

STUDY DESIGN. The COAPT trial design has been published previously (12). In brief, COAPT was a multicenter, randomized, controlled, open-label trial of transcatheter MV repair with the MitraClip in patients with heart failure and moderate to severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally tolerated GDMT. Patients had LVEF between 20% and 50%, LV end-systolic diameter ≤70 mm, and absence of severe pulmonary hypertension or moderate or severe RV dysfunction.

Tricuspid valve (TV) disease requiring surgery was also an exclusion criterion; otherwise patients with any severity of TR could be enrolled. Patients were randomized 1:1 to receive the MitraClip plus GDMT or GDMT alone. Transthoracic echocardiographic follow-up was performed at 1, 6, 12, 18, and 24 months after randomization. All transthoracic echocardiograms

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were analyzed by an independent echocardiographic core laboratory (MedStar Health Research Institute, Washington, DC). The primary effectiveness endpoint was all heart failure-related hospitalizations (HFH) within 24 months, assessed when all patients had completed at least 1 year of follow-up. At the time of the present report, all patients had reached the 2-year follow-up.

The protocol was approved by the Institutional Review Board at each participating center, and all patients provided written informed consent. Abbott sponsored the trial and provided statistical support for the present analysis. The investigators had unrestricted access to the data and accept responsibility for the integrity of the present report.

ECHOCARDIOGRAPHIC CORE LABORATORY ANALYSIS. For qualification purposes, MR severity was required to be assessed by the core lab as 3+ or higher, according to a pre-specified multiparametric algorithm created for the COAPT trial (11) adapted from the criteria recommended by the American Society of Echocardiography Guidelines (13). TR severity analysis was similarly performed using a multiparametric qualitative approach and graded as none/trace, mild, moderate, and severe (13). Assessment of other echocardiographic variables has been previously described (11).

STATISTICAL ANALYSIS. For the present analysis, patients with core laboratory-graded none, trace, and mild TR were grouped (≤Mild TR) and compared with those with moderate, moderate-severe, or severe TR (≥Mod TR). Baseline characteristics were summarized with mean ± SD for continuous measures and proportions for categorical variables. Between treatment groups, variables were compared with the Student's *t*-test for the continuous measures, chi-square or Fisher exact test for categorical variables, and Wilcoxon rank sum test for ordinal data.

For time-to-first event analyses, event rates were estimated by the Kaplan-Meier method and compared with the log-rank test. Changes in echocardiographic parameters over time were calculated as the difference between the baseline and follow-up visits. Analysis of covariance was performed to compare changes over time adjusted for baseline values. Multivariable Cox proportional hazards models were performed with covariates including TR severity, randomized treatment, an interaction term of TR severity and treatment, baseline New York Heart Association (NYHA) functional class, Society of Thoracic Surgeons (STS) score, chronic kidney disease, LV end-systolic diameter, LV end-diastolic volume, LVEF, MR severity, and RV systolic pressure. A 2-sided p value of <0.05 was considered statistically significant for all superiority tests. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

TABLE 1 Baseline Clinical and Laboratory Characteristics According to the Severity of Baseline Tricuspid Regurgitation

	≤Mild TR (n = 501)	≥Mod TR (n = 98)	p Value
Age, yrs	72.0 ± 11.3	73.7 ± 10.4	0.17
Male	65.5 (328/501)	58.2 (57/98)	0.17
BMI, kg/m^2	27.3 ± 5.9	26.0 ± 5.7	0.06
NYHA functional class III or IV	57.4 (287/500)	78.6 (77/98)	<0.0001
History of atrial fibrillation or flutter	54.9 (275/501)	59.2 (58/98)	0.43
Diabetes mellitus	36.7 (184/501)	38.8 (38/98)	0.70
History of anemia	21.4 (107/501)	32.7 (32/98)	0.02
STS score ≥8	46.4 (231/498)	68.4 (67/98)	<0.0001
Chronic kidney disease	70.9 (348/491)	85.4 (82/96)	0.003
Creatinine clearance, ml/min	51.1 ± 27.1	41.2 ± 24.9	0.001
BNP, pg/ml	886.0 ± 896.1	1,715.5 ± 1,854.2	<0.0001
NT-proBNP, pg/ml	4,889.0 ± 6,880.9	9,061.9 ± 9,790.4	0.02
Ischemic cardiomyopathy	60.7 (304/501)	57.1 (56/98)	0.51
KCCQ	53.5 ± 22.7	47.4 ± 23.7	0.02
6MWD, m	252.0 ± 123.9	190.4 ± 115.1	<0.0001
ACE inhibitor, ARB, or ARN inhibitor	70.3 (352/501)	51.0 (50/98)	0.0002
Beta-blocker	90.6 (454/501)	87.8 (86/98)	0.38
Aldosterone antagonist	52.3 (262/501)	38.8 (38/98)	0.01
Diuretic	89.4 (448/501	88.8 (87/98)	0.85

Values are mean ± SD or % (n/N).

≤Mild TR = none/trace/mild tricuspid regurgitation; ≥Mod TR = moderate/severe tricuspid regurgitation; 6MWD = 6-min walk distance; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ARN = angiotensin receptor-neprilysin; BMI = body mass index; BNP = brain natriuretic protein; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-pro-BNP = N-terminal pro b-type natriuretic peptide; NYHA = New York Heart Association; STS = Society of Thoracic Surgery.

RESULTS

PATIENTS. Among the 614 randomized patients, 599 baseline echocardiograms (98%) were adequate for TR assessment at the core laboratory, comprising the present study population. TR was graded as none/trace in 12 patients (2.0%), mild in 489 (81.6%), moderate in 92 (15.4%), moderate-severe in 5 of 599 (0.8%), and severe in 1 patient (0.2%). Thus, 501 patients (83.6%) had ≤Mild TR, and 98 patients (16.4%) had ≥Mod TR. Baseline clinical characteristics are listed in Table 1. Patients with ≥Mod TR compared with ≤Mild TR had higher NYHA functional class and STS score, more frequently had a history of anemia and chronic kidney disease, and had higher B-type natriuretic and N-terminal pro-B-type natriuretic peptide levels. Patients with ≥Mod TR also had lower (worse) Kansas City Cardiomyopathy Questionnaire summary scores, shorter 6-min walk distances, and less use of inhibitors of the renin-angiotensin axis.

Baseline echocardiographic parameters according to TR severity are listed in Table 2. Despite having

TABLE 2 Baseline Echocardiographic Parameters According to the Severity of Baseline Tricuspid Regurgitation

	≤Mild TR (n = 501)	≥Mod TR (n = 98)	p Value
LVEF, %	31.2 ± 9.2	32.0 ± 10.1	0.47
LV end-diastolic dimension, cm	6.2 ± 0.7	6.0 ± 0.7	0.03
LV end-systolic dimension, cm	5.3 ± 0.9	5.1 ± 0.9	0.007
LVEDV, ml	196.4 ± 72.9	172.1 ± 56.2	0.002
LVESV, ml	137.6 ± 60.0	117.9 ± 44.0	0.003
Stroke volume, ml	58.8 ± 22.6	54.2 ± 22.7	0.08
LA volume, ml	90.9 ± 36.4	95.0 ± 57.2	0.37
RV end-diastolic area, cm^2	26.51 ± 7.05	29.12 ± 7.92	0.005
RV end-systolic area, cm^2	18.21 ± 6.06	19.85 ± 6.18	0.04
RV fractional area change, %	32.01 ± 9.18	32.07 ± 7.86	0.96
RVSP, mm Hg	43.0 ± 13.1	50.0 ± 14.9	<0.0001
Tricuspid regurgitation			
(0) None	2.4 (12/501)	0.0 (0/98)	0.12
(1+) Mild	97.6 (489/501)	0.0 (0/98)	<0.0001
(2+) Moderate	0.0 (0/501)	93.9 (92/98)	<0.0001
(3+) Moderate to severe	0.0 (0/501)	5.1 (5/98)	<0.0001
(4+) Severe	0.0 (0/501)	1.0 (1/98)	0.02
Mitral regurgitation			
(3+) Moderate to severe	56.1 (281/501)	31.6 (31/98)	<0.0001
(4+) Severe	43.9 (220/501)	68.4 (67/98)	<0.0001
EROA by PISA, cm^2	0.40 ± 0.14	0.46 ± 0.20	0.0005

Values are mean ± SD or n/N (%).

EROA = effective regurgitant orifice area; LA = left atrium; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; PISA = proximal isovelocity surface area; RV = right ventricle; RVSP = right ventricular systolic pressure; other abbreviations as in Table 1.

TABLE 3 Discharge Severity of Mitral and Tricuspid Regurgitation in Patients Treated With MitraClip According to the Severity of Baseline Tricuspid Regurgitation

	≤Mild TR (n = 233)	≥Mod TR (n = 34)	p Value
Mitral regurgitation			0.0172
(0) None	0.9 (2/223)	0.0 (0/34)	
(1+) Mild	83.9 (187/223)	67.6 (23/34)	
(2+) Moderate	10.8 (24/223)	26.5 (9/34)	
(3+) Moderate to severe	3.1 (7/223)	5.9 (2/34)	
(4+) Severe	1.3 (3/223)	0.0 (0/34)	
Tricuspid regurgitation			<0.0001
(0) None	2.4 (5/210)	0.0 (0/33)	
(1+) Mild	84.3 (177/210)	48.5 (16/33)	
(2+) Moderate	11.9 (25/210)	51.5 (17/33)	
(3+) Moderate to severe	1.4 (3/210)	0.0 (0/33)	
(4+) Severe	0.0 (0/210)	0.0 (0/33)	

Values are % (n/N). Wilcoxon rank-sum test was performed to compare the 2 groups for ordinal responses.

Abbreviations as in Table 1.

greater MR as assessed by the proximal isovelocity surface area-calculated effective regurgitant orifice area (EROA), patients with ≥Mod TR compared with ≤Mild TR had smaller LV end-diastolic volume and left ventricular end-systolic volume. Patients with ≥Mod TR also had larger RV size, higher RV systolic pressure, and lower cardiac output. RV and LV systolic function were similar between the groups.

Among the 501 patients with ≤Mild TR, 255 were assigned to MitraClip plus GDMT and 246 were assigned to GDMT alone. Among the 98 patients with ≥Mod TR, 44 and 54 were assigned to MitraClip plus GDMT versus GDMT alone, respectively.

IN-HOSPITAL OUTCOMES (MitraClip COHORT). The median length of stay in the hospital was 2.0 days (IQR: 1.0 to 3.0 days). There were more deaths before discharge in MitraClip-treated patients with baseline ≥Mod TR compared with ≤Mild TR (5.1% vs. 0.8%; p = 0.03). The severity of MR and TR at discharge in 267 MitraClip-treated patients in whom a pre-discharge transthoracic echocardiogram was performed are shown in Table 3. Significantly fewer patients with ≥Mod TR compared with ≤Mild TR achieved mild MR from the MitraClip at the time of discharge. Approximately one-half of the patients with baseline ≥Mod TR had only mild TR after MitraClip treatment. Conversely, 13.3% of patients with ≤Mild TR at baseline had ≥Mod TR at discharge after MitraClip treatment.

30-DAY REDUCTION IN MR AND TR. Treatment with MitraClip compared with GDMT alone resulted in substantially greater reductions in MR severity at 30 days, regardless of the severity of baseline TR (Supplemental Table 1). In contrast, the changes in TR grade from baseline to 30 days in both patients with ≤Mild TR and those with ≥Mod TR at baseline were similar after MitraClip treatment and GDMT alone.

CLINICAL OUTCOMES. The median duration of follow-up for the entire cohort was 24.1 months (IQR: 11.7 to 35.9 months). In the entire cohort, patients with baseline ≥Mod TR compared with ≤Mild TR had increased 30-day, 1-year, and 2-year rates of the composite outcomes of death or HFH and death from cardiovascular cause or HFH, as well as death, cardiovascular death, and HFH individually (Table 4). As shown in Table 5, ≥Mod TR in the GDMT-only arm was associated with increased rates of all-cause death or HFH at both 1 and 2 years. By multivariable analysis, the presence of baseline ≥Mod TR in the GDMT-only cohort was an independent predictor of 2-year all-cause death or HFH (hazard ratio [HR]: 1.59; 95% confidence interval [CI]: 1.09 to 2.33; $p_{interaction}$ = 0.11), HFH (HR: 1.65; 95% CI: 1.07 to 2.54), and cardiovascular death (HR: 1.65; 95% CI: 1.00 to 2.73). Conversely, in the MitraClip arm, although 30-day rates of death were greater in patients with ≥Mod TR, the 1-year and 2-year rates of death and of HFH, and the composite of death or HFH, were similar in

patients with baseline ≥Mod TR and ≤Mild TR in both unadjusted and adjusted analyses (Table 5, Supplemental Table 2). There were no significant interactions between treatment and baseline TR severity on outcomes at any time period (Table 5).

The Central Illustration and Figure 1 show the time-to-first event curves for the major outcomes according to baseline TR severity and treatment. Patients with ≥Mod TR at baseline treated with GDMT had the worst outcomes. The 2-year rates of all-cause death or HFH, cardiovascular death or HFH, and all-cause death and HFH alone were consistently reduced by MitraClip compared with GDMT alone, irrespective of baseline TR grade ($p_{interaction}$ = 0.23, 0.19, 0.29, and 0.21, respectively).

TABLE 4 Outcomes at 30 Days, 1 Year, and 2 Years According to the Severity of Baseline Tricuspid Regurgitation in the Entire Cohort

	≥Mod TR (n = 98)	≤Mild TR (n = 501)	HR (95% CI)	p Value
30-day events				
Death or HFH	11.3 (11)	5.2 (26)	2.27 (1.12–4.60)	0.02
Cardiovascular death or HFH	11.3 (11)	5.0 (25)	2.36 (1.16–4.80)	0.01
Death				
All-cause	4.1 (4)	1.2 (6)	3.49 (0.99–12.37)	0.04
Cardiovascular	4.1 (4)	1.0 (5)	4.18 (1.12–15.55)	0.02
HFH	8.3 (8)	4.6 (23)	1.87 (0.83–4.17)	0.12
1-yr events				
Death or HFH	50.1 (47)	38.2 (190)	1.49 (1.08–2.05)	0.01
Cardiovascular death or HFH	48.3 (45)	36.2 (177)	1.53 (1.10–2.12)	0.01
Death				
All-cause	31.1 (29)	19.7 (97)	1.77 (1.17–2.68)	0.006
Cardiovascular	26.3 (24)	15.7 (75)	1.90 (1.20–3.01)	0.005
HFH	42.4 (37)	30.6 (146)	1.52 (1.06–2.18)	0.02
2-yr events				
Death or HFH	66.2 (61)	53.8 (263)	1.44 (1.09–1.90)	0.01
Cardiovascular death or HFH	65.9 (60)	50.4 (241)	1.54 (1.16–2.05)	0.002
Death				
All-cause	50.4 (46)	33.3 (160)	1.78 (1.28–2.47)	0.0005
Cardiovascular	45.0 (39)	27.2 (125)	1.93 (1.35–2.77)	0.0003
HFH	57.3 (48)	43.5 (199)	1.49 (1.09–2.04)	0.01

Values are % (n) unless otherwise indicated. Rates are Kaplan-Meier estimates, % (n events).
CI = confidence interval; HFH = heart failure hospitalization; HR = hazard ratio; other abbreviations as in Table 1.

DISCUSSION

Prior studies have described the deleterious impact of TR on clinical outcomes across a wide spectrum of cardiac disorders (14). To our knowledge, COAPT is the first randomized trial to afford a comparison of the impact of TR on intermediate-term outcomes in medically treated patients and after transcatheter repair of severe secondary MR in patients with heart failure. The major findings of our study are as follows:

- Greater severity of baseline TR was associated with greater severity of MR, higher RV systolic pressure, and more severe clinical and functional impairment, despite smaller LV volumes.
- Despite correction of MR with the MitraClip, the severity of TR was not significantly changed at 30 days compared with GDMT alone.
- The presence of ≥Mod TR at baseline was strongly associated with adverse 2-year outcomes in patients treated with GDMT alone but not after the MitraClip.
- The benefits of the MitraClip in terms of improving survival and reducing HFH over a 2-year period were present and consistent in patients with baseline ≤Mild TR and ≥Mod TR.

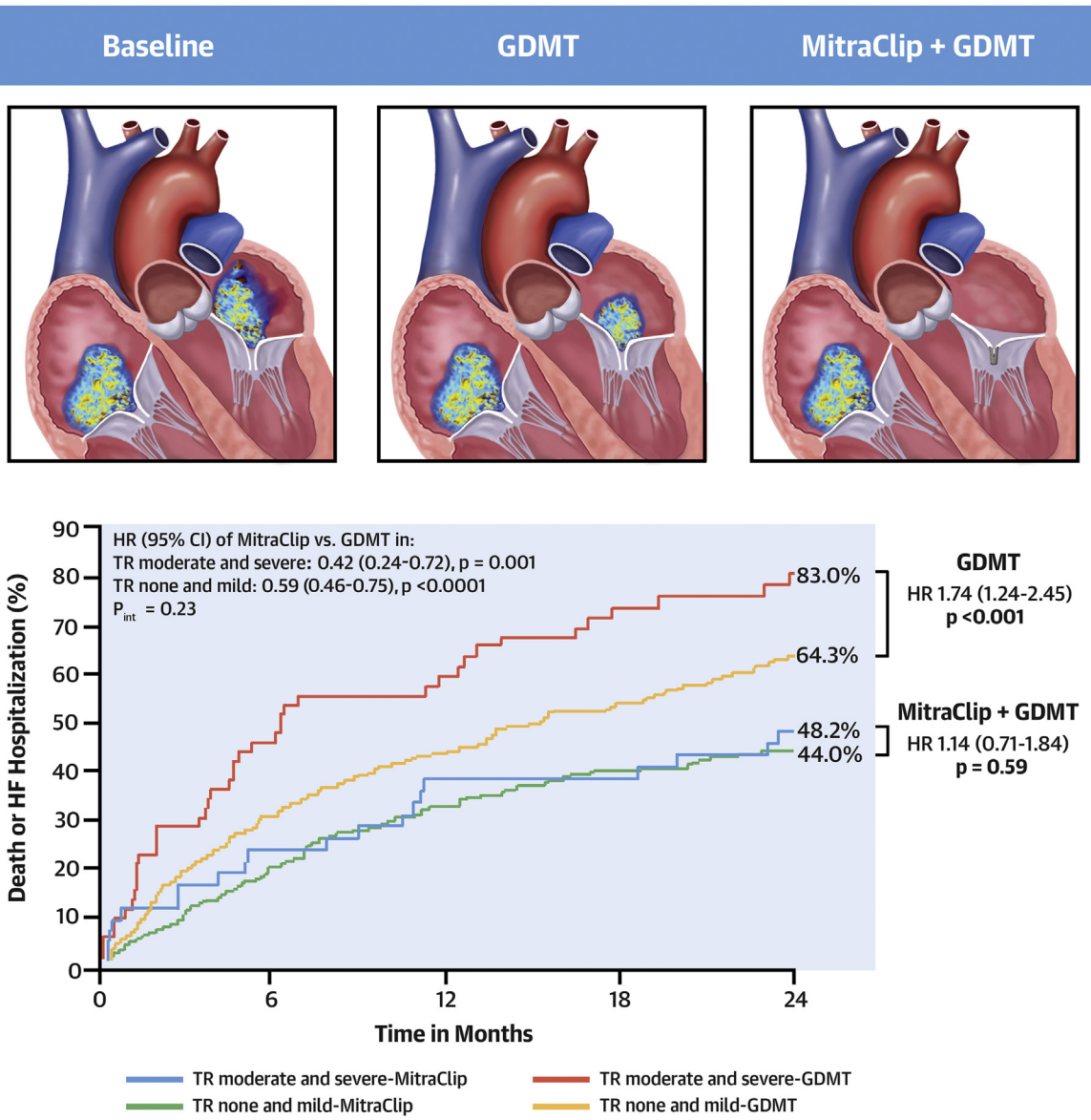
Longstanding increased pulmonary pressures may result in progressive dilatation of the RV with

TABLE 5 Outcomes According to the Baseline Severity of Tricuspid Regurgitation in the Randomized Groups

	MitraClip + GDMT			GDMT alone			
	≥Mod TR (n = 44)	≤Mild TR (n = 255)	HR (95% CI)	≥Mod TR (n = 54)	≤Mild TR (n = 246)	HR (95% CI)	$p_{interaction}$
30-day events							
Death or HFH	11.4 (5)	4.7 (12)	2.54 (0.89–7.20)	11.2 (6)	5.7 (14)	2.05 (0.79–5.35)	0.77
Death	9.1 (4)	1.2 (3)	8.00 (1.79–35.77)	0.0 (0)	1.2 (3)	N/A	0.99
HFH	12.6 (32)	12.6 (32)	1.35 (0.59–3.05)	16.8 (9)	11.0 (27)	1.61 (0.76–3.42)	0.76
1-yr events							
Death or HFH	38.3 (16)	32.7 (83)	1.23 (0.72–2.10)	59.4 (31)	44.0 (107)	1.63 (1.09–2.43)	0.40
Death	23.9 (10)	18.5 (47)	1.42 (0.72–2.82)	36.6 (19)	21.0 (50)	2.00 (1.18–3.39)	0.45
HFH	59.2 (24)	53.9 (136)	1.12 (0.72–1.72)	70.1 (36)	61.1 (145)	1.37 (0.95–1.97)	0.50
2-yr events							
Death or HFH	48.2 (20)	44.0 (111)	1.14 (0.71–1.84)	83.0 (41)	64.3 (152)	1.74 (1.24–2.45)	0.16
Death	34.1 (14)	27.5 (69)	1.36 (0.77–2.42)	63.6 (32)	39.8 (91)	2.02 (1.35–3.03)	0.29
HFH	74.5 (30)	67.2 (167)	1.13 (0.77–1.67)	95.4 (47)	78.6 (182)	1.51 (1.10–2.09)	0.28

Values are % (n) unless otherwise indicated. Rates are Kaplan-Meier estimates, % (n events).
GDMT = guideline-directed medical therapy; other abbreviations as in Tables 1 and 4.

CENTRAL ILLUSTRATION **2-Year Cumulative Rates of Death or Hospitalization for Heart Failure According to the Severity of Baseline Tricuspid Regurgitation and Randomization to Transcatheter Mitral Valve Repair Plus Guideline-Directed Medical Therapy Versus Guideline-Directed Medical Therapy Alone**



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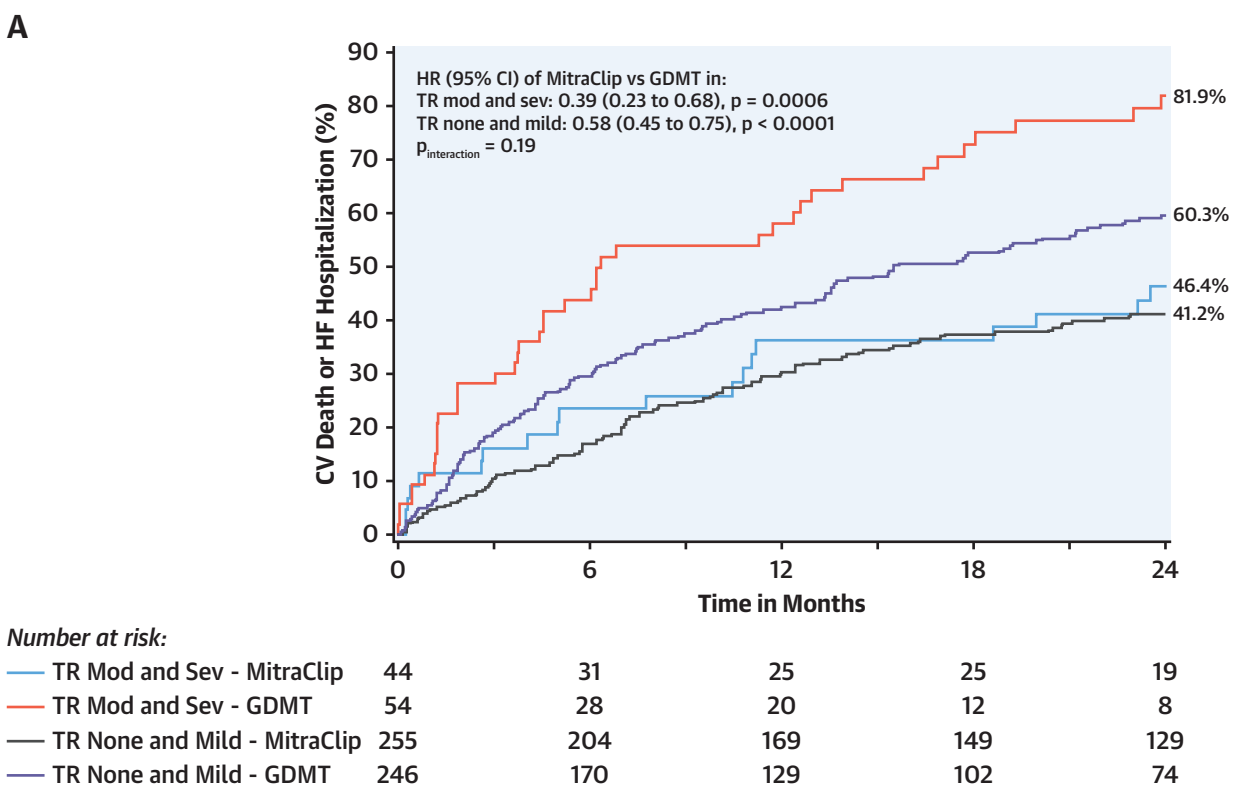
The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial randomized patients with moderate to severe or severe secondary mitral regurgitation to maximally tolerated guideline-directed medical therapy (GDMT) alone or MitraClip plus GDMT. The impact of ≤Mild tricuspid regurgitation (TR) and ≥Mod TR at baseline were evaluated. At 2 years, the composite rate of death or heart failure hospitalization was higher in patients with ≥Mod TR compared to those with ≤Mild TR treated with GDMT alone (83.0% vs. 64.3%; HR: 1.74; 95% CI: 1.24 to 2.45; p = 0.001) but not in those treated with MitraClip (48.2% vs. 44.0%; HR: 1.14; 95% CI: 0.71 to 1.84; p = 0.59). ≤Mild TR = none/trace/mild tricuspid regurgitation; ≥Mod TR = moderate/severe tricuspid regurgitation; CI = confidence interval; HF = heart failure; HR = hazard ratio; int = interaction.

FIGURE 1 2-Year Kaplan-Meier Time-to-First Event Outcomes by Treatment Group and Severity of Baseline Tricuspid Regurgitation



(A) Cardiovascular death or heart failure hospitalization. **(B)** All-cause death. **(C)** Heart failure hospitalization. CV = cardiovascular; GDMT = guideline-directed medical therapy; HF = heart failure; HR = hazard ratio; mod = moderate; sev = severe; TR = tricuspid regurgitation.

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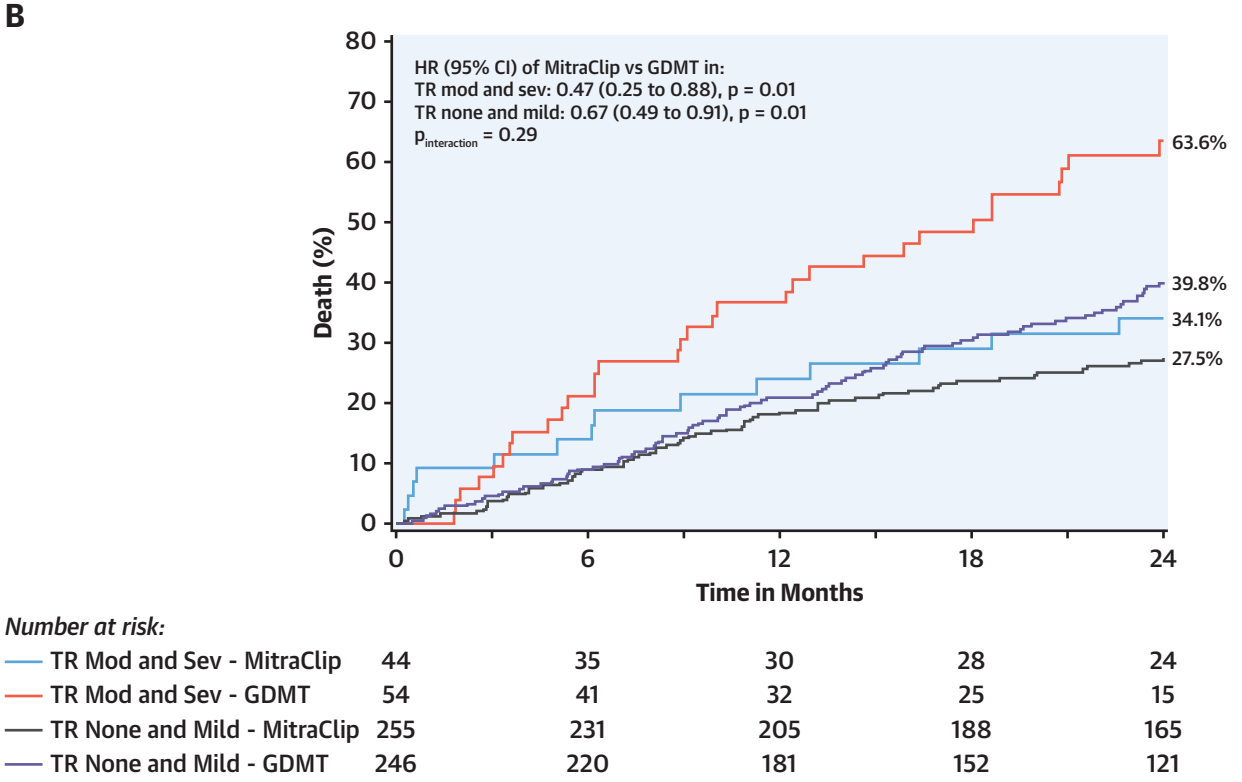
tricuspid leaflet tethering and progressive TR (15,16). The findings of the current study support this pathophysiological mechanism, with greater severity of TR associated with worse MR, as assessed by proximal isovelocity surface area EROA, with lower cardiac output and higher RV systolic pressure. Interestingly, patients with more severe TR not only had greater MR severity but also had smaller LV volumes and larger RV volumes with similar LVEF and RV function. These patients have higher RV systolic pressure and thus may belong to a distinct phenotype of "combined post-capillary and pre-capillary pulmonary hypertension," which results in RV dilatation and at least moderate TR. Smaller LV cavities may then be a result of ventricular interdependence within a fixed pericardial space (16). These patients may also have greater disproportionate MR (17), which may result in higher post-capillary pulmonary pressures and resulting higher RVSP, greater RV dilatation, and more severe TR. Finally, the duration of MR and the presence of mixed primary and secondary disease cannot be excluded.

These baseline differences may in part explain why patients with ≥Mod TR have higher in-hospital mortality. Whether a higher EROA:LV volume ratio predicts greater clinical improvement after transcatheter MV repair in patients with ≥Mod TR at baseline deserves further study.

Moderate or severe TR commonly accompanies secondary MR (18), and simultaneous treatment of both is indicated during left-sided valvular surgery (Class I) (18,19). Recent transcatheter MV repair studies suggest that baseline TR also has a significant impact on outcomes (4–7). Using the national STS/American College of Cardiology Transcatheter Valve Therapy Registry of commercial therapy with the MitraClip, Sorajja et al. (7) reported that the subgroup of patients with severe TR had significantly worse outcomes compared to those without severe TR, with 1-year rates of 38.5%, 31.5%, and 54.3% for death, HFH, and the combined endpoint of death or HFH in the severe TR subgroup, respectively (7). However, 86% of patients in this registry had pure degenerative MV disease. To our knowledge, the current study is

FIGURE 1 Continued



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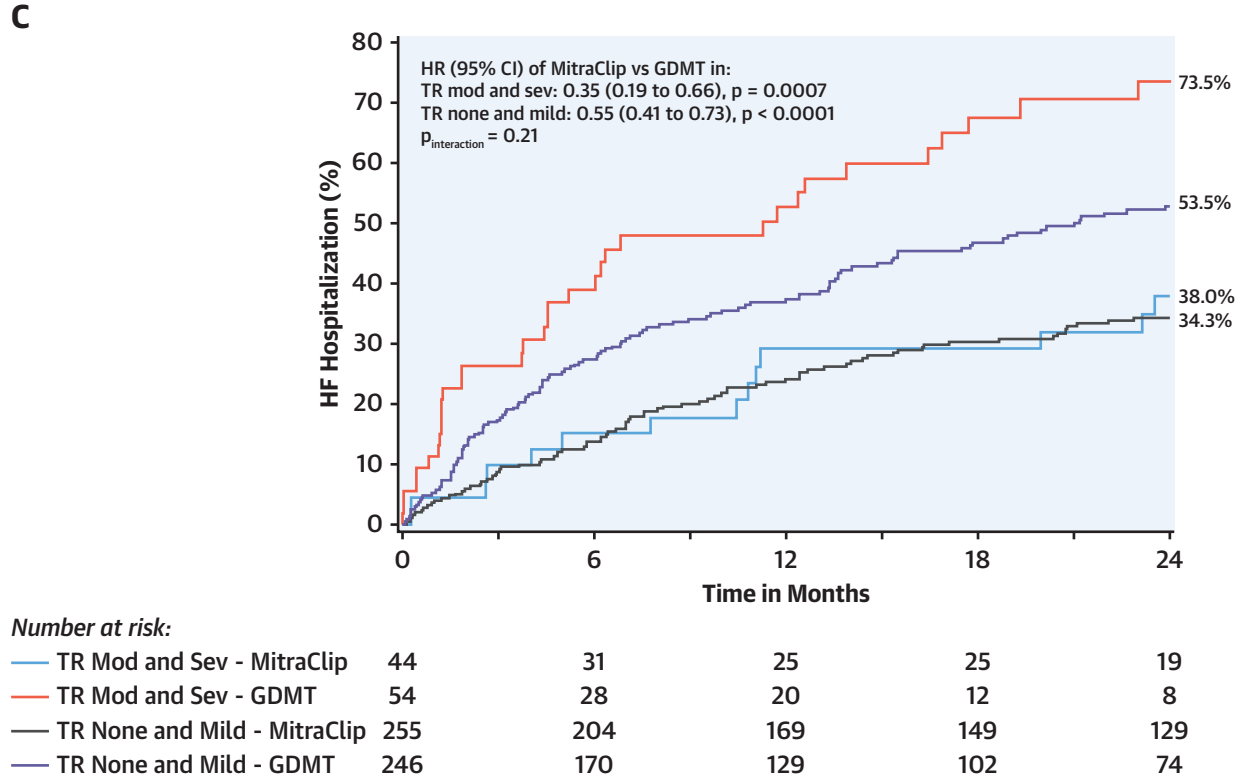
the first to show in a randomized trial of secondary MR that increasing severity of TR portends worse outcomes when treated with GDMT alone and that treatment of secondary MR with the MitraClip is associated with improved clinical outcomes regardless of the level of baseline TR severity and, indeed, may eliminate the impact of baseline TR as a risk factor.

Although the COAPT trial has resulted in changes in U.S. Food and Drug Administration device labeling and societal recommendations for the treatment of selected patients with secondary MR, given the marked reductions in HFH and mortality with MitraClip treatment compared to GDMT alone (20), severe TR was not concomitantly treated along with MR in this trial (10). A recent study combined the outcomes from 2 large registries to examine the outcomes of patients undergoing transcatheter MV repair alone versus concomitant MV with TV repair (21). The 34.8% 1-year mortality rate for isolated transcatheter MV repair reported from that study is comparable to the 1-year morality rate after MitraClip from the present analysis. Concomitant treatment of MR and TR was associated with a further 2-fold-lower mortality rate at 1 year (multivariable adjusted HR: 0.52; p = 0.02). Whether concomitant or sequential therapy for TR should be performed at the time of transcatheter MV repair was not addressed. One could argue that because TR severity improves following isolated transcatheter MV repair in 33% to 58% of patients (5,8,9) and may improve in some patients even with GDMT (as in our study), sequential therapy may be logical if this approach is not associated with worse long-term outcomes. In COAPT, the 30-day risk of all-cause death in MitraClip-treated patients was higher in those with baseline ≥Mod TR compared with ≤Mild TR, although the event rates are small, resulting in wide confidence intervals. Despite this difference, longer-term outcomes at 1 and 2 years were similar in MitraClip-treated patients with ≤Mild TR and ≥Mod TR, suggesting that concomitant TR repair may not be necessary. However, few patients in COAPT had moderate to severe or severe TR. Whether concomitant MR and TR therapy could improve early outcomes with sustained long-term benefit in such patients requires further study. Identifying the predictors of long-term TR improvement after transcatheter mitral valve replacement (TMVR)

FIGURE 1 Continued



alone could also help risk stratify patients and direct therapeutic decision making.

STUDY LIMITATIONS. The COAPT trial excluded patients with severe pulmonary hypertension, moderate or severe RV dysfunction, and TV disease requiring surgery. Few randomized patients had truly severe TR, and thus, whether the present results apply to such patients is unknown. In addition, TR was assessed using the current guideline-recommended multiparametric qualitative methods (13); the variables needed to quantify TR were not collected. As such, whether TR quantification (which has not yet been standardized nor adopted by guidelines) might have provided additional insights is unknown (13,22). How the outcomes of the present study may have varied in patients with severe RV dysfunction or pulmonary hypertension are also unknown and deserves further study (23). In addition, a more robust assessment of RV mechanics, such as RV free wall strain, could be useful in further defining appropriate patient populations for therapy but was not measured in the current study. Finally, the current study evaluated the association of baseline TR with subsequent outcomes. Future planned analyses from COAPT include assessment of late TR regression or progression following MitraClip therapy, the effect of residual post-procedure TR on outcomes, and the prognostic interactions between TR, RV dysfunction, and pulmonary hypertension.

CONCLUSIONS

In the COAPT trial of patients with heart failure and severe secondary MR who remained symptomatic despite maximally tolerated GDMT, the concomitant presence of moderate or severe TR at baseline was associated with more severe MR, higher pulmonary pressures, and worse heart failure signs and symptoms. Patients with at least moderate compared to lesser degrees of TR at baseline who were treated with GDMT alone had worse outcomes. Conversely, long-term survival and freedom from HFH were similar after secondary MR treatment with the MitraClip in patients with both ≤Mild TR and ≥Mod TR at baseline.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Although patients with severe mitral regurgitation who have heart failure and worsening TR treated with guideline-recommended medical therapy alone face a high risk of adverse clinical outcomes over 2 years, those treated with the Mitra-Clip enjoy a more favorable prognosis.

TRANSLATIONAL OUTLOOK: Although the MitraClip appears to mitigate adverse outcomes associated with baseline TR, further research is needed to determine whether concomitant or sequential treatment of TR can improve outcomes further.

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KEY WORDS heart failure, mitral regurgitation, tricuspid regurgitation

APPENDIX For the supplemental tables, please see the online version of this paper.