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Pulmonary Hypertension in Transcatheter Mitral Valve Repair for Secondary Mitral Regurgitation

The COAPT Trial

Ori Ben-Yehuda, MD,[a,*] Bahira Shahim, MD, PhD,[a,*] Shmuel Chen, MD, PhD,[a,b] Mengdan Liu, MS,[a] Bjorn Redfors, MD, PhD,[a] Rebecca T. Hahn, MD,[a,b] Federico M. Asch, MD,[c] Neil J. Weissman, MD,[c] Diego Medvedofsky, MD,[c] Rishi Puri, MD,[d] Samir Kapadia, MD,[d] Anna Sannino, MD, PhD,[e] Paul Grayburn, MD,[e] Saibal Kar, MD,[f] Scott Lim, MD,[g] JoAnn Lindenfeld, MD,[h] William T. Abraham, MD,[i] Michael J. Mack, MD,[e] Gregg W. Stone, MD[a,j]

ABSTRACT

BACKGROUND Pulmonary hypertension worsens prognosis in patients with heart failure (HF) and secondary mitral regurgitation (SMR).

OBJECTIVES This study sought to determine whether baseline pulmonary hypertension influences outcomes of transcatheter mitral valve repair (TMVr) in patients with HF with SMR.

METHODS In the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial, 614 patients with HF with moderate-to-severe or severe SMR were randomized to TMVr with the MitraClip plus guideline-directed medical therapy (GDMT) (n = 302) versus GDMT alone (n = 312). Baseline pulmonary artery systolic pressure (PASP) estimated from echocardiography was categorized as substantially increased (≥50 mm Hg) versus not substantially increased (<50 mm Hg).

RESULTS Among 528 patients, 184 (82 TMVr, 102 GDMT) had PASP of ≥50 mm Hg (mean: 59.1 ± 8.8 mm Hg) and 344 (171 TMVr, 173 GDMT) had PASP of <50 mm Hg (mean: 36.3 ± 8.1 mm Hg). Patients with PASP of ≥50 mm Hg had higher 2-year rates of death or HF hospitalization (HFH) compared to those with PASP of <50 mm Hg (68.8% vs. 49.1%; adjusted hazard ratio: 1.52; 95% confidence interval: 1.17 to 1.97; p = 0.002). Rates of death or HFH were reduced by TMVr versus GDMT alone, irrespective of baseline PASP ($p_{interaction}$ = 0.45). TMVr reduced PASP from baseline to 30 days to a greater than GDMT alone (adjusted least squares mean: -4.0 vs. -0.9 mm Hg; p = 0.006), a change that was associated with reduced risk of death or HFH between 30 days and 2 years (adjusted hazard ratio: 0.91 per -5 mm Hg PASP; 95% confidence interval: 0.86 to 0.96; p = 0.0009).

CONCLUSIONS Elevated PASP is associated with a worse prognosis in patients with HF with severe SMR. TMVr with the MitraClip reduced 30-day PASP and 2-year rates of death or HFH compared with GDMT alone, irrespective of PASP. (J Am Coll Cardiol 2020;76:2595-606) © 2020 by the American College of Cardiology Foundation.

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From the [a]Cardiovascular Research Foundation, New York, New York; [b]Columbia University Medical Center/NewYork-Presbyterian Hospital, New York, New York; [c]Medstar Health Research Institute, Washington, DC; [d]Cleveland Clinic, Cleveland, Ohio; [e]Baylor Scott & White Health, Plano, Texas; [f]Los Robles Regional Medical Center, Thousand Oaks, California; [g]University of Virginia, Charlottesville, Virginia; [h]Vanderbilt University Medical Center, Nashville, Tennessee; [i]Ohio State University Medical Center, Columbus, Ohio; and [j]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York. *Drs. Ben-Yehuda and Shahim contributed equally to this work. Alexander Opotowsky, MD, MMSc, served as Guest Associate Editor for this paper. Deepak L. Bhatt, MD, MPH, served as Guest Editor-in-Chief for this paper.
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ABBREVIATIONS AND ACRONYMS

GDMT = guideline-directed medical therapy

HF = heart failure

HFH = heart failure hospitalization

HR = hazard ratio

IVC = inferior vena cava

LVEF = left ventricular ejection fraction

LVESD = left ventricular end-systolic diameter

MR = mitral regurgitation

PASP = pulmonary artery systolic pressure

PHTN = pulmonary hypertension

RAP = right arterial pressure

RV = right ventricular

TMVr = transcatheter mitral valve repair

Pulmonary hypertension (PHTN) is present in 15% to 30% of patients with mitral regurgitation (MR) and may occur in up to 64% of patients with MR with New York Heart Association functional class III or IV status (1,2). Current guidelines provide a Class IIa recommendation for mitral valve surgery in patients with primary (degenerative) MR and pulmonary artery systolic pressure (PASP) of >50 mm Hg, although surgical risks are increased with PHTN (3,4). In contrast, surgical interventions have not been shown to be beneficial in patients with heart failure (HF) and severe MR secondary to left ventricular dysfunction who remain symptomatic despite optimal medical therapy, regardless of PASP levels (3,4). Recent uncontrolled single-center and registry-based studies (mostly in patients with degenerative MR) suggest that edge-to-edge transcatheter mitral valve repair (TMVr) with the MitraClip (Abbott, Santa Clara, California) is safe and may improve outcomes in high-surgical risk patients with PHTN (5–7). Less evidence supports TMVr treatment of severe MR in patients with HF with PHTN.

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The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial demonstrated reduced rates of HF hospitalization (HFH) and improved survival in patients with HF with moderate-to-severe or severe secondary MR after TMVr with the MitraClip plus guideline-directed medical therapy (GDMT) compared with GDMT alone. In the present analysis from the COAPT trial, we sought to assess the association between PASP and adverse outcomes in patients with HF and secondary MR undergoing TMVr and to evaluate the effectiveness of TMVr in reducing pulmonary pressures and improving clinical outcomes compared to GDMT alone.

METHODS

STUDY DESIGN. The COAPT trial design (8) and primary results (9) have been previously published. In brief, COAPT (NCT01626079) was a multicenter, randomized, controlled, open-label trial of TMVr with the MitraClip device in patients with HF and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally tolerated GDMT. Patients had a left ventricular ejection fraction (LVEF) between 20% and 50%, left ventricular end-systolic diameter (LVESD) of ≤70 mm, and absence of severe PHTN (defined as pulmonary artery systolic pressure of >70 mm Hg as assessed by echocardiography or right heart catheterization despite vasodilator therapy) or moderate or severe right ventricular (RV) failure. Patients were randomized 1:1 to receive TMVr plus GDMT or GDMT alone and are followed up at regular intervals through 5 years. At the present time, all patients have completed the 2-year follow-up. The protocol was approved by the investigational review board at each participating center, and all patients provided written informed consent.

ECHOCARDIOGRAPHIC CORE LABORATORY ANALYSIS. Transthoracic echocardiograms were performed at baseline and at 1, 6, 12, 18, and 24 months after randomization and were analyzed by an independent core laboratory (MedStar Health Research Institute, Washington, DC). Among patients who were identified as possible trial candidates at the sites, the echocardiographic core laboratory was also responsible for confirming the presence of 3+ or 4+ secondary mitral regurgitation. MR severity was graded by following a pre-specified multiparametric algorithm created for the COAPT trial (10) adapted from the criteria recommended by the American Society of Echocardiography 2003 guidelines (11).

ESTIMATION OF PASP. The maximum peak tricuspid regurgitant velocity was recorded from any view with continuous-wave Doppler imaging and was used to determine the PASP with the simplified Bernoulli equation: PASP = 4 × (peak tricuspid regurgitant velocity) + mean right arterial pressure. The mean right arterial pressure (RAP) was estimated from the inferior vena cava (IVC) diameter and the respiratory changes with inspiration as follows: IVC of <20 mm and collapses of >50% = RAP of 5 mm Hg; IVC of <20 mm and collapses of <50% = RAP of 10 mm Hg; IVC of >20 mm and collapses of >50% = RAP of 15 mm Hg; and IVC of >20 mm and collapses of <50% = RAP of 20 mm Hg. PASP was assumed to equate to the RV systolic pressure in the absence of pulmonic stenosis or RV outflow tract obstruction.

Substantially increased PASP was defined as PASP of ≥50 mm Hg based on current guidelines recommending surgery as a Class IIa indication in patients with severe primary MR (3,4) given evidence that PASP of ≥50 mm Hg is associated with worse short- and long-term outcomes with conservative care in such patients (7,12–14). The impact of PASP was also analyzed as a continuous variable.

TABLE 1 Clinical and Laboratory Characteristics of the Patients According to Baseline PASP

	PASP of ≥50 mm Hg (n = 184)	PASP of <50 mm Hg (n = 344)	p Value
Clinical			
Age, yrs	72.9 ± 10.8	71.7 ± 11.9	0.26
Female	30.4 (56/184)	40.4 (139/344)	0.02
BMI, kg/m^2	26.3 ± 5.3	27.2 ± 5.8	0.09
Diabetes	42.9 (79/184)	33.1 (114/344)	0.03
Hypertension	80.4 (148/184)	79.9 (275/344)	0.89
Hypercholesterolemia	50.5 (93/184)	54.1 (186/344)	0.44
Previous myocardial infarction	53.8 (99/184)	48.8 (168/344)	0.28
Previous percutaneous coronary intervention	45.1 (83/184)	46.5 (160/344)	0.76
Previous coronary artery bypass grafting	43.5 (80/184)	38.7 (133/344)	0.28
Previous stroke or transient ischemic attack	10.3 (19/184)	13.7 (47/344)	0.27
Peripheral vascular disease	20.1 (37/184)	18.3 (63/344)	0.62
Chronic obstructive pulmonary disease	22.3 (41/184)	24.7 (85/344)	0.53
History of atrial fibrillation or flutter	56.0 (103/184)	53.8 (185/344)	0.63
Creatinine clearance, ml/minute	44.5 ± 23.7	52.1 ± 28.6	0.002
History of anemia	30.4 (56/184)	20.3 (70/344)	0.01
Society of Thoracic Surgeons score	9.2 ± 5.9	7.7 ± 5.9	0.004
Related to heart failure			
Cause of cardiomyopathy			
Ischemic	63.6 (117/184)	59.0 (203/344)	0.31
Nonischemic	36.4 (67/184)	41.0 (141/344)	0.31
New York Heart Association functional class			
I	0.0 (0/183)	0.3 (1/344)	0.47
II	36.1 (66/183)	37.5 (129/344)	0.75
III	53.6 (98/183)	55.2 (190/344)	0.71
IVa (ambulatory)	10.4 (19/183)	7.0 (24/344)	0.17
Hospitalization for heart failure within 1 year	57.1 (105/184)	59.9 (206/344)	0.53
Previous cardiac resynchronization therapy	37.5 (69/184)	35.5 (122/344)	0.64
Previous implantation of defibrillator	58.2 (107/184)	64.2 (221/344)	0.17
B-type natriuretic peptide level, pg/ml	1,390.0 (1,473.5)	863.0 (941.9)	<0.0001
N-terminal pro-B-type natriuretic peptide level, pg/ml	7,427.7 ± 9,497.8	4,698.0 ± 6,364.4	0.05

Values are mean ± SD or % (n/N).
BMI = body mass index; PASP = pulmonary artery systolic pressure.

STATISTICAL ANALYSIS. Patients were grouped according to PASP of <50 mm Hg versus ≥50 mm Hg. Baseline characteristics were summarized with mean ± SD or median (interquartile range) for continuous measures and proportions for categorical variables. Between treatment groups, variables were compared with Student's *t*-test for the continuous measures and chi-square or Fisher exact test for categorical variables. Changes in continuous echocardiographic parameters over time were calculated as the difference between the baseline and follow-up visits. Analysis of covariance was performed to compare mean changes in PASP over time adjusted for baseline values. For time to first event analyses, event rates were estimated by the Kaplan-Meier method and compared with Cox regression. Multivariable Cox proportional hazards models were adjusted for the following covariates based on their previously established relationship to prognosis in HF: age, sex, diabetes mellitus, hypertension, hypercholesterolemia, prior myocardial infarction, coronary artery disease, prior atrial fibrillation, chronic obstructive pulmonary disease, history of anemia, creatinine clearance of ≤60 ml/min, New York Heart Association funtional classification III or IV, LVEF, LVESD, MR severity, and randomized treatment. In addition, interaction terms between PASP categories and treatment assignment were included to assess whether the effect of TMVR plus GDMT versus GDMT alone differed according to PASP status. Nonlinear relationships between PASP and the risk of clinical outcomes were explored by using penalized splines with 2 degrees of freedom (15). All p values are 2-tailed, and $p < 0.05$ was considered significant for all analyses. Statistical analyses were performed by using SAS 9.4 (SAS Institute, Cary, North Carolina).

TABLE 2 Echocardiographic Core Laboratory Measures According to Baseline PASP

	PASP of ≥50 mm Hg (n = 184)	PASP of <50 mm Hg (n = 344)	p Value
Pulmonary artery systolic pressure, mm Hg	59.1 ± 8.8	36.3 ± 8.1	<0.0001
Severity of mitral regurgitation			
Moderate to severe (3+)	40.8 (75/184)	55.5 (191/344)	0.001
Severe (4+)	59.2 (109/184)	44.5 (153/344)	0.001
Effective regurgitant orifice area, cm^2	0.42 ± 0.15	0.41 ± 0.16	0.36
Left ventricular end-systolic dimension, cm	5.2 ± 0.9	5.3 ± 0.8	0.31
Left ventricular end-diastolic dimension, cm	6.1 ± 0.7	6.2 ± 0.7	0.39
Left ventricular end-systolic volume, ml	131.0 ± 57.3	136.0 ± 59.4	0.37
Left ventricular end-diastolic volume, ml	188.7 ± 68.4	194.9 ± 73.9	0.36
Left ventricular ejection fraction, mean, %	32.0 ± 10.1	31.3 ± 8.9	0.39
≤40%	80.2 (138/172)	82.0 (268/327)	0.64
Tricuspid regurgitation			
None: 0	1.1 (2/182)	0.9 (3/340)	0.81
Mild: 1+	73.1 (133/182)	85.0 (289/340)	0.001
Moderate: 2+	24.7 (45/182)	12.9 (44/340)	0.0006
Moderate to severe: 3+	1.1 (2/182)	0.9 (3/340)	0.81
Severe: 4+	0.0 (0/182)	0.3 (1/340)	0.46
Left atrial volume, ml	93.8 ± 43.2	90.4 ± 38.9	0.35

Values are mean ± SD or % (n/N).
PASP = pulmonary artery systolic pressure.

RESULTS

STUDY POPULATION AND PATIENT CHARACTERISTICS. Between December 2012 and June 2017, 614 patients were enrolled in COAPT at 78 centers in the United States and Canada: 302 were randomized to TMVr with the MitraClip plus GDMT and 312 to GDMT alone. Baseline PASP values could be assessed in the echocardiographic core laboratory in 528 (86.0%) patients, constituting the current study population. The distribution of PASP was non-normal and left skewed (Supplemental Figure 1) with a median of 43.1 mm Hg (interquartile range: 34.0 to 53.0), ranging from 13.0 to 112.0 mm Hg. PASP was substantially elevated (≥50 mm Hg) in 184 of 528 patients (34.8%). The mean age of the cohort was 72.1 ± 11.5 years, 63.1% were men, and the mean LVEF was 31.6% ± 9.4%.

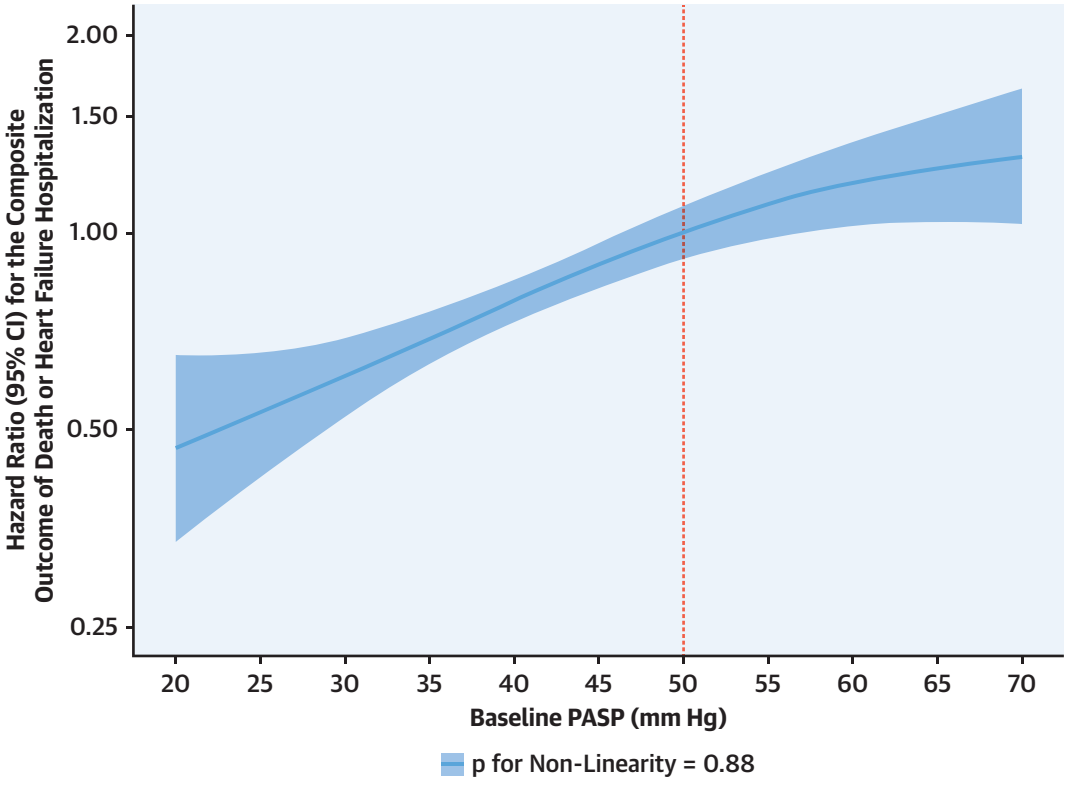
The baseline characteristics of patients with PASP of ≥50 mm Hg (n = 184) and PASP of <50 mm Hg (n = 344) are shown in Tables 1 and 2. Patients with PASP of ≥50 mm Hg were more frequently male and more frequently had diabetes and a history of anemia, had higher mean N-terminal pro-B-type natriuretic peptide levels and higher Society of Thoracic Surgeons operative risk scores. Patients with PASP of ≥50 mm Hg also were more likely to have severe (4+) MR and moderate (vs. mild) tricuspid regurgitation. At baseline, fewer patients with PASP of ≥50 mm Hg were treated with antagonists of the renin-angiotensin system, but this difference did not remain significant during the course of the study (Supplemental Table 1). The baseline characteristics of patients excluded because of an absent baseline PASP value were similar to the characteristics of those

TABLE 3 2-Year Risks of Adverse Outcomes According to Baseline PASP in All Patients

	PASP of ≥50 mm Hg (n = 184)	PASP of <50 mm Hg (n = 344)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Death or hospitalization for heart failure	68.8 (124)	49.1 (163)	1.70 (1.34–2.14)	<0.0001	1.52 (1.17–1.97)	0.002
Death	48.1 (85)	29.9 (97)	1.86 (1.39–2.49)	<0.0001	1.57 (1.14–2.16)	0.006
Cardiovascular death	41.3 (69)	23.8 (74)	1.98 (1.43–2.75)	<0.0001	1.70 (1.19–2.45)	0.004
Noncardiovascular death	11.6 (16)	7.9 (23)	1.47 (0.78–2.79)	0.23	1.15 (0.56–2.36)	0.70
Hospitalization for heart failure	56.9 (92)	39.2 (122)	1.67 (1.27–2.18)	0.0002	1.46 (1.08–1.97)	0.02

Values are Kaplan-Meier estimates, % (n), unless otherwise indicated.
CI = confidence interval; HR = hazard ratio; PASP = pulmonary artery systolic pressure.

FIGURE 1 Unadjusted Association Between Baseline Pulmonary Artery Systolic Pressure as a Continuous Variable and the Relative Hazard of 2-Year Death or Heart Failure Hospitalization in All Patients



HRs are referenced to a PASP value of 50 mm Hg where the hazard ratio is set to 1. PASP was <20 mm Hg or >70 mm Hg in 4% (21 of 528) of patients; data for these PASP values are not shown given the small sample sizes. **Shaded areas** represent the 95% CIs for the HR at each pressure. The p values refer to the linear term for log (PASP). The p value of 0.88 is consistent with the relationship being linear.
CI = confidence interval; HR = hazard ratio; PASP = pulmonary artery systolic pressure.

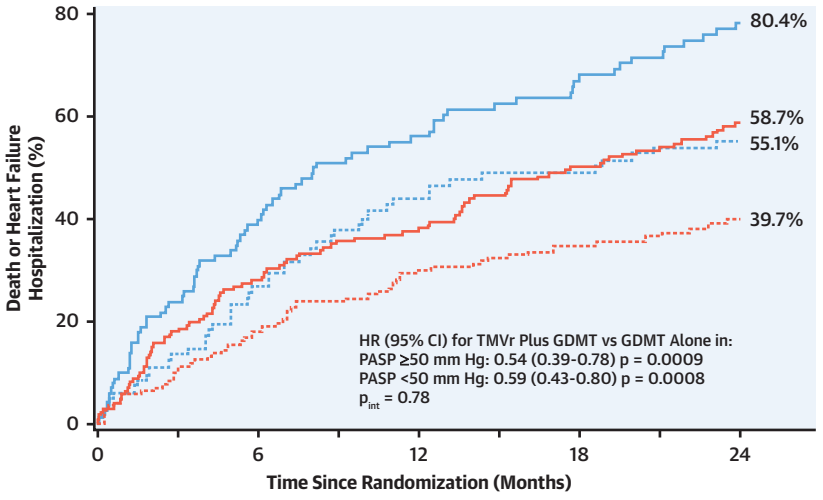
who were included in the present study (Supplemental Table 2).

CLINICAL OUTCOMES ACCORDING TO BASELINE PASP. The median duration of follow-up for the entire cohort was 24.0 months (interquartile range: 10.9 to 35.9 months). In the entire study population, compared with patients with baseline PASP of <50 mm Hg, patients with PASP of ≥50 mm Hg had higher unadjusted (hazard ratio [HR]: 1.70; 95% CI: 1.34 to 2.14; p < 0.0001) and adjusted (HR: 1.52; 95% CI: 1.17 to 1.97; p = 0.002) risks of the 2-year composite endpoint of death or HFH. The 2-year risks of death, cardiovascular death, and HFH were also increased in patients with higher baseline PASP (**Table 3**). The association between PASP and the risk of adverse outcomes was similar when PASP was modeled as a continuous variable (**Figure 1**, Supplemental Figure 2). The relationship was linear; every 10-mm Hg increase in PASP was associated with an 18% increase in the 2-year risk of death or HFH (adjusted HR: 1.18; 95% CI: 1.08 to 1.30; p = 0.0004). This prognostic relationship was present in patients treated with TMVr plus GDMT as well as GDMT alone (Supplemental Figure 3).

CLINICAL OUTCOMES ACCORDING TO TREATMENT COHORT. Compared with GDMT alone, TMVr plus GDMT consistently reduced the 2-year rates of the composite endpoint of death or HFH in patients with baseline PASP of <50 mm Hg (adjusted HR: 0.59; 95% CI: 0.42 to 0.82) and ≥50 mm Hg (adjusted HR: 0.48; 95% CI: 0.32 to 0.72) ($p_{interaction} = 0.45$) (**Central Illustration**, A, **Table 4**). The benefits of TMVr in reducing the 2-year risk of death or HFH were

CENTRAL ILLUSTRATION **2-Year Rates of the Composite Outcome of Death or Heart Failure Hospitalization in Patients With Heart Failure With Secondary Mitral Regurgitation Randomized to Transcatheter Mitral Valve Repair Plus Guideline-Directed Medical Therapy Versus Guideline-Directed Medical Therapy Alone**

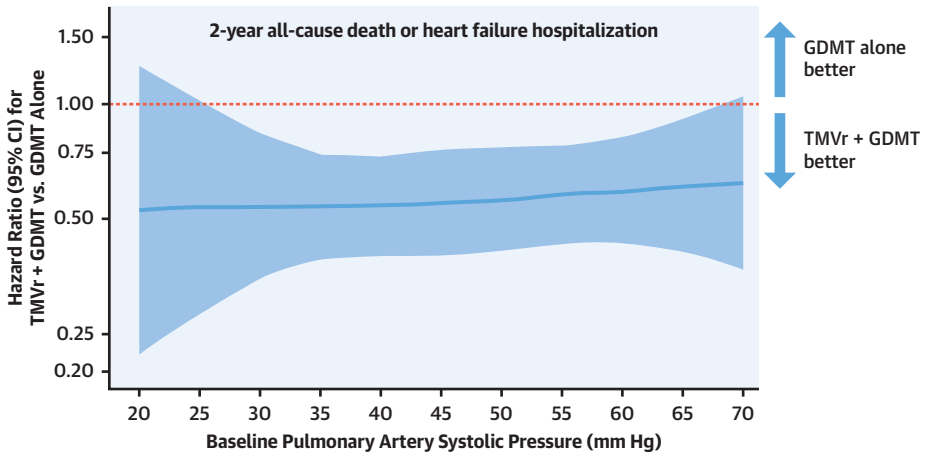
A



No. at risk:

PASP ≥50 mm Hg TMVr Plus GDMT	82	60	45	41	34
PASP ≥50 mm Hg GDMT Alone	102	61	41	30	19
PASP <50 mm Hg TMVr Plus GDMT	171	137	117	107	92
PASP <50 mm Hg GDMT Alone	173	124	99	77	58

B



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(A) Kaplan-Meier time to first event rates for the composite of death or HFH in patients with substantial PHTN (≥50 mm Hg) and without substantial PHTN (<50 mm Hg). The reduction in death or HFH after treatment with MitraClip plus GDMT versus GDMT alone was consistent in patients with and without substantial PHTN ($p_{interaction}$ = 0.78). **(B)** Unadjusted 2-year relative risk for the composite outcome of death or HFH after treatment with MitraClip plus GDMT versus GDMT alone according to baseline PASP as a continuous variable. **Shaded areas** represent the 95% CIs for the HR at each baseline PASP. The shaded interval being completely below the **dashed horizontal line** is consistent with the upper bound of the 95% CI of the HR being <1. PASP was <20 mm Hg or >70 mm Hg in 4% (21 of 528) of patients; data for these PASP values are not shown given the small sample sizes. The linear HR relationship demonstrates that MitraClip plus GDMT reduced the rates of death or HFH consistently across the range of PASP enrolled in the COAPT trial. CI = confidence interval; GDMT = guideline-directed medical therapy; HFH = heart failure hospitalization; HR = hazard ratio; PASP = pulmonary artery systolic pressure; PHTN = pulmonary hypertension; TMVr = transcatheter mitral valve repair with the MitraClip.

TABLE 4 Two-Year Risks of Adverse Outcomes According to Baseline PASP and Randomized Treatment

	PASP of <50 mm Hg			PASP of ≥50 mm Hg			
	TMVr Plus GDMT (n = 171)	GDMT Alone (n = 173)	Adjusted HR (95% CI)	TMVr Plus GDMT (n = 82)	GDMT Alone (n = 102)	Adjusted HR (95% CI)	$p_{interaction}$
Death or hospitalization for heart failure	39.7 (66)	58.7 (97)	0.59 (0.42–0.82)	55.1 (45)	80.4 (79)	0.48 (0.32–0.72)	0.45
Death	26.2 (43)	33.7 (54)	0.69 (0.45–1.05)	38.0 (31)	57.1 (54)	0.58 (0.36–0.93)	0.60
Cardiovascular death	20.4 (32)	27.3 (42)	0.67 (0.41–1.10)	30.4 (23)	50.7 (46)	0.49 (0.28–0.84)	0.39
Noncardiovascular death	7.2 (11)	8.8 (12)	0.73 (0.30–1.78)	11.0 (8)	13.1 (8)	1.17 (0.40–3.45)	0.52
Hospitalization for heart failure	29.9 (46)	48.4 (76)	0.51 (0.35–0.75)	41.5 (30)	70.2 (62)	0.38 (0.23–0.61)	0.32

Values are Kaplan-Meier estimates, % (n), unless otherwise indicated.

GDMT = guideline-directed medical therapy; TMVr = transcatheter mitral valve repair; other abbreviations as in Table 3.

consistent across the range of baseline PASP studied (Central Illustration, B). Similarly, the beneficial effects of TMVr in reducing the individual outcomes of death, cardiovascular death, and HFH were consistent in patients with and without substantial PHTN (Figures 2 and 3, Table 4). The treatment effects of TMVr compared with GDMT alone were consistent in the patients who were excluded because of an absent baseline PASP value and those who were included in the present study (Supplemental Table 3).

IMPACT OF EARLY CHANGES IN PASP FROM BASELINE TO 30 DAYS. At 1 month, 198 of 253 patients (78.3%) randomized to TMVr and 212 of 275 patients (77.1%) randomized to GDMT alone were alive and had adequate assessment of PASP in the echocardiographic core laboratory. Mean PASPs at 1 month were 40.3 ± 11.9 mm Hg and 43.9 ± 14.0 mm Hg, respectively. The paired least squares mean change in PASP from baseline to 30 days was -4.0 ± 0.8 mm Hg (n = 198) after TMVr and -0.9 ± 0.8 mm Hg (n = 212) after GDMT (difference between groups: -3.1 ± 1.1 mm Hg; p = 0.006). A reduction in PASP from baseline to 30 days was independently associated with a reduced risk of the composite outcome of death or HFH between 30 days and 2 years in both treatment cohorts (Table 5).

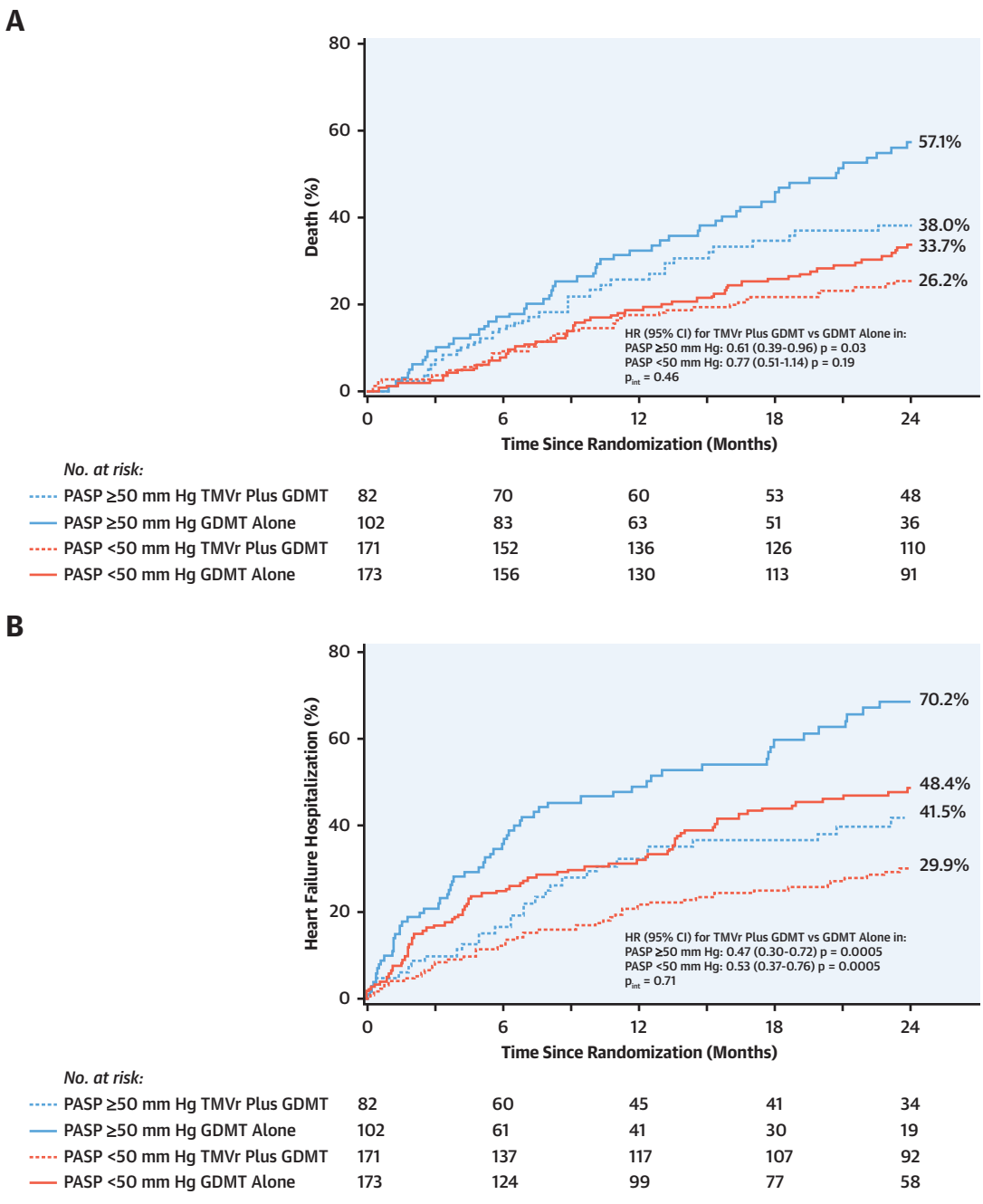
DISCUSSION

The major findings of the present analysis from the COAPT trial, in which patients with HF and moderate-to-severe or severe secondary MR were randomized to TMVr with the MitraClip plus GDMT or GDMT alone, are as follows. 1) Substantially elevated estimated PASP at baseline was associated with a higher 2-year risk of the composite endpoint of death or HFH, as well as death and HFH individually, with similar adverse effects in patients treated with TMVr plus GDMT and GDMT alone. 2) TMVr was associated with a reduction in estimated PASP within the first 30 days following treatment, a reduction that was independently associated with reduced 30-day to 2-year rates of death or HFH. 3) The beneficial effects of treatment with TMVr plus GDMT compared with GDMT alone were consistent in patients with and without a substantial elevation in estimated baseline PASP and were evident across the range of PASPs seen in the trial.

The finding that elevated PASP (≥50 mm Hg) at baseline conferred worse outcomes at 2 years in patients with HF and secondary MR extends the results of previous single-center and registry-based studies (5–7). The magnitudes of the mortality risk associated with substantially elevated PASP levels were similar in those reports to that seen in the present study. However, those earlier studies did not take into account the etiology of MR (primary vs. secondary) or the severity of MR and lacked data on post-procedure pulmonary pressures. To our knowledge, the present analysis is the first large, multicenter, randomized clinical trial demonstrating that baseline PHTN is a strong negative prognostic factor in patients with HF and secondary MR. In this regard, elevated PASP was not only associated with a worse prognosis when categorized as a dichotomous variable of ≥50 mm Hg; a linear increase in the risk of death or HFH with continuously increasing PASP was apparent. After adjustment for baseline covariates, every 10-mm Hg increase in baseline PASP was associated with an 18% increase in the 2-year risk of death or HFH. These findings emphasize the arbitrary nature of the threshold of 50 mm Hg in PASP as indication for mitral valve surgery that has been present in the guidelines for the management of valvular heart disease since 1998 (16). There are few data to support such a dichotomous cutpoint.

Importantly, a reduction in PASP from baseline to 30 days (whether achieved by TMVr or GDMT) was independently associated with reduced rates of death or HFH from 30 days to 2 years in both the TMVr and

FIGURE 2 Kaplan-Meier Time to First Event Analyses According to Baseline PASP and Randomized Therapy

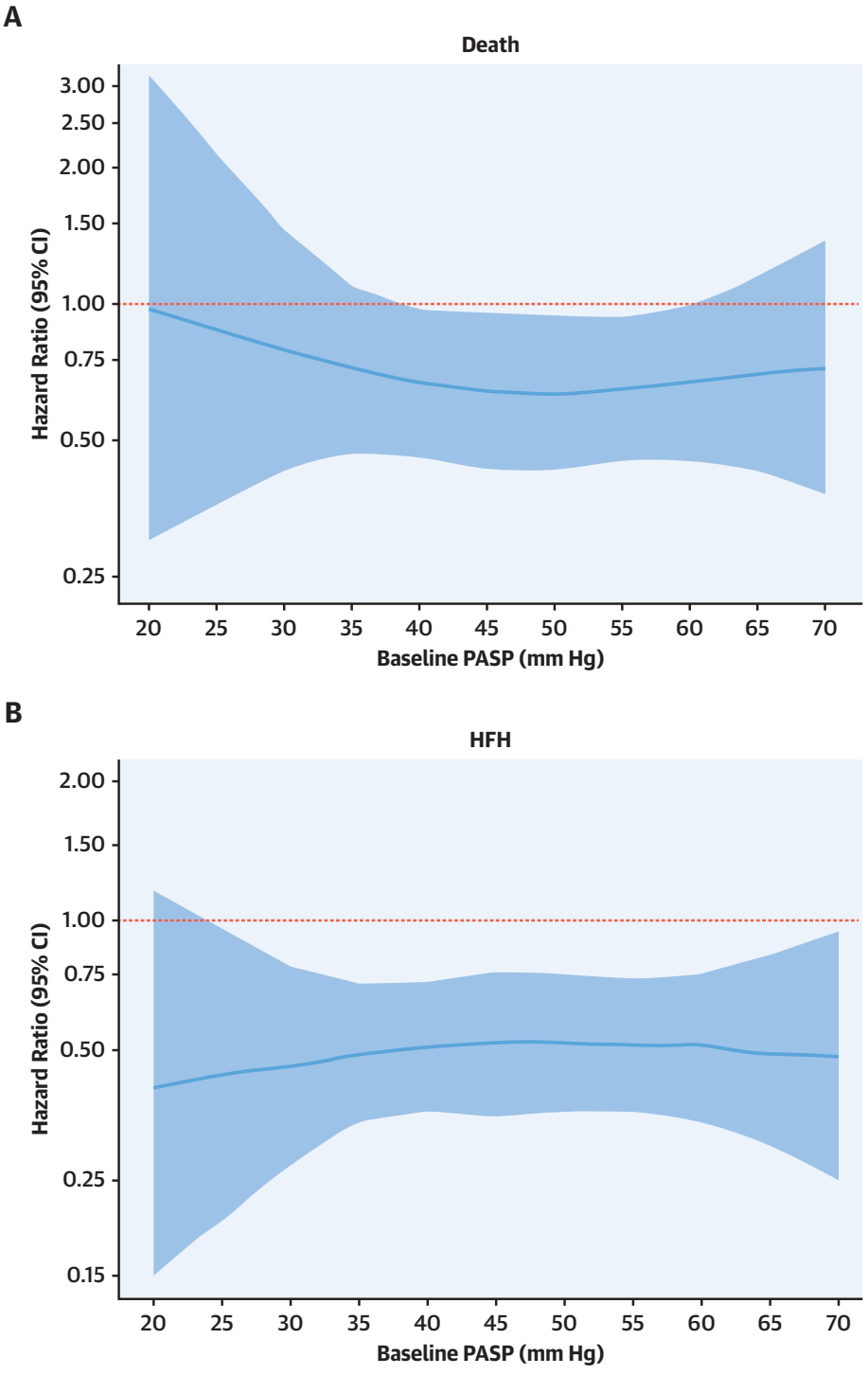


(A) Death. **(B)** Heart failure hospitalization. CI = confidence interval; GDMT = guideline-directed medical therapy; HR = hazard ratio; PASP = pulmonary artery systolic pressure; TMVr = transcatheter mitral valve repair.

GDMT-alone arms. TMVr reduced PASP at 30 days to a greater degree than GDMT alone, which likely contributed to the marked 2-year improvement in prognosis in patients with HF treated with the MitraClip in the COAPT trial.

The underlying pathogenesis of PHTN in left-sided heart failure is complex and frequently multifactorial (17). Elevated left atrial filling pressure, which occurs as a consequence of systolic, diastolic, or valvular heart disease, contributes directly to elevations in

FIGURE 3 Unadjusted 2-Year HRs of Treatment With TMVr Compared With GDMT Alone According to Baseline PASP as a Continuous Variable



(A) Death. **(B)** Heart failure hospitalization (HFH). The benefits with TMVr were consistent across the range of pulmonary artery pressures studied in the trial, although few patients had low or very high pulmonary pressures, and as such, the CIs are wide at the extremes. **Shaded areas** represent the 95% CIs for the HR at each baseline PASP. PASP was <20 mm Hg or >70 mm Hg in 4% (21 of 528) of patients; data for these PASP values are not shown given the small sample sizes. Abbreviations as in Figures 1 and 2.

TABLE 5 Risks of Adverse Outcomes Between 30 Days and 2 Years Associated With a 5-mm Hg Decrease in PASP From Baseline to 30 Days

	Unadjusted HR (95% CI)	$p_{unadjusted}$	Adjusted HR (95% CI)	$p_{adjusted}$
Death or hospitalization for heart failure	0.89 (0.84–0.94)	<0.0001	0.91 (0.86–0.96)	0.0009
Death	0.92 (0.85–0.99)	0.02	0.94 (0.88–1.02)	0.12
Cardiovascular death	0.90 (0.83–0.97)	0.01	0.92 (0.85–1.01)	0.07
Hospitalization for heart failure	0.88 (0.83–0.94)	<0.0001	0.90 (0.85–0.96)	0.002

There were no significant interactions between the effects of the reduction in PASP from baseline to 30 days and randomization to TMVR plus GDMT versus GDMT alone of the 30-day to 2-year rates of composite death or hospitalization for heart failure, death, cardiovascular death, or hospitalization for heart failure (p values for interaction = 0.96, 0.97, 0.57, and 0.66, respectively). The following covariates were included in the adjusted model: age, sex, diabetes mellitus, hypertension, hypercholesterolemia, prior myocardial infarction, coronary artery disease, prior atrial fibrillation, chronic obstructive pulmonary disease, history of anemia, creatinine clearance ≤60 ml/min, New York Heart Association functional classification III or IV, left ventricular ejection fraction, left ventricular end-systolic diameter, mitral regurgitation severity, and randomized treatment.

Abbreviations as in Tables 3 and 4.

pulmonary venous pressure through passive transmission (18). At later stages of PHTN, some patients may have a combination of a passive component resulting from pulmonary venous hypertension and a pre-capillary component driven by structural and functional changes in the pulmonary arterial vessels caused by chronically elevated pressures (19,20). Distal pulmonary arteries may be affected by intimal fibrosis and medial hypertrophy, which may lead to a fixed component of elevated pulmonary pressures (19,20). Both pre- and post-capillary PHTN can cause RV dilatation and hypertrophy, which, in turn, might lead to severe tricuspid regurgitation, further exacerbating RV dysfunction (21). Even at this late stage of PHTN, PASP might be reduced by effective treatment of MR, as seen in some surgical studies (22–24). However, long-term studies regarding changes in pulmonary pressures after surgery are limited. The persistence of significant PHTN after mitral valve intervention may be due to residual MR, persistent systolic and diastolic dysfunction, and/or as chronic microvascular changes. Patients with severe fixed PHTN (unresponsive to active vasodilator therapy in the catheterization lab) and those with moderate or severe RV dysfunction were excluded from COAPT. Whether MitraClip treatment of severe MR would be safe and effective in these patients cannot be answered by the present study. However, the relative TMVr-induced reductions in death and HFH were consistent over the range of PASPs included in the COAPT trial, although the absolute benefits were greater in higher-risk patients with PHTN.

STUDY LIMITATIONS. PASP was not measured by right heart catheterization, which is the gold standard; however, the correlation with echocardiography measurements is strong, and therefore, echocardiography is the standard clinical tool for evaluating pulmonary hypertension in patients with HF, particularly in the outpatient arena. In 6 studies of patients with left heart disease, the r value was 0.83 (25). Moreover, when echocardiography estimations were made within 1 day of right heart catheterization, there was a strong correlation (r = 0.88). Second, because of limitations of echocardiography in assessing PASP, 14% of patients in the COAPT trial had missing baseline PASP values and were excluded from the analysis. Third, all COAPT patients were symptomatic (New York Heart Association functional classes II, III, or IVa) despite the use of maximally tolerated doses of GDMT (with more than one-third of patients having undergone cardiac resynchronization therapy) and had 3+ or 4+ secondary MR, LVEF of 20% to 50%, and frequent comorbidities. Whether the MitraClip would have similar effects on PASP and prognosis in patients who are less or more critically ill than those studied is unknown. Furthermore, PASP of >70 mm Hg based on echocardiography or right heart catheterization was an exclusion criterion, unless active systemic vasodilator therapy in the catheterization laboratory demonstrated a substantial reduction in pulmonary vascular resistance to vasodilator challenge. Our results, therefore, may not apply to patients with severe fixed PHTN unresponsive to vasodilator therapy. Our results also do not apply to use of non-MitraClip TMVr or replacement technologies or to patients with degenerative MR. Finally, longer-term follow-up (currently planned for 5 years) is necessary to determine the durability and long-term impact of the MitraClip in patients with HF and secondary MR complicated by PHTN.

CONCLUSIONS

In the COAPT trial, patients with HF with moderate-to-severe or severe secondary MR had a progressively worse prognosis with increasing PASP. TMVr with the MitraClip reduced PASP to a greater degree than GDMT alone. An early reduction in PASP was a strong independent predictor of improved long-term clinical outcomes. Finally, TMVr resulted in reduced

2-year rates of death and HFH, regardless of baseline PASP.

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AUTHOR DISCLOSURES

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ADDRESS FOR CORRESPONDENCE: Dr. Ori Ben-Yehuda, Cardiovascular Research Foundation, 1700 Broadway, 9th Floor, New York, New York 10019. E-mail: obenyehuda@crf.org.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with severe secondary MR and PHTN, TMVr with the MitraClip is associated with more favorable 2-year outcomes than guideline-directed medical therapy alone.

TRANSLATIONAL OUTLOOK: Future research is needed to evaluate the longer-term impact of TMVr in patients with heart failure and PHTN and to identify additional therapies to improve outcomes in this high-risk cohort.

REFERENCES

1. Maeder MT, Weber L, Buser M, et al. Pulmonary hypertension in aortic and mitral valve disease. Front Cardiovasc Med 2018;5:40.

2. Inohara T, Vemulapalli S. Percutaneous edge-to-edge leaflet repair: a solution to the risk-treatment paradox of mitral regurgitation complicated by pulmonary hypertension? Eur J Heart Fail 2018;20:595–7.

3. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67–119.

4. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70:252–89.

5. Ahmed A, Akintoye E, Adegbala O, et al. In-hospital outcomes of transcatheter mitral valve repair with MitraClip in patients with pulmonary hypertension: insights from the National Inpatient Sample. Catheter Cardiovasc Interv 2019;94:E30–6.

6. Al-Bawardy R, Vemulapalli S, Thourani VH, et al. Association of pulmonary hypertension with clinical outcomes of transcatheter mitral valve repair. JAMA Cardiol 2019;5:47–56.

7. Tigges E, Blankenberg S, von Bardeleben RS, et al. Implication of pulmonary hypertension in patients undergoing MitraClip therapy: results from the German transcatheter mitral valve interventions (TRAMI) registry. Eur J Heart Fail 2018;20:585–94.

8. Mack MJ, Abraham WT, Lindenfeld J, et al. Cardiovascular outcomes assessment of the MitraClip in patients with heart failure and secondary mitral regurgitation: design and rationale of the COAPT trial. Am Heart J 2018;205:1–11.

9. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018;379:2307–18.

10. Asch FM, Grayburn PA, Siegel RJ, et al. Echocardiographic outcomes after transcatheter leaflet approximation in patients with secondary mitral regurgitation: the COAPT trial. J Am Coll Cardiol 2019;74:2969–79.

11. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.

12. Barbieri A, Bursi F, Grigioni F, et al. Prognostic and therapeutic implications of pulmonary hypertension complicating degenerative mitral regurgitation due to flail leaflet: a multicenter long-term international study. Eur Heart J 2011;32:751–9.

13. Ghoreishi M, Evans CF, DeFilippi CR, et al. Pulmonary hypertension adversely affects short- and long-term survival after mitral valve operation for mitral regurgitation: implications for timing of surgery. J Thorac Cardiovasc Surg 2011;142:1439–52.

14. Matsumoto T, Nakamura M, Yeow WL, et al. Impact of pulmonary hypertension on outcomes in patients with functional mitral regurgitation undergoing percutaneous edge-to-edge repair. Am J Cardiol 2014;114:1735–9.

15. Eilers, PHC, Marx BD. Flexible smoothing with B-splines and penalties. Statist Sci 1996;11:89–121.

16. Crawford MH, Souchek J, Oprian CA, et al. Determinants of survival and left ventricular performance after mitral valve replacement. Department of Veterans Affairs Cooperative Study on Valvular Heart Disease. Circulation 1990;81:1173–81.

17. Magne J, Pibarot P, Sengupta PP, Donal E, Rosenhek R, Lancellotti P. Pulmonary hypertension in valvular disease: a comprehensive review on pathophysiology to therapy from the HAVEC Group. J Am Coll Cardiol Img 2015;8:83–99.

18. Greiner S, Jud A, Aurich M, et al. Reliability of noninvasive assessment of systolic pulmonary artery pressure by Doppler echocardiography compared to right heart catheterization: analysis in a large patient population. J Am Heart Assoc 2014;3:e001103.

19. Ben-Yehuda O, Rubin LJ. Pulmonary hypertension overlap syndromes: A real entity? J Am Coll Cardiol 2016;68:379–81.

20. Pietra GG, Capron F, Stewart S, et al. Pathologic assessment of vasculopathies in pulmonary hypertension. J Am Coll Cardiol 2004;43:25S–32S.

21. Magne J, Pibarot P, Sengupta PP, Donal E, Rosenhek R, Lancellotti P. Pulmonary hypertension in valvular disease: a comprehensive review on pathophysiology to therapy from the HAVEC Group. J Am Coll Cardiol Img 2015;8:83–99.

22. Foltz BD, Hessel EA 2nd., Ivey TD. The early course of pulmonary artery hypertension in patients undergoing mitral valve replacement with cardioplegic arrest. J Thorac Cardiovasc Surg 1984;88:238–47.

23. Morrow AG, Oldham HN, Elkins RS, Braunwald E. Prosthetic replacement of the mitral valve. Preoperative and postoperative clinical and hemodynamic assessments in 100 patients. Circulation 1967;35:962–79.

24. Tempe DK, Hasija S, Datt V, et al. Evaluation and comparison of early hemodynamic changes after elective mitral valve replacement in patients with severe and mild pulmonary arterial hypertension. J Cardiothorac Vasc Anesth 2009;23:298–305.

25. Finkelhor RS, Lewis SA, Pillai D. Limitations and strengths of doppler/echo pulmonary artery systolic pressure-right heart catheterization correlations: a systematic literature review. Echocardiography 2015;32:10–8.

KEY WORDS heart failure, mitral regurgitation, mitral valve repair, pulmonary hypertension, transcatheter

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