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Impact of COPD on Outcomes After MitraClip for Secondary Mitral Regurgitation

The COAPT Trial

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ABSTRACT

OBJECTIVES The aim of this study was to examine the relationship between chronic obstructive pulmonary disease (COPD) and outcomes after transcatheter mitral valve repair (TMVr) for severe secondary mitral regurgitation.

BACKGROUND TMVr with the MitraClip improves clinical and health-status outcomes in patients with heart failure and severe (3+ to 4+) secondary mitral regurgitation. Whether these benefits are modified by COPD is unknown.

METHODS COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) was an open-label, multicenter, randomized trial of TMVr plus guideline-directed medical therapy (GDMT) versus GDMT alone. Patients on corticosteroids or continuous oxygen were excluded. Multivariable models were used to examine the associations of COPD with mortality, heart failure hospitalization (HFH), and health status and to test whether COPD modified the benefit of TMVr compared with GDMT.

RESULTS Among 614 patients, 143 (23.2%) had COPD. Among patients treated with TMVr, unadjusted analyses demonstrated increased 2-year mortality in those with COPD (hazard ratio [HR]: 2.08; 95% confidence interval [CI]: 1.33 to 3.26), but this association was attenuated after risk adjustment (adjusted HR: 1.48; 95% CI: 0.87 to 2.52). Although TMVr led to reduced 2-year mortality among patients without COPD (adjusted HR: 0.47; 95% CI: 0.33 to 0.67), for patients with COPD, 2-year all-cause mortality was similar after TMVr versus GDMT alone (adjusted HR: 0.94; 95% CI: 0.54 to 1.65; $p_{int} = 0.04$), findings that reflect offsetting effects on cardiovascular and noncardiovascular mortality. In contrast, TMVr reduced HFH (adjusted HR: 0.48 [95% CI: 0.28 to 0.83] vs. 0.46 [95% CI: 0.34 to 0.63]; $p_{int} = 0.89$) and improved both generic and disease-specific health status to a similar extent compared with GDMT alone in patients with and without COPD ($p_{int} > 0.30$ for all scales).

CONCLUSIONS In the COAPT trial, COPD was associated with attenuation of the survival benefit of TMVr versus GDMT compared with patients without COPD. However, the benefits of TMVr on both HFH and health status were similar regardless of COPD. (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation [The COAPT Trial] [COAPT]; NCT01626079)
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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

COPD = chronic obstructive pulmonary disease

CV = cardiovascular

GDMT = guideline-directed medical therapy

HF = heart failure

HFH = heart failure hospitalization

HR = hazard ratio

KCCQ = Kansas City Cardiomyopathy Questionnaire

QOL = quality of life

SF-36 = Medical Outcomes Study Short Form Health Survey

SMR = secondary mitral regurgitation

TMVr = transcatheter mitral valve repair

Transcatheter mitral valve repair (TMVr) with the MitraClip (Abbott Vascular, Santa Clara, California) improves survival, reduces heart failure hospitalization (HFH), and improves quality of life (QOL) in patients with heart failure (HF) and severe (3+ or 4+) secondary mitral regurgitation (SMR) who remain symptomatic despite maximally tolerated guideline-directed medical therapy (GDMT) (1). Chronic obstructive pulmonary disease (COPD) (2–5) is common among patients with HF and severe SMR, which presents a challenge in diagnosis (i.e., determining the primary etiology of dyspnea) and poses a dilemma in selection of optimal treatment. In particular, patients with COPD may have less survival benefit from invasive treatments because of competing mortality risks; they may also have residual breathlessness and reduced QOL even after treatment for valvular heart disease, a finding that has been noted in patients with COPD undergoing transcatheter aortic valve replacement (6).

To date, little is known about the impact of COPD on either the QOL or survival benefit of MitraClip treatment for patients with HF and severe SMR. Understanding this relationship should help inform the optimal treatment of patients with this challenging combination. To address these this gaps in knowledge, we used data from the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial to evaluate the impact of COPD on survival, HFH, and health status after MitraClip treatment for SMR and whether COPD affects the benefit of TMVr compared with GDMT for such patients.

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METHODS

The COAPT trial design (7) and primary results (1) have been described previously. Briefly, COAPT was a randomized, multicenter, open-label trial of TMVr with the MitraClip device in patients with HF with reduced left ventricular systolic function (ejection fraction 20% to 50%) and moderate to severe (3+) or severe (4+) SMR despite the use of maximally tolerated GDMT. Patients were randomized in a 1:1 fashion to TMVr with the MitraClip plus GDMT versus GDMT alone and were followed for 2 years for clinical and health-status outcomes. The Institutional Review Board at each participating site approved the study, and all patients provided informed, written consent to participate.

Relevant exclusion criteria for the COAPT trial included severe chronic lung disease that required either chronic oral corticosteroid use or continuous home oxygen. Patients treated with inhaled steroids or nighttime-only oxygen were not excluded, however. Additional exclusion criteria included marked left ventricular dilatation (left ventricular end-systolic dimension >7 cm), symptomatic right ventricular HF with moderate or severe right ventricular dysfunction, tricuspid or aortic valve disease requiring surgery or intervention, and severe pulmonary hypertension (pulmonary artery systolic pressure >70 mm Hg, as estimated by echocardiography or measured during right heart catheterization, and unresponsive to vasodilator therapy). All patients were screened by a central eligibility committee prior to enrollment.

OUTCOMES. The primary clinical outcomes of our study were death, HFH, and the composite of death or HFH. In addition, health status was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Medical Outcomes Study Short Form Health Survey (SF-36). The KCCQ is a HF disease-specific health status measure that consists of 23 questions across 5 domains including physical limitation, social limitation, QOL, symptoms, and self-efficacy. The physical limitation, social limitation, symptoms, and QOL domains are combined into an overall summary score, which ranges from 0 to 100, with higher scores indicating better health status and QOL (8). On an individual patient level, changes in the KCCQ overall summary score (KCCQ-OS) of 5, 10, and 20 points are considered small, moderate, and large, respectively (9). The SF-36 is a generic health status measure consisting of a physical component score and a mental component score. Scores are scaled to a mean of 50 for the U.S. population, with a standard deviation of 10, and a change of 2.5 points is considered to be clinically meaningful (10).

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD and were compared using Student's *t*-tests. Categorical variables are presented as counts and proportions and were compared using the chi-square test or Fisher exact test, as appropriate. Event rates for death and the composite of death or HFH were estimated using the Kaplan-Meier method, while rates for HFH were estimated using the cumulative incidence function. The univariate association between COPD and time-to-first event variables was assessed using the log-rank statistic,

except for HFH, which was assessed using a Fine-Gray subdistribution model. For the health-status outcomes, these univariate associations were tested using analysis of covariance, adjusting for baseline values.

Multivariable models were then used to assess whether the presence of baseline COPD was associated with each of the outcomes in the TMVr group. For death and the composite of death or HFH, we used Cox proportional hazards models, and for all other outcomes including HFH, cardiovascular (CV) death and non-CV death, we used Fine-Gray subdistribution models to account for competing risks. For each outcome, we included the following variables: COPD, age, sex, diabetes mellitus, chronic kidney disease, ischemic (vs. nonischemic) etiology of cardiomyopathy, anemia, left ventricular ejection fraction <40% (vs. ≥40%), hypertension, history of stroke or transient ischemia attack, atrial fibrillation, and peripheral vascular disease. Model results are expressed as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses of the continuous health status measures were performed using multiple linear regression including the same covariates, and the effect of COPD was expressed as the adjusted mean value along with its 95% CI. We then used multivariable models to assess whether the presence of COPD modified the treatment effect of TMVr on each of the outcomes within the overall study population. Each of these models was identical to the models used to examine the association of COPD with outcomes in the TMVr group but also included covariates for treatment group and the interaction of COPD with treatment group.

All p values are 2-sided, and p values <0.05 were considered to represent statistical significance without adjustment for multiple comparisons. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

STUDY POPULATION. Between December 2012 and June 2017, a total of 614 patients were enrolled in the COAPT trial, among whom 143 (23.2%) had diagnoses of COPD. Baseline characteristics are shown in Table 1. Patients with COPD had higher Society of Thoracic Surgeons Predicted Risk of Mortality scores and were more likely to have New York Heart Association functional class III or IV HF compared with those without COPD. Patients with COPD were more likely to have coronary artery disease, peripheral vascular disease, ischemic cardiomyopathy, anemia, prior coronary artery bypass grafting, and prior myocardial infarction. In addition, patients with COPD had higher left ventricular ejection fractions and worse baseline disease-specific and generic health status than patients without COPD. The median duration of follow-up was 654 days (interquartile range: 259 to 731 days) for the COPD group and 731 days (interquartile range: 393 to 731 days) for the group without COPD.

TABLE 1 Baseline Characteristics

	COPD (n = 143)	No COPD (n = 471)	p Value
Sociodemographic and clinical characteristics			
Age, yrs	72.2 ± 8.9	72.2 ± 11.8	0.96
Male	95 (66.4)	298 (63.3)	0.49
Body mass index, kg/m^2	26.9 ± 5.7	27.1 ± 6.0	0.70
STS PROM (mitral valve repair)	7.6 ± 5.8	5.2 ± 5.3	<0.001
STS PROM (mitral valve replacement)	9.6 ± 5.9	7.7 ± 5.8	<0.001
NYHA functional class III or IV, %	101 (70.6)	272 (57.9)	0.006
Supplemental oxygen (part-time)	20 (14.0)	0 (0.0)	<0.001
Ischemic cardiomyopathy	98 (68.5)	275 (58.4)	0.03
Diabetes mellitus	63 (44.1)	166 (35.2)	0.056
Coronary artery disease	116 (81.1)	330 (70.1)	0.009
Peripheral vascular disease	45 (31.5)	64 (13.6)	<0.001
Anemia	43 (30.1)	101 (21.4)	0.03
Prior coronary artery bypass graft	68 (47.6)	179 (38.0)	0.04
Prior myocardial infarction	90 (62.9)	226 (48.0)	0.002
Atrial fibrillation	75 (52.4)	252 (53.5)	0.82
Chronic kidney disease	103/140 (73.6)	338/461 (73.3)	0.95
Echocardiographic characteristics			
Left ventricular ejection fraction, %	33 ± 11	31 ± 9	0.009
Left ventricular end-diastolic diameter, cm	6.1 ± 0.7	6.2 ± 0.7	0.29
Left ventricular end-diastolic volume, ml	187 ± 65	194 ± 73	0.31
Effective regurgitant orifice area, cm^2	0.42 ± 0.16	0.41 ± 0.15	0.52
Health status measures			
KCCQ overall summary score	46.1 ± 24.3	54.3 ± 22.3	<0.001
SF-36 physical component score	30.7 ± 9.3	33.4 ± 9.5	0.003
SF-36 mental component score	43.0 ± 13.6	46.9 ± 12.5	0.001
Randomization			
TMVr plus GDMT	71 (49.7)	231 (49.0)	0.90
GDMT alone	72 (50.3)	240 (51.0)	

Values are mean ± SD or n (%).

COPD = chronic obstructive pulmonary disease; GDMT = guideline-directed medical therapy; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association; SF-36 = Medical Outcomes Study Short Form Health Survey; STS PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; TMVr = transcatheter mitral valve repair.

IMPACT OF COPD ON OUTCOMES AFTER TMVr. In unadjusted analyses of patients who were randomized to TMVr plus GDMT, COPD was associated with a greater risk for death and the composite of death or HFH (Table 2). However, after multivariable adjustment, these associations were no longer statistically significant. These findings were unchanged after the addition of tricuspid regurgitation severity, right ventricular systolic pressure, and right ventricular fractional area change to the multivariable model (Supplemental Table 1). Patients with COPD also had lower KCCQ overall summary scores at 1 and 2 years

TABLE 2 Clinical Outcomes in the Transcatheter Mitral Valve Repair Group, Stratified by COPD

	COPD (n = 71)	No COPD (n = 231)	Unadjusted HR or Mean Difference (95% CI)*	Adjusted HR or Mean Difference (95% CI)†	Multivariable p Value
2-yr outcomes					
Death	43.4 (30)	23.5 (53)	2.08 (1.33 to 3.26)	1.48 (0.87 to 2.52)	0.15
HF hospitalization	37.1 (26)	30.4 (69)	1.27 (0.81 to 1.98)	1.06 (0.63 to 1.78)	0.84
Death or HF hospitalization	57.1 (40)	41.0 (93)	1.58 (1.09 to 2.28)	1.15 (0.75 to 1.77)	0.53
Quality-of-life measures					
KCCQ-OS					
1 month	66.7 ± 22.9	72.1 ± 20.5	−5.4 (−11.3 to 0.6)	−6.2 (−12.7 to 0.3)	0.06
1 yr	64.4 ± 25.6	73.9 ± 20.7	−9.6 (−16.6 to −2.5)	−10.4 (−18.1 to −2.7)	0.01
2 yrs	62.9 ± 27.8	73.2 ± 21.9	−10.3 (−19.2 to −1.4)	−9.9 (−19.6 to −0.1)	0.05
SF-36 PCS					
1 month	36.5 ± 9.5	39.9 ± 9.0	−3.4 (−6.0 to −0.7)	−3.1 (−6.0 to −0.2)	0.04
1 yr	34.8 ± 9.9	39.7 ± 10.0	−4.9 (−8.1 to −1.7)	−5.1 (−8.7 to −1.5)	0.01
2 yrs	34.8 ± 10.3	39.5 ± 10.2	−4.7 (−8.7 to −0.6)	−4.5 (−9.0 to −0.2)	0.04
SF-36 MCS					
1 month	50.8 ± 12.5	51.5 ± 11.2	−0.7 (−4.0 to 2.6)	−0.3 (−3.9 to 3.4)	0.88
1 yr	51.1 ± 11.7	51.4 ± 10.5	−0.3 (−3.8 to 3.1)	0.74 (−3.0 to 4.5)	0.69
2 yrs	49.4 ± 13.2	50.9 ± 11.9	−1.5 (−6.3 to 3.3)	−0.1 (−5.5 to 5.4)	0.98

Values are % (n) or mean ± SD. *Unadjusted HR based on proportional hazards regression or Fine-Gray subdistribution models for time-to-event variables and t-tests for health status measures. †Adjusted HR based on proportional hazards regression or Fine-Gray subdistribution models; adjusted mean differences based on multiple linear regression.

CI = confidence interval; HF = heart failure; HR = hazard ratio; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire overall summary score; MCS = mental component score; PCS = physical component score; other abbreviations as in Table 1.

than patients without COPD in univariate and multivariable analysis (Table 2). COPD was associated with lower SF-36 physical component scores at 1 month, 1 year, and 2 years, whereas COPD was not associated with SF-36 mental component scores at any follow-up time point (Table 2).

IMPACT OF COPD ON THE BENEFIT OF TMVr. In patients with HF and severe SMR, the presence of COPD modified the benefit of TMVr with respect to 2-year mortality (Table 3, Central Illustration). Specifically, among patients with COPD, there was no significant mortality benefit of TMVr versus GDMT alone (adjusted HR: 0.94; 95% CI: 0.54 to 1.65), whereas TMVr led to a substantial reduction in mortality for patients without COPD (adjusted HR: 0.47; 95% CI: 0.33 to 0.67; $p_{int} = 0.04$). This differential mortality benefit was explained by an excess of non-CV mortality among COPD patients treated with TMVr (adjusted HR: 2.79 with COPD vs. 0.43 without COPD; $p_{int} = 0.04$), whereas the benefits of TMVr on CV mortality were consistent regardless of the presence or absence of COPD (adjusted HR: 0.68 vs. 0.50; $p_{int} = 0.45$).

In contrast to its effects on mortality, COPD did not modify the benefits of TMVr with respect to HFH (adjusted HR: 0.47 [95% CI: 0.28 to 0.80] with COPD vs. 0.47 [95% CI: 0.34 to 0.64] without COPD; $p_{int} = 0.96$) (Table 3, Central Illustration). For the composite of death or HFH (Figure 1), the benefit of TMVr compared with GDMT alone was also consistent regardless of the presence or absence of COPD (adjusted HR: 0.63 [95% CI: 0.40 to 1.00] vs. 0.49 [95% CI: 0.37 to 0.64]; $p_{int} = 0.34$). In analyses restricted to the COPD subgroup, there was no evidence of a differential effect of TMVr versus GDMT according to the need for home oxygen (Supplemental Table 2).

Finally, there was no evidence that the presence of COPD modified the benefit of TMVr on health-status outcomes (Table 4). At 1-year follow-up, TMVr led to an improvement in the KCCQ overall summary score of 13.3 points (95% CI: 3.6 to 23.0) in patients with COPD and 11.0 points (95% CI: 6.1 to 15.9) in patients without COPD ($p_{int} = 0.68$). At 2-year follow-up, results were similar, with a mean improvement in the KCCQ overall summary score of 13.5 points (95% CI: 0.8 to 26.2) in patients with COPD and 12.5 points (95% CI: 6.4 to 18.6) in those without COPD ($p_{int} = 0.89$). Results for the SF-36 physical component and mental component scores showed similar patterns (Table 4). The QOL benefit of TMVr was also consistent among patients with COPD who received intermittent home oxygen compared with those who did not (Supplemental Table 3).

DISCUSSION

The major findings from this post hoc analysis of the COAPT trial are as follows. First, a substantial proportion of patients with refractory HF and SMR had concomitant COPD, which was associated with more

TABLE 3 Two-Year Clinical Outcomes of TMVr Plus GDMT Versus GDMT Alone, Stratified by COPD

	TMVr + GDMT (n = 302)	GDMT Alone (n = 312)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Multivariable p Value for Interaction
Death					0.04
COPD	43.4 (30)	39.7 (25)	1.13 (0.67–1.93)	0.94 (0.54–1.65)	
No COPD	23.5 (53)	43.8 (100)	0.49 (0.35–0.69)	0.47 (0.33–0.67)	
Cardiovascular death					0.45
COPD	31.2 (19)	34.6 (21)	0.79 (0.42–1.45)	0.68 (0.35–1.30)	
No COPD	20.4 (45)	36.9 (81)	0.53 (0.37–0.76)	0.50 (0.34–0.75)	
Noncardiovascular death					0.04
COPD	17.8 (11)	7.8 (4)	2.79 (0.90–8.66)	2.21 (0.65–7.43)	
No COPD	3.9 (8)	10.8 (19)	0.43 (0.19–0.97)	0.48 (0.20–1.14)	
HF hospitalization					0.96
COPD	37.1 (26)	56.1 (36)	0.59 (0.36–0.97)	0.47 (0.28–0.80)	
No COPD	30.4 (69)	51.7 (122)	0.49 (0.36–0.66)	0.47 (0.34–0.64)	
Death or HF hospitalization					0.34
COPD	57.1 (40)	68.0 (44)	0.77 (0.50–1.18)	0.63 (0.40–1.00)	
No COPD	41.0 (93)	66.8 (157)	0.49 (0.38–0.64)	0.49 (0.37–0.64)	

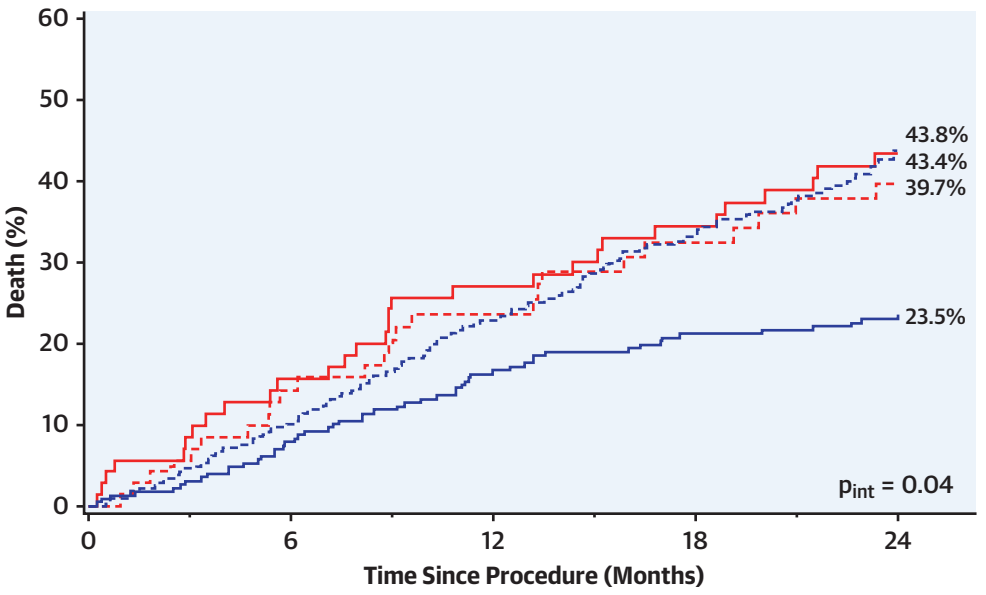
Values are % (n), unless otherwise indicated.
Abbreviations as in Tables 1 and 2.

frequent comorbidities and worse baseline health status. Second, among patients treated with TMVr, COPD was associated with increased 2-year mortality; however, after adjustment for baseline differences, there was no association between the presence of COPD and 2-year clinical outcomes, including death and HFH. Third, among patients treated with TMVr, COPD was associated with worse disease-specific and generic health status throughout the 2-year follow-up period. Finally (and most important), the presence of COPD led to attenuation of the benefit of TMVr in patients with HF with severe SMR. Specifically, in contrast to the findings among patients with no COPD, patients with COPD derived no overall survival benefit from TMVr (although CIs were wide), findings that appear to derive from offsetting effects of TMVr on CV and non-CV mortality among patients with COPD. However, these findings did not apply to other outcomes, including HFH and QOL, for which the benefits of TMVr compared with GDMT were consistent regardless of the presence or absence of COPD.

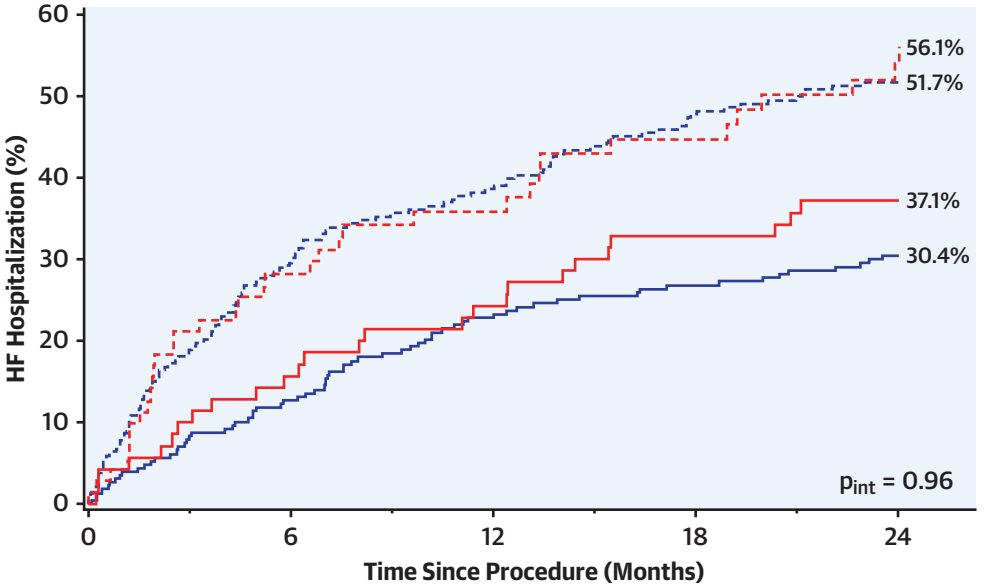
These findings add to existing knowledge of the relationship between COPD and outcomes in patients with MR. In a small study, COPD was associated with increased short-term mortality in patients who underwent TMVr as well as in those who underwent surgical mitral valve replacement (11). More recently, a European TMVr registry consisting of mostly patients with SMR (63%) demonstrated that COPD was associated with increased mortality at 2-year follow-up (4). However, several larger European TMVr registries did not identify COPD as a predictor of mortality (12–15). In contrast to SMR, COPD has been more consistently identified as a predictor of excess mortality in studies with a preponderance of degenerative mitral regurgitation, such as the American College of Cardiology/Society of Thoracic Surgeons TVT (Transcatheter Valve Therapy) Registry (in which more than 85% of patients were treated for degenerative mitral regurgitation) (5) as well as in the EVEREST II (Endovascular Valve Edge-to-Edge Repair) trial (in which 77% of patients had degenerative mitral regurgitation) (16). It is not clear why COPD has more consistently been associated with excess mortality in patients with degenerative mitral regurgitation than SMR. Patients with SMR have higher mortality compared with those with degenerative mitral regurgitation (5); thus, it is possible that the relative contribution of COPD to mortality is less apparent in patients with SMR, given their higher background rate of mortality due to left ventricular dysfunction and other comorbidities.

Regardless of the precise mechanism, our study adds to prior knowledge, as it is the first study to examine the impact of COPD on outcomes of TMVr within the context of a randomized trial of TMVr versus GDMT. By comparing patient outcomes among patients who were randomized to TMVr versus GDMT, we found that the presence of COPD led to attenuation of the survival benefit of TMVr in patients with refractory SMR; in fact, in COAPT, there was no overall survival advantage with TMVr among patients with COPD (although CIs were relatively wide). However, the benefits of TMVr on CV mortality

CENTRAL ILLUSTRATION Clinical Outcomes During 2-Year Follow-Up



No. at risk:					
COPD - TMVr Plus GDMT	71	59	51	45	34
COPD - GDMT Alone	72	59	45	38	29
No COPD - TMVr Plus GDMT	231	210	187	174	158
No COPD - GDMT Alone	240	213	178	148	116

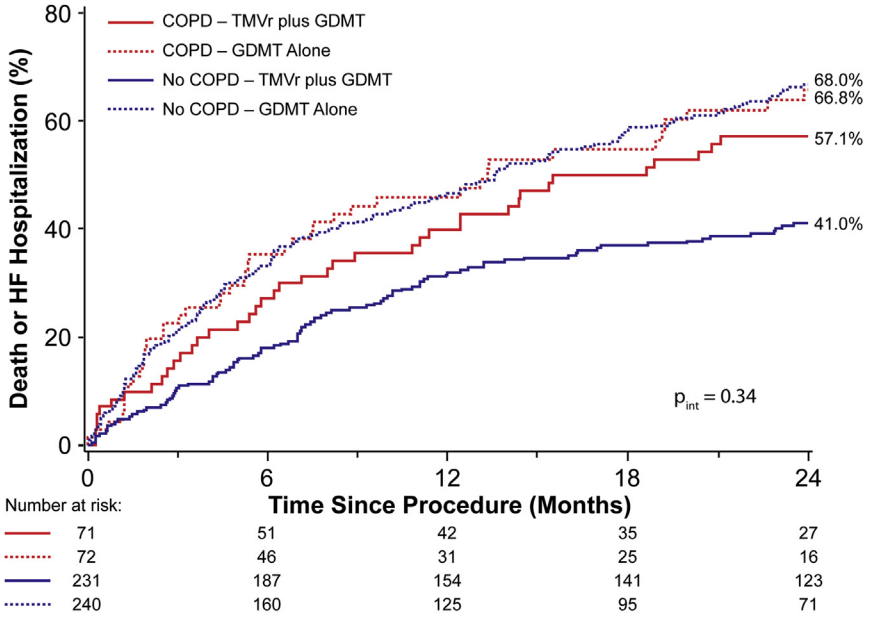


No. at risk:					
COPD - TMVr Plus GDMT	71	51	42	35	27
COPD - GDMT Alone	72	46	31	25	16
No COPD - TMVr Plus GDMT	231	187	154	141	123
No COPD - GDMT Alone	240	160	125	95	71

Saxon, J.T. et al. J Am Coll Cardiol Intv. 2020;13(23):2795–803.

(Top) Time to death. **(Bottom)** Time to first heart failure (HF) hospitalization. Outcomes are shown in 4 groups: treatment (transcatheter mitral valve repair [TMVr] plus guideline-directed medical therapy [GDMT]) with chronic obstructive pulmonary disease (COPD), treatment (TMVr plus GDMT) without COPD, control (GDMT alone) with COPD, and control (GDMT alone) without COPD.

FIGURE 1 **Time to Death or First Heart Failure Hospitalization During 2-Year Follow-Up**



Outcomes are shown in 4 groups: treatment (transcatheter mitral valve repair [TMVr] plus guideline-directed medical therapy [GDMT]) with chronic obstructive pulmonary disease (COPD), treatment (TMVr plus GDMT) without COPD, control (GDMT alone) with COPD, and control (GDMT alone) without COPD.

were consistent regardless of the presence or absence of COPD; it was greater non-CV mortality in patients with COPD treated with TMVr that mitigated the overall survival benefit. Finally, the benefits of TMVr on HFH and health status were not modified by the presence of COPD, demonstrating that even in the absence of a mortality benefit, TMVr does provide important benefits to these patients.

With respect to health status, it is not surprising that COPD is associated with greater health status impairment among patients with MR. An analysis of predominantly patients with degenerative mitral regurgitation from the TVT Registry demonstrated that COPD was associated with worse health status after TMVr (17). In that study, the impact of COPD could be further stratified by disease severity: a greater proportion of patients with mild COPD were "alive and well" at 1 year (defined as being alive with KCCQ overall summary scores ≥60) than those with moderate COPD or severe COPD (56.3% vs. 50.5% vs. 42.8%; $p < 0.001$). Our study both confirms and extends these previous findings by demonstrating that although patients with COPD have worse health status compared with patients without COPD, the health status benefits of TMVr in SMR are similar regardless of the presence of absence of COPD, at least through 2 years of follow-up.

Our findings should help inform patient selection for TMVr. Although TMVr has been shown to improve both clinical and QOL outcomes in select patients with SMR, many patients do not derive meaningful benefit from TMVr. Indeed, among COAPT patients randomized to TMVr, 2-year rates of overall mortality and the composite of death or HFH remained high at 29.1% and 45.7%, respectively (1). Given that COPD is associated with increased long-term mortality in many conditions, we hypothesized that patients with COPD might be less likely to benefit from TMVr. Indeed, although we found that the overall survival benefit of TMVr was attenuated in patients with baseline COPD, there was no evidence that COPD modified the benefit of TMVr with respect to other important outcomes, including HFH and improved QOL. Thus, our study provides evidence that the presence of COPD by itself should not influence the decision to offer TMVr to patients with HF and SMR,

TABLE 4 Change in Health Status Measures From Baseline With TMVr Plus GDMT Versus GDMT Alone, Stratified by COPD

Outcome	TMVr + GDMT (n = 302)	GDMT Alone (n = 312)	Adjusted Mean Difference (95% CI)	Multivariable p Value for Interaction
KCCQ-OS				
1 yr				0.68
COPD	17.6 ± 31.0	2.5 ± 23.9	13.3 (3.6 to 23.0)	
No COPD	16.8 ± 23.6	5.7 ± 24.7	11.0 (6.1 to 15.9)	
2 yrs				0.89
COPD	20.9 ± 30.5	0.4 ± 20.2	13.5 (0.8 to 26.2)	
No COPD	16.7 ± 24.7	4.2 ± 27.9	12.5 (6.4 to 18.6)	
SF-36 PCS				
1 yr				0.60
COPD	3.4 ± 11.5	−1.5 ± 10.5	3.2 (−1.0 to 7.4)	
No COPD	5.5 ± 10.1	1.4 ± 9.5	4.4 (2.3 to 6.5)	
2 yrs				0.82
COPD	3.3 ± 9.8	−2.0 ± 7.6	3.5 (−1.8 to 8.7)	
No COPD	5.3 ± 10.6	1.4 ± 11.1	4.1 (1.6 to 6.6)	
SF-36 MCS				
1 yr				0.37
COPD	7.4 ± 15.4	4.1 ± 14.7	4.9 (−0.3 to 10.0)	
No COPD	3.4 ± 12.4	1.3 ± 13.1	2.2 (−0.4 to 4.8)	
2 yrs				0.59
COPD	8.5 ± 18.2	0.7 ± 13.6)	5.0 (−1.7 to 11.6)	
No COPD	2.8 ± 13.1	−0.5 ± 12.7	2.9 (−0.2 to 6.0)	

Values are mean ± SD.
Abbreviations as in Tables 1 and 2.

although a survival benefit through 2 years should not be expected in patients with COPD.

STUDY LIMITATIONS. First, all subgroup analysis is inherently underpowered. Second, the number of patients with COPD in COAPT was modest, further limiting the statistical power of the interaction testing. Given these issues, it was not possible to rule out moderate quantitative interactions for nonfatal endpoints.

Third, although we did identify that COPD is a modifier of the survival benefit of TMVr in patients with HF with SMR, by design the COAPT trial excluded patients with end-stage lung disease; as such, our findings cannot be generalized to all patients with COPD. Intuitively, patients with very severe COPD would be expected to benefit less and have worse outcomes than those with less severe COPD.

Finally, objective data on the severity of COPD, including pulmonary function tests, were not routinely collected in the COAPT trial. Thus, detailed assessment of the relationship between the severity of COPD and outcomes of TMVr in the HF population was not possible.

CONCLUSIONS

For patients with HF and severe SMR enrolled in the COAPT trial, COPD was common and attenuated the survival benefit of TMVr compared with GDMT alone. Nonetheless, the relative benefits of TMVr with respect to reduced HFH and improved health status were comparable to those seen in patients without COPD. These findings suggest that for patients with HF and severe SMR similar to those enrolled in COAPT, the presence of COPD alone should not influence the decision to perform TMVr. Further study is necessary to determine whether TMVr also improves clinical outcomes in patients with end-stage COPD.

AUTHOR DISCLOSURES

The COAPT trial was sponsored by Abbott Vascular. Dr. Saxon is a proctor for Abbott Vascular. Dr. Cohen has received research grants from and served as a consultant for Abbott Vascular, Edwards Lifesciences, Boston Scientific, and Medtronic. Dr. Kar has received consulting fees from and is an advisory board member for Boston Scientific; has received consulting fees from and holds stock equity in Valcare; and has received consulting fees from W.L. Gore and Medtronic. Dr. Lim has received research grant support from Abbott, Edwards Lifesciences, Medtronic, and Gore; is a consultant for Abbott, Edwards Lifesciences, Keystone Heart, Pipeline, Siemens, Valgen, and Venus; is an advisory board member for Ancora and Venus; and holds equity in 510Kardiac and Venus. Dr. Abraham has received research grant support from Abbott Vascular; and has received consulting income from Abbott Vascular. Dr. Lindenfeld has received research grant support from AstraZeneca; and has received consulting income from Abbott Vascular, AstraZeneca, CVRx, Edwards Lifesciences, Impulse Dynamics, Boehringer Ingelheim, and V-Wave. Dr. Mack served as co-primary investigator for the PARTNER (Placement of Aortic Transcatheter Valve) trial for Edwards Lifesciences and the COAPT trial for Abbott; and served as study chair for the APOLLO trial for Medtronic. Dr. Stone has received speaker or other honoraria from Cook, Terumo, QOOL Therapeutics, and Orchestra Biomed; has served as a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Matrizyme; and has equity and/or options in Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, and Valfix. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? TMVr with the MitraClip improves survival, reduces HFH, and improves health status in patients with HF and severe (3+ or 4+) SMR who remain symptomatic despite maximally tolerated GDMT.

WHAT IS NEW? In the COAPT trial, COPD was common and was associated with attenuated survival benefit of TMVr versus GDMT compared with that seen in patients without COPD. However, the benefits of TMVr on HFH and health status were similar in patients with or without COPD.

WHAT IS NEXT? Further study is necessary to determine whether TMVr also improves clinical outcomes in patients with end-stage COPD, who were excluded from COAPT.

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KEY WORDS chronic obstructive pulmonary disease, heart failure, mitral regurgitation, prognosis, transcatheter mitral valve repair

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