Structural Heart 8 (2024) 100333

Articles and Issues Available at ScienceDirect

Structural Heart

journal homepage: www.structuralheartjournal.org

Original Research

Pulmonary Vein Systolic Flow Reversal and Outcomes in Patients From the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) Trial

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ARTICLE INFO

Article history:
Submitted 8 December 2023
Revised 10 May 2024
Accepted 18 May 2024
Available online 26 June 2024

Keywords:
COAPT trial
Functional mitral regurgitation
Heart failure
Outcomes
Pulmonary vein flow reversal

ABSTRACT

Background: The implications of pulmonary vein (PV) flow patterns in patients with heart failure (HF) and mitral regurgitation (MR) are uncertain. We examined PV flow patterns in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial (NCT01626079), in which patients with HF and moderate-to-severe or severe functional MR were randomized to transcatheter edge-to-edge repair (TEER) with the MitraClip device plus guideline-directed medical therapy (GDMT) vs. GDMT alone. We sought to evaluate the prognostic utility of baseline PV systolic flow reversal (PVSFR) in HF patients with severe MR and to determine whether the presence of PVSFR can discriminate patients most likely to benefit from TEER in COAPT trial patients.

Methods: Patients were categorized by the echocardiographic core laboratory-assessed baseline presence of PVSFR. Two-year outcomes were examined according to PVSFR and treatment.

Results: Baseline PV flow patterns were evaluable in 526/614(85.7%) patients, 48.9% of whom had PVSFR. Patients with PVSFR had more severe MR, reduced stroke volume and cardiac output, greater right ventricular dysfunction, and worse hemodynamics. By multivariable analysis, PVSFR was not an independent predictor of 2-year all-cause death, or heart failure hospitalization (HFH). The reductions in the 2-year rates of all-cause death and HFH with TEER compared with GDMT alone were similar in patients with and without PVSFR ($P_{interaction}$ = 0.40 and 0.12, respectively). The effect of TEER on improving Kansas City Cardiomyopathy Questionnaire scores and 6-minute walk distance were also independent of PVSFR.

Conclusions: In the COAPT trial, PVSFR identified HF patients with severe MR and more advanced heart disease. Patients with and without PVSFR had consistent reductions in mortality, HFH, and improved quality-of-life and functional capacity after TEER.

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https://doi.org/10.1016/j.shj.2024.100333

Clinical Trial Registration: ClinicalTrial.gov IdentifierNCT01626079.

ABBREVIATIONS

EF, ejection fraction; FMR, functional mitral regurgitation; GDMT, guideline-directed medical therapy; HFH, heart failure hospitalization; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; PV, pulmonary vein; PVSFR, pulmonary vein systolic flow reversal; TTE, transthoracic echocardiogram.

Introduction

Doppler echocardiography is the most widely used technique for noninvasive evaluation of cardiac function and hemodynamics. Interrogation of pulmonary vein (PV) flow with spectral Doppler analysis provides important insights into left atrial hemodynamics. Flow from the PV into the left atrium (LA) is characterized by at least 3 phases (Figure 1): systole (represented by the S-wave), early diastole (the D-wave), and late diastole (the A-wave, occurring during atrial contraction and evident as a small wave of flow reversal into the PV). In normal physiologic conditions, both the S- and D-waves demonstrate forward flow into the LA with S-wave dominance (S > D).[1] Any condition that affects LA compliance or pressure, such as abnormalities in left ventricular (LV) contractility or relaxation, mitral valve function, or atrial contractility, will result in abnormal PV flow patterns. The most common causes of abnormal PV flow are LV dysfunction, mitral regurgitation (MR), and atrial fibrillation.[2] Patients with LV dysfunction show blunting of the S-wave, the degree of which directly correlates with elevation in LA and LV end-diastolic pressures (higher pressures, smaller S-wave); in a minority of cases, PV systolic flow reversal (PVSFR) is present. In patients with MR, as the MR severity worsens, the S-wave blunts, and very severe MR frequently results in PVSFR. Isolated atrial fibrillation usually presents with S-wave blunting (without an A-wave), but not PVSFR.

Patients with heart failure (HF) due to LV systolic dysfunction and secondary or functional MR (FMR) suffer from at least two distinctive conditions that may affect LA pressures and PV flow, but little is known about the relationship between PV flow patterns and overall cardiac and hemodynamic function in these patients. In addition, the prognostic value of PVSFR in patients with FMR is incompletely understood. Whether the presence of PVSFR identifies patients who might derive the greatest benefit from surgical or transcatheter treatment of MR is uncertain. In this regard, small studies have reported that PVSFR may be a predictor of a poor prognosis in patients with LV systolic dysfunction and MR,[3] and that its resolution post-transcatheter edge-to-edge repair (TEER) is associated with improved outcomes.[4]

To evaluate the prognostic utility of baseline PVSFR in HF patients with severe MR and to determine whether the presence of PVSFR can discriminate patients most likely to benefit from TEER, we performed the present substudy from the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial.[5] We hypothesized that, among HF patients with 3-4+ FMR, PVSFR would identify patients with more severe FMR, greater cardiac dysfunction and remodeling, and worse clinical outcomes, and that the benefits of TEER would be most pronounced in patients with PVSFR.

Methods

Study Design

The COAPT trial methods have been published previously.[5] In brief, COAPT was a multicenter, randomized, controlled, open-label trial of TEER with the MitraClip device (Abbott, Santa Clara, CA) in 614 patients with HF and moderate-to-severe (3+) or severe (4+) FMR (confirmed by

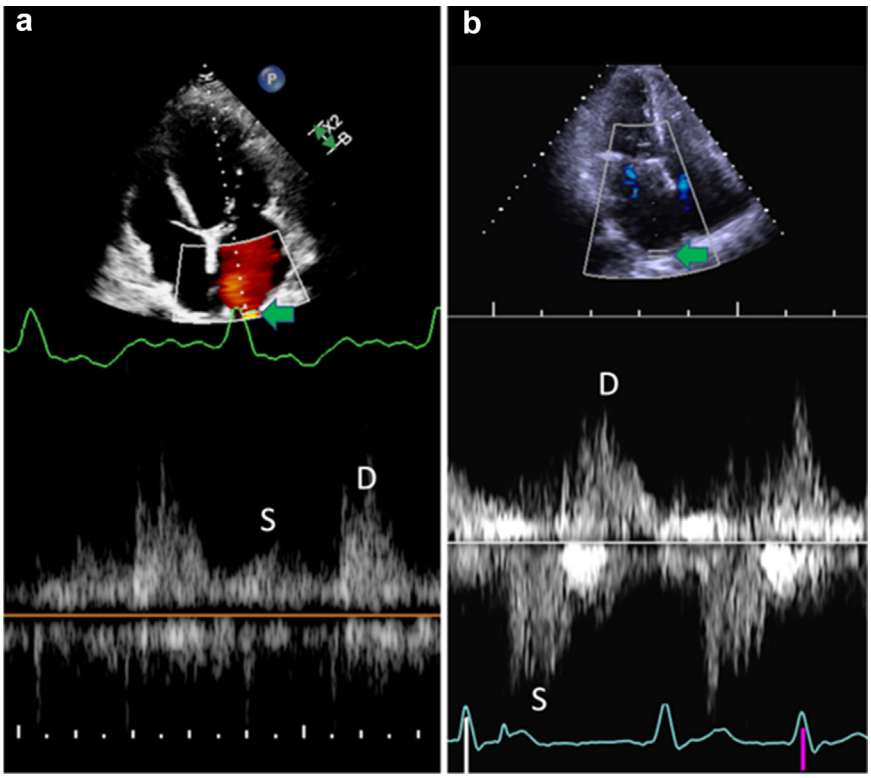

Figure 1. Pulmonary vein flow patterns. Examples of PV flow tracings in patients with moderate LV dysfunction, 4+ MR, and atrial fibrillation enrolled in the COAPT trial. The green arrows point to the sites where sampling for pulsed-wave Doppler interrogation was performed. (a) As left atrial pressure increases (typical in patients with LV dysfunction, MR, and/or atrial fibrillation), there is blunting of the systolic (S) wave, and the diastolic (D) wave becomes dominant. (b) PVSFR typically indicates severe mitral regurgitation; it is uncommon with LV dysfunction and atrial fibrillation without severe MR. Variations of the waveforms in panel A comprise the no PVSFR group in the current analysis, while cases like panel B comprise the PVSFR group

Abbreviations: COAPT, Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; LV, left ventricle; MR, mitral regurgitation; PV, pulmonary vein; PVSFR, pulmonary vein systolic flow reversal.

an independent echocardiographic core laboratory [MedStar Health Research Institute, Washington, DC]) who remained symptomatic (New York Heart Association Class II, III, or IVa [ambulatory]) despite maximally-tolerated guideline-directed medical therapy (GDMT) for HF, including cardiac resynchronization therapy when appropriate. GDMT was required for a minimum of 3 months before randomization. As a result, roughly 90% were on beta blocker at baseline, 70% on angiotensin converting enzyme/angiotensin receptor blocker/angiotensin receptor--neprilysin inhibitor, and 50% on mineralocorticoid receptor antagonist.

Patients had a site-assessed LV ejection fraction (LVEF) between 20% and 50%, an LV end-systolic diameter ≤70 mm, and the absence of severe fixed pulmonary hypertension or moderate or severe symptomatic right ventricular (RV) dysfunction. Patients were randomized 1:1 to receive TEER plus GDMT or GDMT alone. Transthoracic echocardiography (TTE), Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS), and six-minute walk distance (6MWD) were performed at baseline and at prespecified follow-up timepoints. All TTEs were analyzed by the echocardiographic core laboratory. The principal endpoints of interest for the present study were the 2-year rates of all-cause death, HF hospitalization (HFH), the composite of death or HFH, and the improvement in KCCQ-OS and 6MWD from baseline.

The protocol was approved by the institutional review board at each participating center, and all patients provided written informed consent. Abbott sponsored the trial. The investigators had unrestricted access to the data and accepted responsibility for the integrity of the present report. The data that supports the findings of this report may be made available to qualified investigators upon reasonable request. Such requests should be addressed to the COAPT Publications Committee (coapt@crf.org).

Echocardiographic Core Laboratory Analysis

TTEs were acquired at each center following a study-specific protocol that included interrogation of flow in all PVs (by pulsed-wave Doppler) from the apical views. MR severity was assessed by the core lab using a multiparametric algorithm created for the COAPT trial.[6] For the present study, the core lab required an acceptable quality PV pulsed-wave Doppler from at least 1 PV from the apical views. For the present study, post-hoc analysis was performed of the COAPT PV flow images, qualitatively assessing the presence vs. absence of S wave flow reversal (Figure 1). This is different from the previously reported echocardiographic assessment that required measurements of S and D wave peak velocities to grade PVSFR based on the S/D ratio on a 1+ to 4+ scale.[6] Two independent cardiologists analyzed all PV images. Any discrepancies were resolved by consensus or a third reader.

Statistical Analysis

Baseline characteristics were summarized with means ± standard deviations or medians [Q1, Q3] for continuous measures and were compared with the Student's *t*-test or Wilcoxon rank-sum test for nonparametric data. Categorical data were described as proportions and were compared with the chi-square or Fisher's exact test as appropriate. For time-to-first event analyses, event rates were estimated by the Kaplan-Meier method and were compared with the log-rank test. Multivariable Cox proportional hazard models were constructed to examine the independent predictors of outcomes. In addition to PVSFR, the covariates included in these models were age, sex, diabetes, hypertension, history of myocardial infarction, prior coronary artery bypass graft surgery, stroke, peripheral vascular disease, and prior cardiac resynchronization therapy. Interaction terms between randomized treatment arms and PVSFR were included in the multivariable models to assess whether the relative effects of TEER plus GDMT vs. GDMT alone on outcomes were different in patients with vs. without PVSFR. Analysis of covariance was performed to compare the mean changes in quality-of-life (QoL) measures as assessed by the KCCQ-OS and functional capacity as measured by the 6MWD from baseline to follow-up, adjusting for baseline values. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC), and two-sided *p*-values <0.05 were considered to be statistically significant.

Results

Patients and Baseline Characteristics

Among the 614 randomized patients enrolled in the COAPT trial, 526 (85.7%) had recorded PV flows on the baseline TTE that were evaluable for the presence or absence of PVSFR, comprising the current study population. PVSFR was present in 257 (48.9%) of these 526 patients. There were no significant differences in baseline clinical characteristics in patients with and without PVSFR (Table 1). New York Heart Association functional class, B-type natriuretic peptide, and pro-B-type

Table 1
Baseline characteristics according to the presence of pulmonary vein systolic flow reversal

Characteristic	PVSFR (N = 257)	No PVSFR (N = 269)	All patients (N = 526)	*p* value
Age, y	71.1 ± 11.7	72.8 ± 10.8	72.0 ± 11.3	0.10
Sex, male	164 (63.8%)	169 (62.8%)	333 (63.3%)	0.81
Diabetes	108 (42.0%)	91 (33.8%)	199 (37.8%)	0.053
Hypertension	208 (80.9%)	215 (79.9%)	423 (80.4%)	0.77
Hypercholesterolemia	135 (52.5%)	141 (52.4%)	276 (52.5%)	0.98
Chronic obstructive pulmonary disease	59 (23.0%)	65 (24.2%)	124 (23.6%)	0.74
Previous myocardial infarction	127 (49.4%)	141 (52.4%)	268 (51.0%)	0.49
Previous percutaneous coronary intervention	104 (40.5%)	131 (48.7%)	235 (44.7%)	0.058
Previous coronary artery bypass grafting	100 (38.9%)	113 (42.0%)	213 (40.5%)	0.47
Previous stroke/transient ischemic attack	50 (19.5%)	44 (16.4%)	94 (17.9%)	0.35
Peripheral arterial disease	43 (16.7%)	50 (18.6%)	93 (17.7%)	0.58
Cardiomyopathy				
Ischemic	146 (56.8%)	169 (62.8%)	315 (59.9%)	0.16
Nonischemic	111 (43.2%)	100 (37.2%)	211 (40.1%)	0.16
NYHA class				
I	0 (0%)	1 (0.4%)	1 (0.2%)	0.33
II	92 (35.8%)	110 (40.9%)	202 (38.4%)	0.23
III or IV	165 (64.2%)	158 (58.7%)	323 (61.4%)	0.20
B-type natriuretic peptide level, pg/mL	1019.4 ± 971.0	991.2 ± 1320.2	1004.9 ± 1162.5	0.82
N-terminal pro-B-type natriuretic peptide level, pg/mL	5086.9 ± 6386.4	6713.3 ± 9632.8	5931.1 ± 8242.5	0.26
KCCQ-OS score	52.1 ± 23.4	52.8 ± 23.2	52.4 ± 23.3	0.75
Six-minute walk distance, meters	238.2 ± 125.9	247.7 ± 127.3	243.1 ± 126.6	0.39

Notes. Data are mean ± SD or n (%).
Abbreviations: KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary; NYHA, New York Heart Association; PVSFR, pulmonary venous systolic flow reversal.

Table 2
Echocardiographic baseline characteristics according to the presence of pulmonary vein systolic flow reversal

Echo parameter	PVSFR (N = 257)	No PVSFR (N = 269)	All patients (N = 526)	*p* value
Multiparametric MR grading				<0.0001
Moderate-to-severe (3+) MR	47 (18.3%)	216 (80.3%)	263 (50.0%)	
Severe (4+) MR	210 (81.7%)	53 (19.7%)	263 (50.0%)	
Severe (4+) MR (by color Doppler)	199 (77.4%)	62 (23.0%)	261 (49.6%)	<0.0001
Mitral EROA–by PISA, cm^2	0.46 ± 0.16	0.36 ± 0.13	0.41 ± 0.15	<0.0001
LVEF, %	31.3 ± 9.0	31.4 ± 9.2	31.4 ± 9.1	0.94
LV GLS, %	−12.2 ± 3.6	−11.8 ± 3.3	−12.0 ± 3.5	0.16
LV forward SV, mL	47.1 ± 14.6	53.9 ± 18.2	50.6 ± 16.9	<0.0001
LV forward cardiac output, L/min	3.4 ± 1.0	3.7 ± 1.1	3.5 ± 1.1	0.0005
LVEDVi, mL/m^2	104.5 ± 33.8	98.5 ± 35.2	101.4 ± 34.6	0.055
LVESVi, mL/m^2	72.8 ± 28.2	69.2 ± 29.6	70.9 ± 29.0	0.17
LA end-diastolic volume, mL	95.1 ± 55.1	94.0 ± 62.6	94.5 ± 58.9	0.84
LA end-systolic volume, mL	137.8 ± 65.6	136.3 ± 72.1	137.1 ± 68.8	0.82
LA GLS, %	12.7 ± 4.5	12.9 ± 4.7	12.8 ± 4.6	0.61
RVSP, mmHg	46.8 ± 13.9	42.3 ± 13.5	44.5 ± 13.9	0.0004
RV GLS, %	−17.1 ± 4.5	−18.3 ± 5.2	−17.7 ± 4.9	0.02

Notes. Data are mean ± SD or n (%).
Severe MR by color Doppler was defined as a large central jet (>50% of LA area) or a holosystolic jet wrapping around the LA.
Abbreviations: EROA, effective regurgitant orifice area; GLS, global longitudinal strain; LA, left atrium; LV, left ventricle; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; MR, mitral regurgitation; PISA, proximal isovelocity surface area; PVSFR, pulmonary vein systolic flow reversal; RV, right ventricle; RVSP, right ventricular systolic pressure; SV, stroke volume.

natriuretic peptide levels were also similar in patients with and without PVSFR, as were the baseline KCCQ-OS and 6MWD (Table 1).

Baseline echocardiographic findings are shown in Table 2. Patients with PVSFR had greater MR severity compared with patients without PVSFR, as evidenced by larger effective regurgitant orifice area, color Doppler jet area, and multiparametric assessment. Although LVEF and LV global longitudinal strain (GLS) were not significantly different between the two groups, LV end-diastolic volumes tended to be larger and forward stroke volumes and cardiac output were significantly lower in patients with PVSFR. LA volumes and LA GLS were similar between patients with and without PVSFR. However, RV systolic pressures were higher, and RV GLS was worse in patients with PVSFR.

Clinical Outcomes

As shown in Table 3, there were no significant differences in the 2-year rates of all-cause mortality, HFH, or the composite of all-cause mortality or HFH, in patients with and without PVSFR after adjusting for differences in baseline clinical covariates in the entire population or in either treatment group separately. No significant interaction was observed between the presence of PVSFR and treatment for mortality and HFH and the composite end-point of death and HFH (Figure 2 and 3). Thus, the effect of TEER was consistent in reducing mortality, HFH, and the composite of both in patients with and without PVSFR.

Table 4 shows the change in KCCQ-OS and 6MWD in paired data of patients from baseline to 30 days, 6 months, 1 year, and 2 years. The improvement in both parameters at each time point with TEER plus GDMT compared with GDMT alone was similar in patients with and without PVSFR.

Discussion

The COAPT trial demonstrated that in patients with HF and moderate-to-severe (3+) or severe (4+) FMR who remain symptomatic despite GDMT, TEER with the MitraClip device improves survival, reduces HFH, and enhances QoL and functional capacity.[5,7] In the present COAPT substudy, we investigated whether the presence of PVSFR on the baseline TTE could serve as a surrogate for the severity of MR and cardiac dysfunction and whether its presence would identify a subgroup of patients more likely to benefit from TEER. The major findings are: 1) PVSFR was present in nearly half of patients enrolled in COAPT, and its presence identified patients with more severe FMR, reduced forward stroke volumes and cardiac output, higher pulmonary artery pressures, and greater RV dysfunction; 2) nonetheless, PVSFR was not an independent predictor of 2-year prognosis among the relatively homogeneous cohort of patients enrolled in this randomized trial; 3) TEER reduced all-cause mortality and HFH and improved QoL as well as functional capacity consistently in patients with and without PVSFR.

Table 3
Two-year clinical outcomes according to the baseline presence of PVSFR

Two-year outcome	Group	Event rate PVSFR present	Event rate PVSFR absent	Adjusted hazard ratio (95% CI) for PVSFR vs. no PVSFR*	*p* value	$P_{interaction}$
All-cause mortality	All patients	36.7% (90)	34.4% (88)	1.13 (0.84-1.51)	0.43	
	GDMT alone	45.9% (50)	41.1% (57)	1.32 (0.82-2.12)	-	0.40
	TEER plus GDMT	29.3% (40)	26.4% (31)	1.02 (0.69-1.49)	-	
Heart failure hospitalization	All patients	46.2% (96)	46.6% (109)	0.97 (0.74-1.27)	0.82	
	GDMT alone	55.2% (57)	59.5% (80)	1.27 (0.82-1.97)	-	0.12
	TEER plus GDMT	39.1% (49)	31.4% (35)	0.82 (0.58-1.16)	-	
Death or heart failure hospitalization	All patients	55.8% (125)	57.6% (146)	0.99 (0.78-1.25)	0.93	
	GDMT alone	66.6% (74)	70.2% (101)	1.23 (0.85-1.79)	-	0.14
	TEER + GDMT	47.2% (65)	42.4% (50)	0.86 (0.63-1.16)	-	

Abbreviations: GDMT, guideline-directed medical therapy; PVSFR, pulmonary venous systolic flow reversal; TEER, transcatheter edge-to-edge repair.
* Event rates are expressed as Kaplan-Meier estimated percentages (number of events). Adjusted for age, male sex, diabetes, hypertension, previous myocardial infarction, previous coronary artery bypass grafting, previous stroke, peripheral vascular disease, and prior cardiac resynchronization therapy.

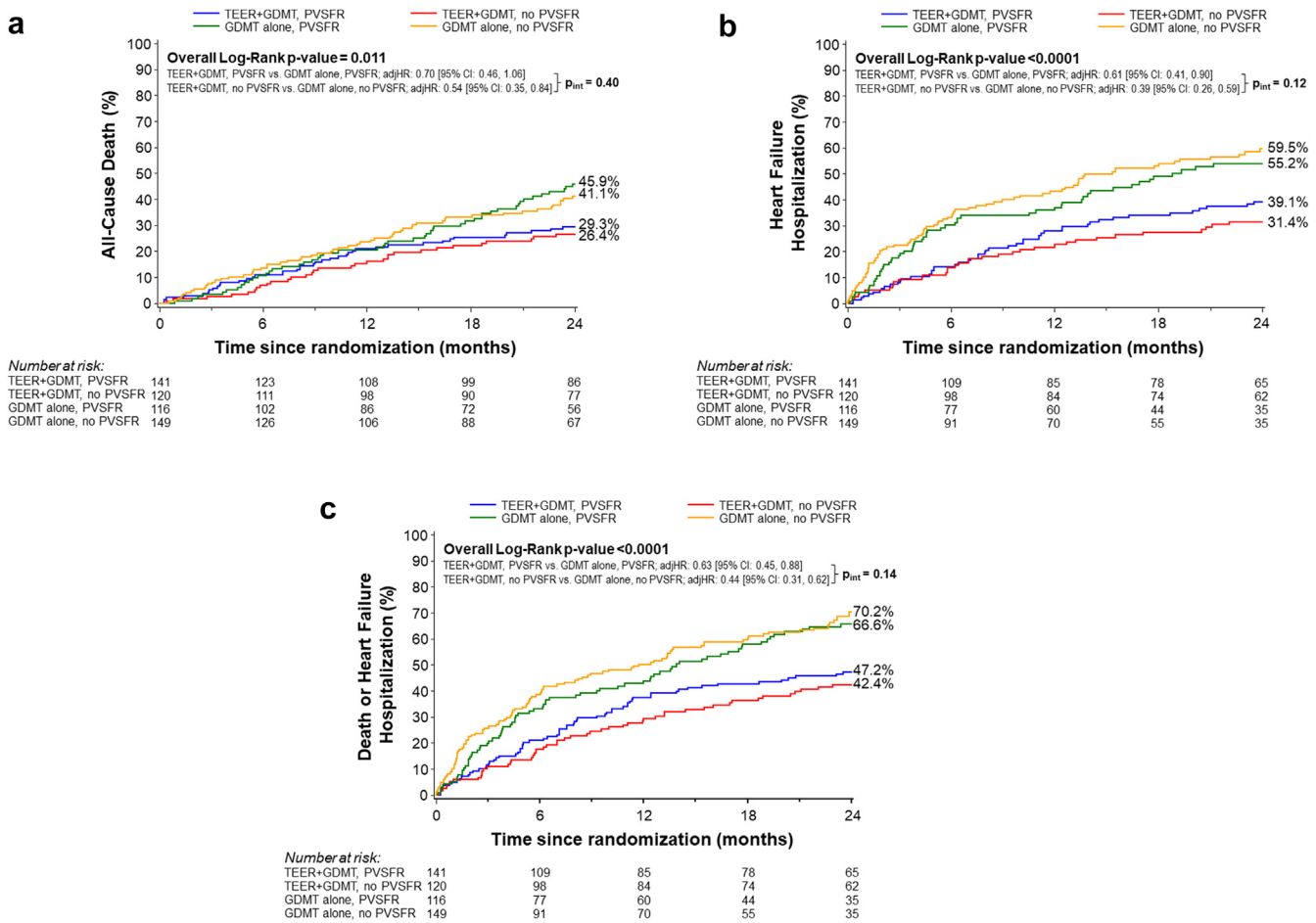

Figure 2. Time-to-first event Kaplan-Meier curves according to baseline presence of PVSFR and treatment through 2-year follow-up. (a) All-cause mortality; (b) heart failure hospitalizations; (c) death and heart failure hospitalizations

Abbreviations: adjHR, adjusted hazard ratio; GDMT, guideline-directed medical therapy; p_{int}, $P_{interaction}$; PVSFR, pulmonary vein systolic flow reversal; TEER, transcatheter edge-to-edge repair.

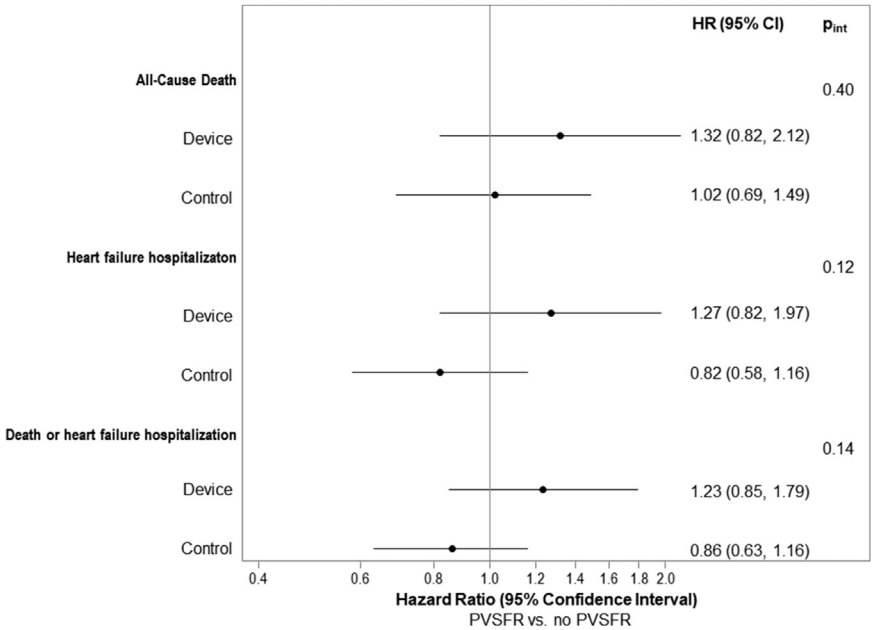

Figure 3. Forest plot of the HRs and 95% CIs for 2-year outcomes in patients with PVSFR compared with those without PVSFR according to treatment arm

Abbreviations: HR, hazard ratio; p_{int}, $P_{interaction}$; PVSFR, pulmonary vein systolic flow reversal.

Table 4
Quality-of-life and functional outcomes during follow-up according to the baseline presence of PVSFR

	PVSFR			No PVSFR			$P_{interaction}$
	TEER plus GDMT	GDMT alone	LSM of the difference (95% CI)	TEER plus GDMT	GDMT alone	LSM of the difference (95% CI)	
KCCQ-OS score							
Change from baseline to 30 d	17.5 ± 22.1 (n = 128)	1.0 ± 18.4 (n = 103)	16.52 (10.23, 22.81)	14.3 ± 22.5 (n = 112)	2.8 ± 18.5 (n = 126)	13.72 (7.53, 19.91)	0.41
Change from baseline to 6 mo	17.5 ± 23.8 (n = 117)	5.6 ± 22.4 (n = 87)	11.74 (4.16, 19.33)	16.9 ± 26.4 (n = 102)	4.9 ± 23.6 (n = 110)	14.34 (6.96, 21.72)	0.53
Change from baseline to 1 y	16.1 ± 27.7 (n = 96)	5.9 ± 26.4 (n = 74)	8.84 (0.28, 17.41)	4.5 ± 23.1 (n = 92)	4.8 ± 22.2 (n = 85)	11.83 (3.49, 20.17)	0.52
Change from baseline to 2 y	14.8 ± 26.8 (n = 77)	1.5 ± 30.1 (n = 51)	10.57 (-0.12, 21.26)	16.9 ± 26.2 (n = 71)	4.7 ± 23.7 (n = 64)	13.92 (3.73, 24.12)	0.56
6-min walk distance (meters)							
Change from baseline to 30 d	27.6 ± 103.6 (n = 118)	0.8 ± 79.6 (n = 92)	30.51 (−0.53, 61.55)	31.7 ± 102.5 (n = 105)	2.6 ± 87.2 (n = 112)	41.45 (11.08, 71.81)	0.52
Change from baseline to 6 mo	19.4 ± 100.9 (n = 110)	10.6 ± 104.2 (n = 76)	7.75 (−27.64, 43.13)	20.8 ± 97.0 (n = 92)	−0.6 ± 93.3 (n = 92)	26.49 (−8.56, 61.53)	0.33
Change from baseline to 1 y	28.9 ± 112.1 (n = 83)	4.3 ± 115.3 (n = 67)	27.44 (−14.43, 69.31)	30.7 ± 84.7 (n = 79)	10.1 ± 120.0 (n = 73)	25.32 (16.09, 66.73)	0.93
Change from baseline to 2 y	8.3 ± 106.6 (n = 65)	7.8 ± 172.6 (n = 41)	4.72 (−53.04, 62.48)	8.9 ± 98.0 (n = 56)	8.7 ± 99.9 (n = 49)	3.84 (−52.81, 60.48)	0.98

Notes. Values are mean ± standard deviation. LSM differences and *p*-values were calculated from analysis of covariance for paired changes over time adjusted for baseline values.
Abbreviations: GDMT, guideline-directed medical therapy; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary; LSM, least square means; PVSFR, pulmonary vein systolic flow reversal; TEER, transcatheter edge-to-edge repair.

In patients with cardiomyopathy and LV dysfunction, the development of FMR further increases left atrial pressure and reduces forward cardiac output. In individual patients, prognosis may be determined by the absolute and relative severity of LV impairment vs. MR (conditioned by involvement of the right heart). It has been suggested that TEER may be best suited for patients in whom MR is especially severe relative to the degree of LV dysfunction or dilatation, a concept referred to as "disproportionate MR."[8] However, while this conceptual framework is of potential utility when applied to group means, it has been difficult to derive a metric of mitral:LV disproportionality that can be used to discriminate individual patients more likely to benefit from TEER.[9]

Current American Society of Echocardiography guidelines recommend grading MR severity with a comprehensive multiparametric approach such as that used in COAPT.[10] Among the proposed parameters the American Society of Echocardiography recommends, PV flow is unique in that it does not evaluate the MR itself but instead assesses the retrograde hemodynamic impact of the regurgitant mitral flow on the LA and pulmonary vasculature. While elevated LA pressures and blunted systolic PV flows may be present in patients with LV dysfunction or atrial fibrillation (coexisting conditions in most patients with FMR), PVSFR has been shown to be highly specific for severe MR (specificity 80%-98%, sensitivity 60%-70%).[11-14] In a retrospective analysis, Ikenaga et al. described the potential utility of abnormal PV flow patterns from transesophageal echocardiography, with lower S/D-wave ratios (specifically, the systolic to diastolic velocity-time integral ratio) after TEER correlating with higher LA pressures and worse outcomes.[15]

In the current COAPT analysis, we explored whether the presence of PVSFR could serve as a simple readily assessable parameter to help identify HF patients with severe MR who would have distinctive responses to TEER. In this regard, previous analyses from COAPT reported that greater baseline severity of pulmonary hypertension, RV dysfunction, and tricuspid regurgitation are associated with worse clinical outcomes, but to a similar degree in patients treated with TEER plus GDMT vs. GDMT alone.[16-18] Nor did greater LV dilatation or LVEF reduction identify patients more likely to benefit from TEER treatment.[6] In the present study, the presence of PVSFR was associated not only with greater severity of FMR but also with numerous parameters of advanced multichamber cardiac compromise, with greater LV and RV dilatation and/or dysfunction, increased pulmonary artery pressures, and reduced stroke volume and cardiac output. However, PVSFR was not a predictor of prognosis in the circumscribed group of patients with HF and FMR enrolled in COAPT (bounded by strict enrollment criteria), and the improvement in survival and HFH with TEER was similar in patients with and without PVSFR. There were no significant interactions between the presence vs. absence of PVSFR and the relative improvements in mortality, freedom from HFH, QoL, and functional capacity conferred by TEER. While patients with PVSFR had more severe MR, the similar beneficial effect of TEER in patients with and without PVSFR suggests that TEER may be of benefit in patients with less than severe MR, as newer data from the EXPAND G4 study suggests (add ref Rogers J et al. JACC Interv 2023; 16:1474). Of course, this is just hypothesis-generating, and further mechanistic studies will be needed to better understand these effects.

Study Limitations

In the COAPT study, high-quality PV flow recordings on the baseline TTE sufficient for quantitative PV flow velocity measurements were not obtained in a substantial number of cases due to echogenicity or incomplete PV tracings. For this reason, we analyzed PV flows for the present study in a qualitative manner (PVSFR vs. no PVSFR), which increased the eligible proportion of our population (only 14.3% were not evaluable). While better tracings may have been obtained with transesophageal echocardiography, these were not collected in the COAPT trial, and their results may vary from TTE due to lower pressures from volume restriction or anesthesia during transesophageal echocardiography. Invasive LA and PV pressure measurements pre- and immediately

post-intervention may also have further clarified the role of PV flow in characterization of hemodynamic patterns but were not collected in COAPT. Similarly, significant missing data during follow-up prevents proper evaluation of the changes in PV flow over time. Secondly, although the present study is the largest prospective study to examine the frequency and impact of PVSFR in HF patients with severe FMR treated with TEER plus GDMT and GDMT alone, we may have been underpowered to detect all relationships between PVSFR and outcomes and all significant interactions between the treatment arms and subgroups. Third, although our results were adjusted for historically important clinical covariates, we cannot rule out the potential role of unmeasured confounders. Fourth, whether the results would be different with longer-term follow-up is also unknown; we truncated follow-up at 2 years in the present study as this was the time period after which patients in the control arm were allowed to crossover and be treated with the MitraClip device. Fifth, it is possible that by not having all 4 PV tracings on every patient, we could have missed PVSFR in some patients with eccentric MR jets due to ischemic MR. Finally, quantitative analysis of PV velocities was prespecified in COAPT, but the present qualitative analysis was not. These post-hoc analyses should thus be considered hypothesis-generating.

Conclusions

In the COAPT trial, treatment of severe FMR with TEER plus GDMT compared with GDMT alone reduced the rate of death, HFH, and improved QoL and functional capacity through 2-year follow-up consistently in patients with and without baseline PVSFR. The presence of PVSFR on the baseline TTE identified patients with greater MR severity and more extensive heart disease but with similar relative prognostic benefits from TEER as in patients without baseline PVSFR.

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Ethics Statement

Institutional review board/ethics committee approval was obtained from all sites that participated in the COAPT trial, and all patients signed informed consent. Abbott sponsored the trial and provided funding to the Cardiovascular Research Foundation (New York, NY) for statistical support for the present analysis. The investigators had unrestricted access to the data and accept responsibility for the integrity of the present report.

Funding

The COAPT trial was sponsored by Abbott (Santa Clara, CA) and designed collaboratively by the principal investigators and the sponsor.

Disclosure Statement

F. M. Asch is the Director of the Core Laboratories at MedStar Health Research Institute, which has institutional contracts (no personal compensation) with Abbott, Neovasc, Ancora, Mitralign, Medtronic, Boston Scientific, Edwards Lifesciences, Biotronik, and Livanova. S. H. Little is a consultant for Caption Health, Inc. B. Redfors reports consultant fees from Pfizer and Boehringer Ingelheim. N. J. Weissman reports institutional contracts (no personal compensation) with Abbott, Neovasc, Mitralign, Medtronic, Boston Scientific, Edwards Lifesciences, Biotronik, and Livanova. P. A. Grayburn has received grant support and consulting fees from Edwards Lifesciences and Neochord, as well as research funding from Boston Scientific, Medtronic, and Tendyne. S. Kar reports consulting fees from Boston Scientific, W. L. Gore, and Medtronic and consulting fees/stock equity from Valcare. S. Lim has received research grant support from Abbott, Edwards, Medtronic, and Gore; is a consultant to Abbott, Edwards, Keystone Heart, Pipeline, Siemens, Valgen, and Venus; participates on the advisory board for Ancora and Venus; and holds equity in 510Kardiac and Venus. W. T. Abraham receives research grant support from Abbott Vascular and is supported by the National Institutes of Health–National Heart, Lung, and Blood Institute (National Institutes of Health 1 UG3 / UH3 HL140144-01, 08/01/18-07/31/22, "Impact of Low Flow Nocturnal Oxygen Therapy on Hospital Readmission/Mortality in Patients with Heart Failure and Central Sleep Apnea (LOFT-HF)"; he has also received consulting income from Abbott Vascular and speaker honoraria from Impulse Dynamics. J. Lindenfeld receives research grant support from AstraZeneca and consulting income from Abbott Vascular, CVRx, Edwards Lifesciences, RESMED, Relypsa, Boehringer Ingelheim, and V-Wave. M. J. Mack reports nonfinancial relationships: he has served as co-primary investigator for the PARTNER 3 Trial (Edwards Lifesciences) and the COAPT trial (Abbott) and served as study chair for the APOLLO trial (Medtronic). G. W. Stone reports speaker honoraria from Medtronic, Pulnovo, and Infraredx; receives consultant fees from Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Vectorious, Miracor, Neovasc, Abiomed, Ancora, Elucid Bio, Occlutech, CorFlow, Apollo Therapeutics, Impulse Dynamics, Vascular Dynamics, Shockwave, V-Wave, Cardiomech, Gore, and Amgen; has equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Xenter. Institutional disclosures: G. W. Stone's employer, Mount Sinai Hospital, receives research support from Abbott, Abiomed, Bioventrix, Cardiovascular Systems Inc, Phillips, Biosense-Webster, Shockwave, Vascular Dynamics, and V-wave. Family disclosure: G. W. Stone's daughter is an employee at IQVIA. The other authors had no conflicts to declare.

Acknowledgments

The coauthors would like to thank Clayton Snyder, MPH (Clinical Trials Center, Cardiovascular Research Foundation) for his contribution to the statistical analysis and revision of this manuscript.

Review Statement

The review of this paper was managed by guest editor Robert Siegel, MD.

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