JACC: CARDIOVASCULAR INTERVENTIONS VOL. 13, NO. 20, 2020

PUBLISHED BY ELSEVIER

Baseline Functional Capacity and Transcatheter Mitral Valve Repair in Heart Failure With Secondary Mitral Regurgitation

Umar I. Malik, MD,[a] Andrew P. Ambrosy, MD,[a,b] Ivy A. Ku, MD,[a] Jacob M. Mishell, MD,[a] Saibal Kar, MD,[c,d] D. Scott Lim, MD,[e] Brian K. Whisenant, MD,[f] David J. Cohen, MD, MSc,[g] Suzanne V. Arnold, MD, MHA,[g,h] Lak N. Kotinkaduwa, PhD,[i] JoAnn Lindenfeld, MD,[j] William T. Abraham, MD,[k] Michael J. Mack, MD,[l] Gregg W. Stone, MD,[i,m]

ABSTRACT

OBJECTIVES The aim of this study was to determine the prognostic utility of baseline functional status and its impact on the outcomes of transcatheter mitral valve repair (TMVr) in patients with heart failure (HF) with secondary mitral regurgitation (SMR).

BACKGROUND The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial demonstrated that TMVr with the MitraClip in patients with HF with moderate to severe or severe SMR improved health-related quality of life. The clinical utility of a baseline assessment of functional status for evaluating prognosis and identifying candidates likely to derive a robust benefit from TMVr has not been previously studied in patients with HF with SMR.

METHODS The COAPT study was a multicenter, randomized, controlled, parallel-group, open-label trial of TMVr with the MitraClip plus guideline-directed medical therapy (GDMT) versus GDMT alone in patients with HF, left ventricular ejection fraction 20% to 50%, and moderate to severe or severe SMR. Baseline functional status was assessed by 6-min walk distance (6MWD).

RESULTS Patients with 6MWD less than the median (240 m) were older, were more likely to be female, and had more comorbidities. After multivariate modeling, age ($p = 0.005$), baseline hemoglobin ($p = 0.007$), and New York Heart Association functional class III/IV symptoms ($p < 0.0001$) were independent clinical predictors of 6MWD. Patients with 6MWD <240 m versus ≥240 m had a higher unadjusted and adjusted rate of the 2-year composite of all-cause death or HF hospitalization (64.4% vs. 48.6%; adjusted hazard ratio: 1.53; 95% confidence interval: 1.19 to 1.98; $p = 0.001$). However, there was no interaction between baseline 6MWD and the relative effectiveness of TMVr plus GDMT versus GDMT alone with respect to the composite endpoint ($p = 0.633$).

CONCLUSIONS Baseline assessment of functional capacity by 6MWD was a powerful discriminator of prognosis in patients with HF with SMR. TMVr with the MitraClip provided substantial improvements in clinical outcomes for this population irrespective of baseline functional capacity. (J Am Coll Cardiol Intv 2020;13:2331–41) © 2020 by the American College of Cardiology Foundation.

From the [a]Department of Cardiology, The Permanente Medical Group, San Francisco, California; [b]Division of Research, Kaiser Permanente Northern California, Oakland, California; [c]Los Robles Regional Medical Center, Thousand Oaks, California; [d]Bakersfield Heart Hospital, Bakersfield, California [e]Division of Cardiology, University of Virginia, Charlottesville, Virginia; [f]Intermountain Medical Center Heart Institute, Salt Lake City, Utah; [g]University of Missouri-Kansas City, Kansas City, Missouri; [h]Saint Luke's Mid America Heart Institute, Kansas City, Missouri; [i]Clinical Trials Center, Cardiovascular Research Foundation, New York, New York; [j]Vanderbilt Heart and Vascular Institute, Nashville, Tennessee; [k]Division of Cardiovascular Medicine, The Ohio State University, Columbus, Ohio; [l]Baylor Scott & White Health, Plano, Texas; and [m]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York. The COAPT trial was sponsored by Abbott and was designed collaboratively by the principal investigators and the sponsor. Dr. Ambrosy has received significant research funding from Abbott Vascular, Novartis, Amarin, the National Heart, Lung, and Blood Institute, the National Institute on Aging, the

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2020.07.030

ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

6MWT = 6-min walk test

CI = confidence interval

GDMT = guideline-directed medical therapy

HF = heart failure

HR = hazard ratio

LV = left ventricular

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

SMR = secondary mitral regurgitation

TMVr = transcatheter mitral valve repair

Heart failure (HF) is a burgeoning public health problem with an estimated worldwide prevalence of 38 million (1,2). Secondary mitral regurgitation (SMR) is a common sequela of HF and occurs as a result of progressive left ventricular (LV) dilatation and remodeling with apical and lateral displacement of the papillary muscles and chordal apparatus (3). The presence of SMR in patients with HF with a reduced LV ejection fraction (LVEF) has been associated with impaired quality of life, functional limitations, increased rate of hospitalization, and reduced survival despite guideline-directed medical therapy (GDMT) and cardiac resynchronization therapy (4–6). The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial previously reported that in patients with HF and moderate to severe or severe SMR who remained symptomatic despite maximally tolerated GDMT alone at enrollment, treatment with the MitraClip (Abbott Vascular, Santa Clara, California) improved health-related quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire and functional capacity as measured by the 6-min walk test (6MWT) and reduced the 2-year rates of death and HF hospitalization (7–9).

Although patients with HF often experience marked functional limitations, the presence of which has been strongly associated with decreased survival (10–14), GDMT and aerobic exercise training have had minimal impact on functional outcomes (15,16). As a result, it is particularly notable that transcatheter mitral valve repair (TMVr) in the COAPT trial resulted in a between-group improvement in 6-min walk distance (6MWD) from baseline to 12 months of about 60 m (7,8); however, the clinical utility of a baseline assessment of functional status for evaluating prognosis and identifying potential candidates likely to derive a robust benefit from TMVr has not been previously studied in patients with HF and SMR. Thus, the objectives of the present pre-specified analysis of the COAPT trial were: 1) to identify independent clinical predictors of baseline functional status; 2) to evaluate the association between baseline functional status and the risk for subsequent morbidity and mortality; and 3) to explore whether baseline functional status affected the relative benefits of TMVr plus GDMT versus GDMT alone on the composite and individual outcomes of all-cause death and HF hospitalization.

SEE PAGE 2342

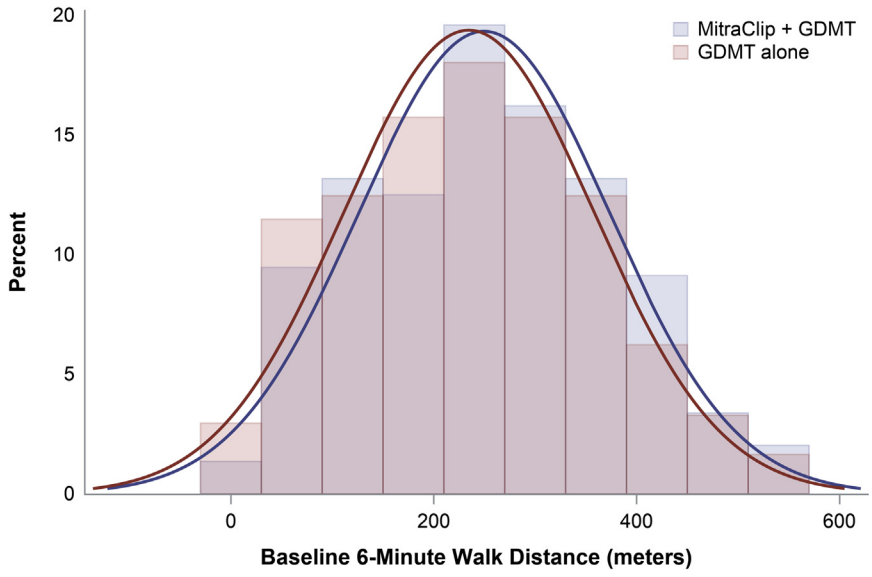
METHODS

STUDY OVERVIEW. The study design (7) and primary results (8) of the COAPT trial (NCT01626079) have been previously published. Briefly, COAPT was a multicenter, randomized, controlled, parallel-group, open-label trial of TMVr with the MitraClip in patients with HF of ischemic or nonischemic etiology, LVEFs of 20% to 50%, and moderate to severe (3+) or severe (4+) SMR who remained symptomatic (New York Heart Association [NYHA] functional class II, III, or ambulatory IV) despite the use at the time of enrollment of maximally tolerated GDMT and cardiac resynchronization therapy

National Institute of Diabetes and Digestive and Kidney Diseases, and the Kaiser Permanente Northern California Community Benefit Program; and has received modest reimbursement for travel from Novartis. 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 Vascular; and has received consulting income from Abbott Vascular. Dr. Whisenant is a consultant for Edwards Lifesciences, Boston Scientific, Gore, and NeoChord. Dr. Cohen has received research grant support from Abbott, Medtronic, Edwards Lifesciences, and Boston Scientific; and has received consulting income from Abbott, Medtronic, Edwards Lifesciences, Boston Scientific. 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. Abraham has received research grant support from Abbott Vascular; and has received consulting income from Abbott Vascular. Dr. Mack served as co-primary investigator for the PARTNER 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 speaking honoraria from Cook and Terumo; has served as a consultant for Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, and Matrizyme; and has equity or options in Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, the Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, the 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.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

Manuscript received May 19, 2020; revised manuscript received July 14, 2020, accepted July 21, 2020.

FIGURE 1 Baseline Functional Assessment



The distribution of 6-min walk distance by treatment arm. GDMT = guideline-directed medical therapy.

(if appropriate). Selected exclusion criteria included chronic obstructive pulmonary disease requiring home oxygen, valvular heart disease requiring intervention, cerebrovascular accident within 30 days of enrollment, American College of Cardiology/American Heart Association stage D HF, Modified Rankin Scale score ≥4 disability, and life expectancy <12 months because of noncardiac conditions.

A total of 614 patients were randomized to TMVr plus GDMT (device group) versus GDMT alone (control group). Clinical follow-up is currently complete through 2 years in all patients and is ongoing through 5 years. The study complies with the Declaration of Helsinki, the protocol was approved by the locally appointed Institutional Review Board and/or ethics committee at each participating center, and written informed consent was obtained from all study participants.

FUNCTIONAL ASSESSMENTS. The 6MWT was administered per American Thoracic Society guidelines (17) and measured the distance a patient can walk on a flat surface in a 30-m hallway in a period of 6 min. Two small cones were placed at each end of the hallway to mark the turnaround points. Patients chose their own intensity of exercise and were allowed to stop and rest during the test as needed. A total of 601 patients (98%) completed the 6MWT at baseline, before randomization, constituting the present study population. Of the 13 patients without 6MWTs available, 4 patients were unable to perform the test because of symptoms (shortness of breath, acute gout flare, or knee pain), 3 patients had limited mobility due to the use of a wheelchair, and the remaining 6 patients did not have specified reasons for not completing the test.

ENDPOINT DEFINITIONS. Clinical endpoints of interest for the present analysis were the 2-year rates of hospitalization for HF, all-cause death, and the composite of all-cause death or hospitalization for HF. Hospitalization for HF was defined as admission to any inpatient unit or hospital ward for at least 24 h in patients with clinical signs and/or symptoms of HF, resulting in intravenous therapies, mechanical or surgical interventions, or ultrafiltration for worsening HF. All endpoints were adjudicated by an independent clinical events committee.

STATISTICAL ANALYSES. Baseline characteristics and outcomes were dichotomized according to baseline 6MWD above or below the median. Categorical variables are presented as frequency (percentage) and

TABLE 1 Baseline Clinical Characteristics Stratified by Median 6MWD

	6MWD <240 m	6MWD ≥240 m	p Value
Age, yrs	75 ± 10	70 ± 12	<0.001
Male	164 (55.4)	223 (73.1)	<0.001
White or Caucasian race	218 (73.6)	229 (75.1)	0.93
Diabetes	131 (44.3)	93 (30.5)	<0.001
Chronic obstructive pulmonary disease	80 (27.0)	59 (19.3)	0.03
Renal disease	229 (79.2)	202 (67.3)	0.002
History of anemia	83 (28.0)	59 (19.3)	0.01
Ischemic cardiomyopathy	186 (62.8)	180 (59)	0.34
New York Heart Association functional class			
I	0 (0.0)	1 (0.3)	0.32
II	67 (22.6)	170 (55.9)	<0.001
III	183 (61.8)	128 (42.1)	<0.001
IV	46 (15.5)	5 (1.6)	<0.001
Prior stroke	42 (14.2)	29 (9.5)	0.08
Prior transient ischemic attack	22 (7.4)	20 (6.6)	0.67
Coronary artery disease	230 (77.7)	206 (67.5)	0.005
Prior myocardial infarction	154 (52.0)	155 (50.8)	0.77
Prior coronary artery bypass grafting	123 (41.6)	120 (39.3)	0.58
Prior percutaneous coronary intervention	141 (47.6)	137 (44.9)	0.50
History of atrial flutter	31 (10.5)	32 (10.5)	0.99
History of atrial fibrillation	161 (54.4)	160 (52.5)	0.63
Hospitalization 12 months prior to enrollment			
Heart failure	185 (62.5)	159 (52.1)	0.01
Other cardiovascular	35 (11.8)	29 (9.5)	0.36
Noncardiovascular	22 (7.4)	24 (7.9)	0.84
Guideline-directed medical therapy			
ACE inhibitor, ARB, or ARN inhibitor	174 (58.8)	228 (74.8)	<0.0001
Aldosterone antagonist agent	172 (56.4)	172 (56.4)	0.004
Beta-blocker	260 (87.8)	282 (92.5)	0.057
Diuretic agent	260 (87.8)	277 (90.8)	0.24
Prior device implantation			
Implantable cardioverter-defibrillator	75 (25.3)	112 (36.7)	0.003
Cardiac resynchronization therapy	111 (37.5)	111 (36.4)	0.78
Kansas City Cardiomyopathy Questionnaire score	44 ± 22	61 ± 21	<0.001
STS replacement score, %	9.9 ± 6.3	6.4 ± 4.7	<0.001
≥8%	162 (54.7)	92 (30.2)	<0.001
STS repair score, %	7.2 ± 6.3	4.4 ± 4.1	<0.001
≥8%	89 (30.1)	42 (13.8)	<0.001
Vital signs			
Body mass index, kg/m^2	27 ± 6	27 ± 6	0.55
Systolic blood pressure, mm Hg	112 ± 16	111 ± 17	0.34
Heart rate, beats/min	76 ± 12	73 ± 13	0.008

Values are mean ± SD or n (%).

6MWD = 6-min walk distance; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARN = angiotensin receptor-neprilysin; STS = Society of Thoracic Surgeons.

TABLE 2 Baseline Laboratory and Echocardiographic Characteristics Stratified by Median 6MWD

	6MWD <240 m	6MWD ≥240 m	p Value
Laboratory findings			
Creatinine clearance			
Mean, ml/min	44 ± 24	55 ± 28	<0.001
≤60 ml/min	229 (79.2)	202 (67.3)	0.001
BNP, pg/ml	1,219 ± 1,394	796 ± 734	<0.001
NT-proBNP, pg/ml	7,967 ± 10,552	3,883 ± 3,906	0.0009
Serum albumin, g/dl	4.5 ± 4.5	5.6 ± 7.0	0.03
Echocardiography core laboratory findings			
Severity of mitral regurgitation			0.09
Moderate to severe, grade 3+	144 (48.8)	170 (55.7)	
Severe, grade 4+	151 (51.2)	135 (44.3)	
Effective regurgitant orifice area, cm^2	0.4 ± 0.2	0.4 ± 0.2	0.49
Left ventricular ejection fraction			
Mean, %	31 ± 10	31 ± 9	0.73
≤40%	226 (81.0)	238 (83.2)	0.49
Left ventricular end-systolic volume index, ml/m^2	67 ± 28	76 ± 30	0.0004
Left ventricular end-diastolic volume index, ml/m^2	96 ± 32	108 ± 36	<0.001
Regurgitant volume, ml/beat	24 ± 13	30 ± 18	0.003
Right ventricular systolic pressure, mm Hg	46 ± 14	43 ± 13	0.008
Left atrial volume, ml	90 ± 44	93 ± 38	0.37

Values are mean ± SD or n (%).

6MWD = 6-min walk distance; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

were compared using the chi-square or Fisher exact test. Continuous variables are presented as mean ± SD and were compared using Student's *t*-test or the Wilcoxon rank sum test for data not normally distributed. All effectiveness analyses were performed from the time of randomization in the intention-to-treat population. Cumulative clinical event rates were calculated according to the Kaplan-Meier method; the differences in clinical outcomes between the 2 treatment groups were assessed using the log-rank test, and the hazard ratio (HR) and associated 95% confidence interval (CI) were calculated using a Cox proportional hazards model. Multivariate linear regression was used to identify the independent predictors of 6MWD at baseline. Multivariate analyses were performed with 6MWD as a categorical (less than vs. greater than or equal to the median) and continuous (per 10-m decrease) variable. A 2-sided p value of <0.05 was selected as the threshold for statistical significance. All analyses were performed in SAS version 9.4 (SAS Institute, Cary, North Carolina).

TABLE 3 Independent Predictors of 6-Min Walk Distance by Linear Regression

	Estimate (95% CI)	p Value
Demographics		
Age	−3 (−5 to −1)	0.005
Male	34 (−5 to 73)	0.08
Race		
White or Caucasian	Ref.	—
Black or African American vs. white or Caucasian	6 (−40 to 52)	0.81
Hispanic or Latino vs. white or Caucasian	4 (−61 to 68)	0.91
Asian vs. white or Caucasian	−14 (−105 to 77)	0.76
Other vs. white or Caucasian	42 (−56 to 140)	0.40
Vital signs		
Heart rate	−1 (−2 to 1)	0.27
Laboratory findings		
Elevated BNP or NT-proBNP	43 (−20 to 107)	0.18
Serum albumin	2 (−1 to 4)	0.13
Hemoglobin	15 (4 to 25)	0.007
Comorbidities		
Diabetes	−22 (−56 to 12)	0.20
Chronic obstructive pulmonary disease	−26 (−62 to 11)	0.17
Renal disease	−13 (−52 to 25)	0.50
History of anemia	−13 (−54 to 28)	0.54
Cardiovascular history		
Ischemic cardiomyopathy	31 (−18 to 80)	0.22
NYHA functional class		
I vs. II	13 (−196 to 222)	0.90
II	Ref.	—
III vs. II	−100 (−134 to −66)	<0.0001
IV vs. II	−144 (−205 to −83)	<0.0001
Previous stroke or transient ischemic attack	−15 (−53 to 24)	0.45
Coronary artery disease	−6 (−59 to 46)	0.81
History of atrial fibrillation or flutter	16 (−20 to 53)	0.38
Any hospitalization 12 months prior to enrollment	−28 (−62 to 6)	0.11
Guideline-directed medical therapy		
ACE inhibitor, ARB, or ARN inhibitor	13 (−22 to 47)	0.46
Aldosterone antagonist agent	−16 (−49 to 17)	0.33
Beta-blocker	26 (−28 to 79)	0.34
Cardiac resynchronization therapy	10 (−23 to 42)	0.57
Echocardiographic findings		
Severity of mitral regurgitation, grade 4+ vs. 3+	10 (−26 to 47)	0.58
Effective regurgitant orifice area	−68 (−164 to 29)	0.17
Left ventricular ejection fraction	0 (−4 to 4)	0.93
Left ventricular end-systolic volume index	−1 (−4 to 1)	0.31
Left ventricular end-diastolic volume index	2 (−1 to 4)	0.14
Regurgitant volume	0 (−1 to 2)	0.70
Right ventricular systolic pressure	−1 (−2 to 1)	0.30
Left atrial volume	0 (0 to 0)	0.58

CI = confidence interval; NYHA = New York Heart Association; other abbreviations as in Tables 1 and 2.

FUNDING AND MANUSCRIPT PREPARATION. The COAPT trial was sponsored by Abbott. The protocol was designed by the principal investigators and the sponsor in accordance with the Mitral Valve Academic Research Consortium (6,18). The sponsor participated in site selection and in data analysis. We take responsibility for the paper's integrity and controlled its preparation and the decision to publish.

RESULTS

FUNCTIONAL CAPACITY AND PATIENT CHARACTERISTICS. The median baseline 6MWD was 240 m (interquartile range: 146 to 331 m; range 3 to 567 m). The distribution of 6MWD was similar between treatment groups (TMVr plus GDMT vs. GDMT alone) (Figure 1). Patients with 6MWD <240 m were older, were more likely to be female, and had a higher

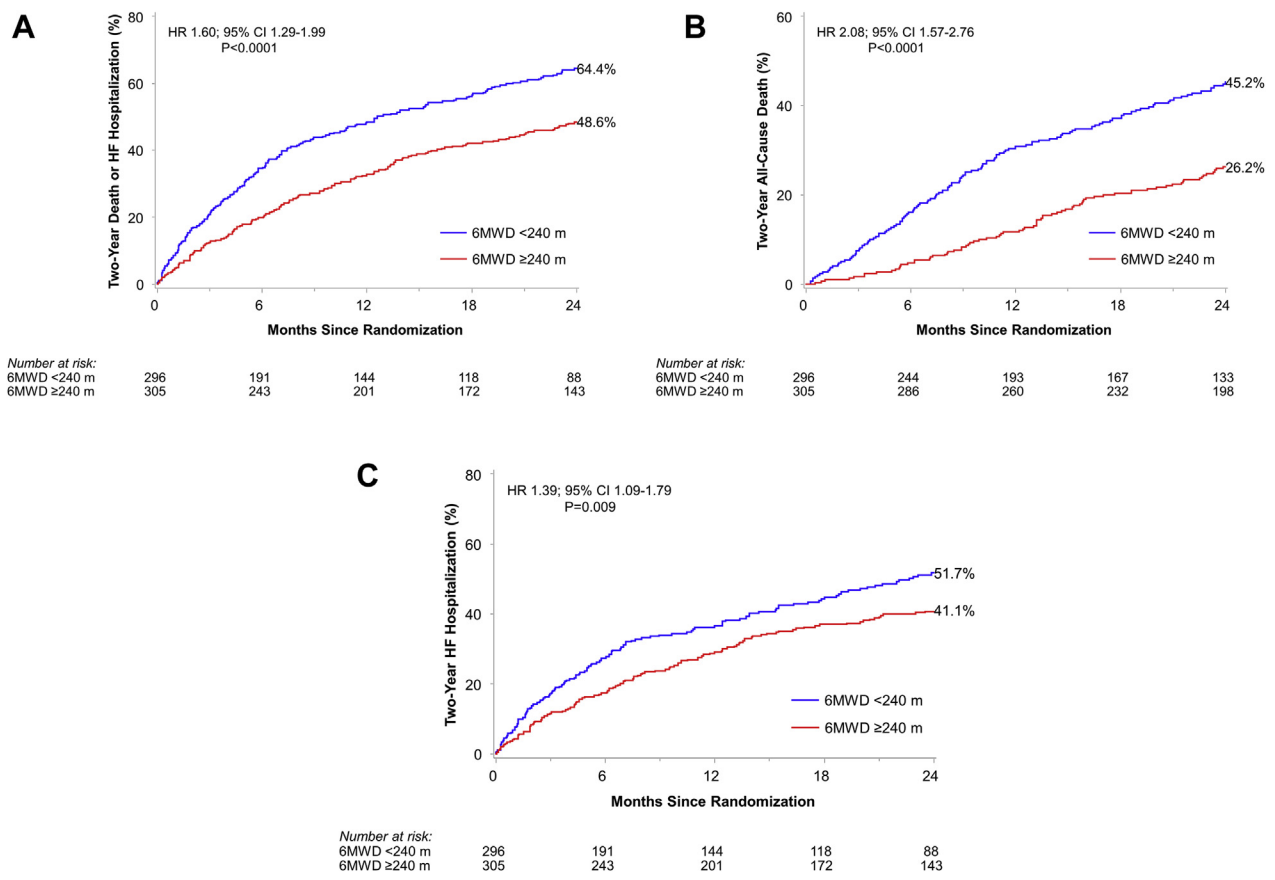
TABLE 4 Association Between 6MWD at Baseline and Clinical Outcomes

	6MWD as a Categorical Variable*				6MWD as a Continuous Variable†			
	Unadjusted Models		Adjusted Models		Unadjusted Models		Adjusted Models	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
All-cause death or HF hospitalization	1.60 (1.29–1.99)	<0.0001	1.53 (1.19–1.98)	0.001	1.02 (1.01–1.03)	<0.0001	1.02 (1.01–1.03)	0.0009
All-cause death	2.08 (1.57–2.76)	<0.0001	1.73 (1.24–2.41)	0.001	1.04 (1.02–1.05)	<0.0001	1.03 (1.01–1.04)	<0.0001
HF hospitalization	1.39 (1.09–1.79)	0.009	1.40 (1.04–1.87)	0.02	1.02 (1.00–1.03)	0.005	1.01 (1.00–1.03)	0.02

Multivariate models adjusted for age, sex, cardiomyopathy, hospitalization 12 months prior to enrollment, atrial fibrillation or flutter, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, anemia, B-type natriuretic peptide; N-terminal pro-B-type natriuretic peptide, left ventricular end-systolic volume index, left ventricular ejection fraction, and severity of mitral regurgitation. *Less than vs. greater than or equal to the median; †Per 10-m decrease.

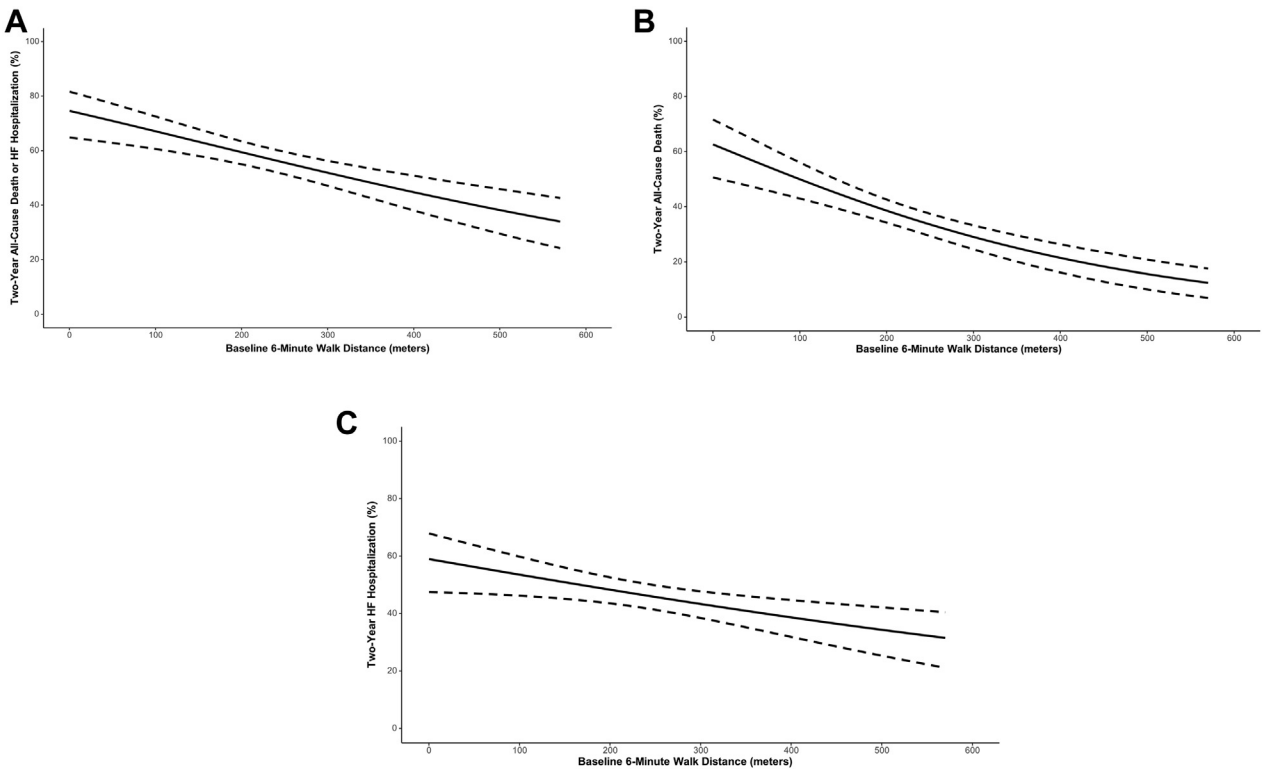
HF = heart failure; HR = hazard ratio; other abbreviations as in Tables 1 and 3.

FIGURE 2 Baseline Functional Status and Outcomes Over Time



The cumulative incidence curves for **(A)** all-cause death or heart failure (HF) hospitalization, **(B)** all-cause death, and **(C)** HF hospitalization stratified by median 6-min walk distance (6MWD). CI = confidence interval; HR = hazard ratio.

FIGURE 3 Baseline Functional Capacity and Crude Event Rates



The unadjusted associations between 6-min walk distance and **(A)** all-cause death or heart failure (HF) hospitalization, **(B)** all-cause death, and **(C)** HF hospitalization at 2 years.

prevalence of comorbidities, including diabetes mellitus, chronic obstructive pulmonary disease, renal disease, and anemia compared with patients with 6MWD ≥240 m (Tables 1 and 2). These patients were also more likely to report NYHA functional class III or IV symptoms, had higher Society of Thoracic Surgeons risk scores, had greater abnormalities in baseline laboratory values (e.g., natriuretic peptides, creatine clearance, albumin), were less likely to tolerate GDMT for HF, and were less likely to have implantable cardioverter-defibrillators.

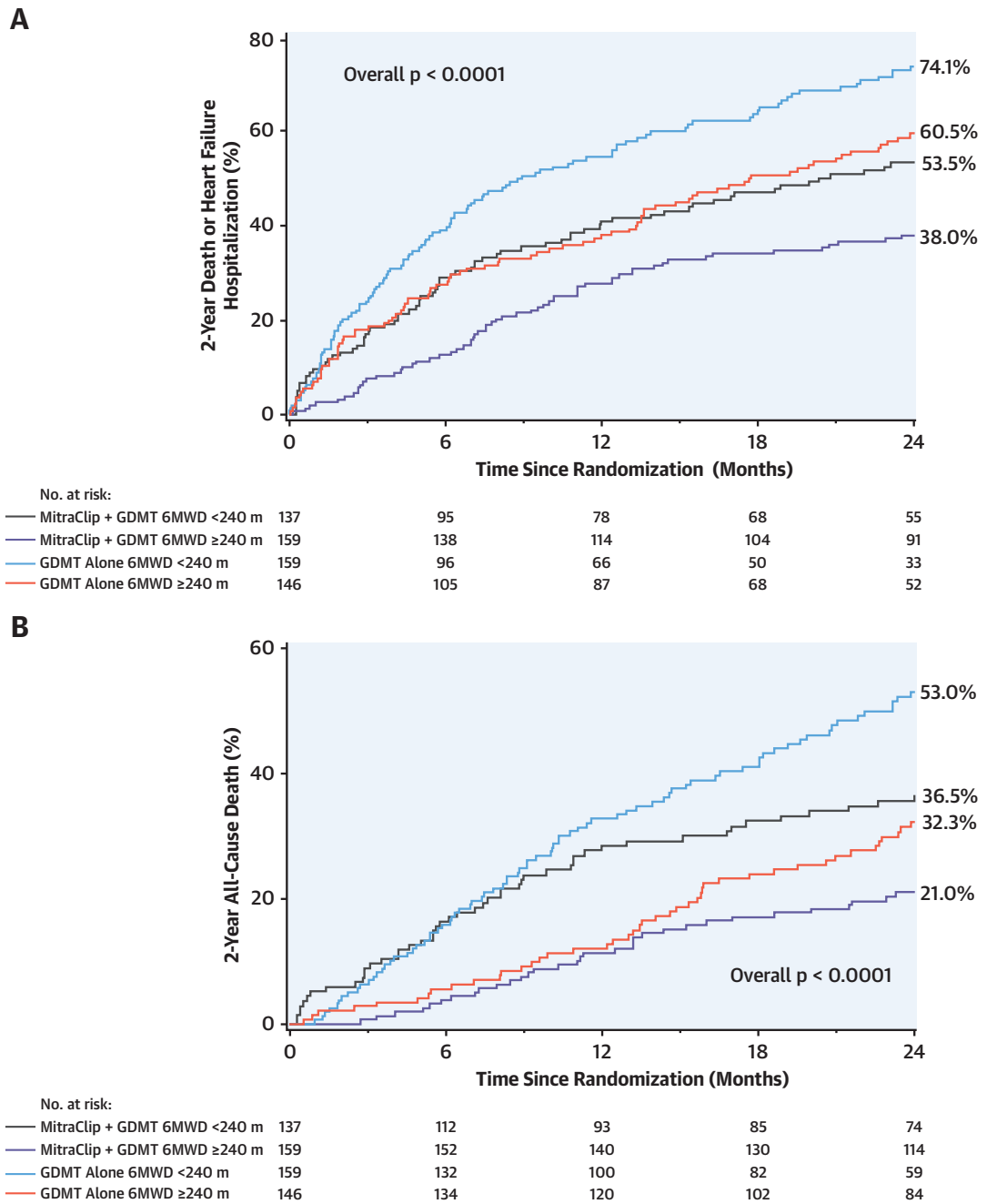
Using multivariate linear regression, older age, baseline hemoglobin, and NYHA functional class III and IV symptoms versus class II symptoms (reference group) were independently associated with lower baseline 6MWD (Table 3).

ASSOCIATION BETWEEN FUNCTIONAL CAPACITY AND CLINICAL OUTCOMES. Patients with 6MWD <240 m versus ≥240 m had significantly higher unadjusted rates of the 2-year composite of all-cause death or HF hospitalization (64.4% vs. 48.6%; HR: 1.60; 95% CI: 1.29 to 1.99; $p < 0.0001$), all-cause death (45.2% vs. 26.2%; HR: 2.08; 95% CI: 1.57 to 2.76; $p < 0.0001$), and HF hospitalization (51.7% vs. 41.1%; HR: 1.39; 95% CI: 1.09 to 1.79; $p = 0.008$) (Table 4, Figure 2). By spline analysis, a linear relationship was noted between baseline 6MWD and these outcomes (Figure 3).

After adjusting for potential confounders, 6MWD remained independently associated with the composite of all-cause death or HF hospitalization over 2 years of follow-up, as well as the individual hazards of all-cause death and HF hospitalization (Table 4).

INTERACTION BETWEEN BASELINE FUNCTIONAL STATUS, TREATMENT, AND OUTCOMES. The 2-year outcomes of patients randomized to TMVr plus GDMT compared with GDMT alone stratified by baseline 6MWD are shown in the Central Illustration. The 2-year rates of the composite of all-cause death or HF hospitalization, as well as

CENTRAL ILLUSTRATION **Baseline Functional Status and Treatment Effect**



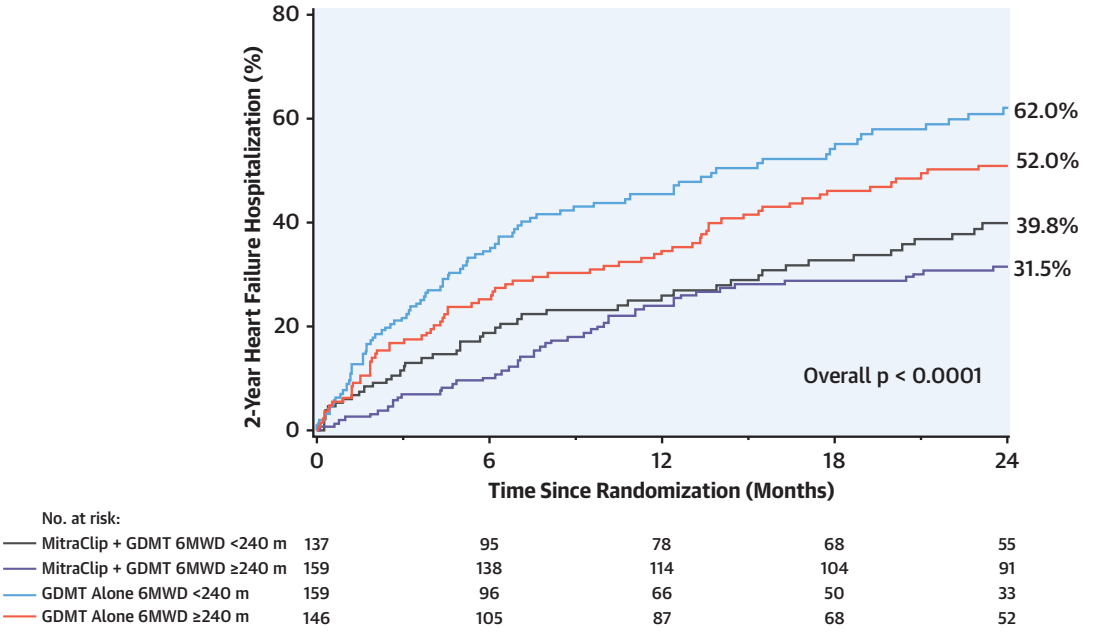
Malik, U.I. et al. J Am Coll Cardiol Intv. 2020;13(20):2331–41.

The cumulative incidence curves for **(A)** all-cause death or heart failure (HF) hospitalization, **(B)** all-cause death, and **(C)** HF hospitalization stratified by median 6-min walk distance (6MWD) and treatment arm. The 2-year rates of the composite of all-cause death or HF hospitalization, as well as the individual rates of all-cause death and HF hospitalization, were reduced by transcatheter mitral valve repair (TMVr) with consistent effects in patients with lower and higher baseline 6MWD. These data suggest that TMVr should not be withheld in otherwise appropriately selected patients solely on the grounds of limited functional capacity. GDMT= Guideline-Directed Medical Therapy.

Continued on the next page

CENTRAL ILLUSTRATION Continued

C



Malik, U.I. et al. J Am Coll Cardiol Intv. 2020;13(20):2331–41.

the individual rates of all-cause death and HF hospitalization, were reduced by TMVr, with consistent effects in patients with lower and higher baseline 6MWD (Table 5).

DISCUSSION

The present study is the first comprehensive and longitudinal evaluation of the association between baseline functional status and clinical characteristics and outcomes in patients with HF and moderate to severe or severe SMR. Patients with reduced 6MWD were older, were more likely to be women, had a higher prevalence of noncardiac comorbidities, and were less likely to tolerate GDMT. However, age, baseline hemoglobin, and NYHA functional class III and IV symptoms were independently associated with poor functional capacity. In addition, functional status was a powerful determinant of prognosis; patients with reduced 6MWD experienced substantially higher rates of mortality and HF hospitalizations regardless of treatment assignment. Most important, TMVr with the MitraClip improved the poor prognosis in this high-risk cohort, to a similar relative degree as

TABLE 5 2-Year Clinical Outcomes According to Baseline Functional Status and Randomized Treatment Assignment

	6MWD <240 m			6MWD ≥240 m			
	TMVr + GDMT	GDMT Alone	HR (95% CI)	TMVr + GDMT	GDMT Alone	HR (95% CI)	$p_{interaction}$
Death or HF hospitalization	53.5% (71)	74.1% (113)	0.60 (0.44-0.80)	38% (60)	60.5% (86)	0.53 (0.38-0.74)	0.633
Death	36.5% (48)	53% (79)	0.66 (0.46-0.94)	21% (33)	32.3% (44)	0.63 (0.40-0.98)	0.923
HF hospitalization	39.8% (46)	61.9% (86)	0.51 (0.36-0.73)	31.5% (48)	51.9% (71)	0.52 (0.36-0.75)	0.953

Event rates are Kaplan-Meier estimates, percentage rate (number of events).

GDMT = guideline-directed medical therapy; TMVr = transcatheter mitral valve repair; other abbreviations as in Tables 1, 3, and 4.

in patients with more preserved baseline functional status.

Although patients with worse functional capacity at baseline exhibited a distinct clinical profile, it is notable that baseline 6MWD did not differ with the etiology of HF (ischemic vs. nonischemic cardiomyopathy), prevalence of cardiac comorbidities, LVEF, severity of SMR, and other echocardiographic parameters. Although older age is widely recognized (17) as a major determinant of functional status, the association in the present study was modest (an ~30-m decrease in 6MWD per decade, considered a clinically relevant difference) (19,20). In contrast, the effect size for NYHA functional class III or IV compared with NYHA functional class II symptoms (~100 to 150 m) was substantially larger, suggesting that there still is some value in this decades-old subjective criterion.

Poor baseline functional status was strongly associated with increased early and late rates of adverse outcomes. Importantly, worse functional status at baseline was associated with an approximately 2-fold increased risk for all-cause death or HF hospitalization, even after adjusting for traditional risk factors. The finding that 6MWD was a powerful discriminator of outcomes in HF with moderate to severe or severe functional SMR is consistent with limited prior studies (21,22) and suggests that this pragmatic and cost-efficient approach to functional testing may be useful in evaluating prognosis at the point of care.

The relative effect of TMVr was consistent in both groups (HR: 0.60 [95% CI: 0.44 to 0.80] vs. 0.53 [95% CI: 0.38 to 0.74], respectively; $p_{interaction} = 0.633$). Despite the worse prognosis in patients with reduced 6MWD, TMVr with the MitraClip provided substantial clinical benefit regardless of baseline functional status; the number needed to treat to prevent 1 death or HF hospitalization within 24 months was 4.9 versus 4.4 in patients with baseline 6MWD less than versus greater than or equal to the median, respectively. MitraClip treatment in these patients with HF with moderate to severe or severe SMR also reduced the individual outcomes of death and HF hospitalization, with similar relative efficacy in patients with lesser and greater baseline functional status. Thus, MR reduction with the MitraClip should not be withheld in otherwise appropriate patients solely on the grounds of limited functional capacity alone. Rather, the decision to refer a patient for TMVr should be individualized and take into account patient factors, echocardiographic parameters (23), and technical considerations.

STUDY LIMITATIONS. Beyond the limitations of the COAPT trial in general (8), several caveats of the present study bear notice. First, almost all patients enrolled in COAPT were able to ambulate for 6 min; only 13 patients did not complete the baseline 6MWT because of symptoms or limitations in mobility. Whether the results of MitraClip treatment would be as or more favorable in nonambulatory patients is unknown.

Second, although the 6MWT is straightforward to administer, cardiopulmonary exercise testing remains the gold standard for assessing exercise capacity as well as for distinguishing the underling etiology of functional limitations (cardiac vs. pulmonary versus peripheral).

Third, the 6MWT has been shown to be reproducible (coefficient of variation = 8%), although sex, body habitus, and motivation may influence the variability of results (17). Nonetheless, in clinical practice only a single test would be administered, and this single test was strongly predictive of subsequent death and HF hospitalization.

Finally, the study findings cannot necessarily be generalized to patients with HF and SMR not otherwise meeting the enrollment criteria of the COAPT trial.

CONCLUSIONS

In the COAPT trial, reduced baseline 6MWD was a strong independent predictor of the 2-year rates of death and HF hospitalization in patients with HF and moderate to severe or severe SMR. Given the simplicity and low-cost nature of the 6MWT, incorporating this assessment in the routine evaluation of patients with HF is thus recommended. Nonetheless, patients with HF enrolled in the COAPT trial derived a robust benefit from TMVr with the MitraClip compared with GDMT alone, irrespective of baseline functional status. Poor 6MWD should thus not be used in isolation to determine a patient's candidacy for TMVr.

ADDRESS FOR CORRESPONDENCE: Dr. Gregg W. Stone, Mount Sinai Hospital, Cardiovascular Research Foundation, 1700 Broadway, 8th Floor, New York, New York 10019. E-mail: gregg.stone@mountsinai.org. Twitter: @GreggWStone.

PERSPECTIVES

WHAT IS KNOWN? Baseline assessment of functional capacity by 6MWD is a powerful discriminator of prognosis in patients with HF and SMR. TMVr with the MitraClip provided substantial improvements in clinical outcomes irrespective of baseline functional capacity.

WHAT IS NEW? As such, poor 6MWD should not be used in isolation to determine a patient's candidacy for TMVr. However, a 6MWT should be incorporated in the routine evaluation of patients with HF, given its simplicity and low-cost nature.

WHAT IS NEXT? Future studies should evaluate the clinical utility of short-term changes in 6MWD for assessing prognosis and identifying potential candidates for TMVr.

REFERENCES

1. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014;63:1123–33.

2. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 2013;6:606–19.

3. Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol 2015;65:1231–48.

4. Sannino A, Smith RL II, Schiattarella GG, Trimarco B, Esposito G, Grayburn PA. Survival and cardiovascular outcomes of patients with secondary mitral regurgitation: a systematic review and meta-analysis. JAMA Cardiol 2017;2:1130–9.

5. Goliasch G, Bartko PE, Pavo N, et al. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. Eur Heart J 2018;39:39–46.

6. Stone GW, Vahanian AS, Adams DH, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 1: clinical trial design principles: a consensus document from the Mitral Valve Academic Research Consortium. J Am Coll Cardiol 2015;66:278–307.

7. 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.

8. 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.

9. Arnold SV, Chinnakondepalli KM, Spertus JA, et al. Health status after transcatheter mitral-valve repair in heart failure and secondary mitral regurgitation: COAPT trial. J Am Coll Cardiol 2019;73:2123–32.

10. Bittner V, Weiner DH, Yusuf S, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. JAMA 1993;270:1702–7.

11. Guazzi M, Dickstein K, Vicenzi M, Arena R. Six-minute walk test and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights. Circ Heart Fail 2009;2:549–55.

12. Ingle L, Rigby AS, Carroll S, et al. Prognostic value of the 6 min walk test and self-perceived symptom severity in older patients with chronic heart failure. Eur Heart J 2007;28:560–8.

13. Forman DE, Fleg JL, Kitzman DW, et al. 6-min walk test provides prognostic utility comparable to cardiopulmonary exercise testing in ambulatory outpatients with systolic heart failure. J Am Coll Cardiol 2012;60:2653–61.

14. Chamberlain AM, McNallan SM, Dunlay SM, et al. Physical health status measures predict all-cause mortality in patients with heart failure. Circ Heart Fail 2013;6:669–75.

15. Flynn KE, Pina IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1451–9.

16. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439–50.

17. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7.

18. Stone GW, Adams DH, Abraham WT, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: a consensus document from the Mitral Valve Academic Research Consortium. J Am Coll Cardiol 2015;66:308–21.

19. Shoemaker MJ, Curtis AB, Vangsnes E, Dickinson MG. Clinically meaningful change estimates for the six-minute walk test and daily activity in individuals with chronic heart failure. Cardiopulm Phys Ther J 2013;24:21–9.

20. Tager T, Hanholz W, Cebola R, et al. Minimal important difference for 6-minute walk test distances among patients with chronic heart failure. Int J Cardiol 2014;176:94–8.

21. Lee CW, Sung SH, Huang WM, et al. Can elderly patients with severe mitral regurgitation benefit from trans-catheter mitral valve repair? Korean Circ J 2019;49:532–41.

22. Ledwoch J, Franke J, Lubos E, et al. Prognostic value of preprocedural 6-min walk test in patients undergoing transcatheter mitral valve repair-insights from the German transcatheter mitral valve interventions registry. Clin Res Cardiol 2018;107:241–8.

23. 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.

KEY WORDS 6-min walk test, functional outcomes, heart failure, mitral regurgitation, morbidity, mortality