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NYHA Functional Classification and Outcomes After Transcatheter Mitral Valve Repair in Heart Failure

The COAPT Trial

Gennaro Giustino, MD,[a] JoAnn Lindenfeld, MD,[b] William T. Abraham, MD,[c] Saibal Kar, MD,[d,e] D. Scott Lim, MD,[f] Paul A. Grayburn, MD,[g] Samir R. Kapadia, MD,[h] David J. Cohen, MD, MSc,[i] Lak N. Kotinkaduwa, PhD,[j] Neil J. Weissman, MD,[k,l] Michael J. Mack, MD,[m] Gregg W. Stone, MD[a,j]

ABSTRACT

OBJECTIVES The aim of this study was to evaluate the outcomes of MitraClip implantation versus guideline-directed medical therapy (GDMT) in patients with secondary mitral regurgitation (SMR) according to baseline functional status as assessed by the widely used New York Heart Association (NYHA) functional classification.

BACKGROUND Patients with heart failure (HF) and impaired functional status at baseline have poor prognosis. Whether the effects of transcatheter repair of secondary SMR in patients with HF are influenced by baseline functional status is unknown.

METHODS In the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial, patients with HF with moderate to severe or severe SMR who remained symptomatic despite maximally tolerated GDMT were randomized to MitraClip implantation versus GDMT alone. Outcomes were evaluated according to baseline functional status as assessed using the NYHA functional classification. The primary endpoint of interest was the rate of death or HF-related hospitalization (HFH) at 2 years in time-to-first-event analyses.

RESULTS Among 613 randomized patients, 240 were in NYHA functional class II (39.2%), 322 were in NYHA functional class III (52.5%), and 51 were in ambulatory NYHA functional class IV (8.3%). Rates of death or HFH were progressively higher with increasing NYHA functional class. Compared with GDMT alone, MitraClip implantation resulted in lower 2-year rates of death or HFH consistently in patients in NYHA functional class II (39.7% vs. 63.7%; hazard ratio [HR]: 0.54; 95% confidence interval [CI]: 0.37 to 0.77), NYHA functional class III (46.6% vs. 65.5%; HR: 0.60; 95% CI: 0.45 to 0.82), and NYHA functional class IV (66.7% vs. 85.2%; HR: 0.55; 95% CI: 0.28 to 1.10; $p_{interaction} = 0.86$). Greater improvements in quality of life at 2 years were observed in patients treated with the MitraClip compared with GDMT irrespective of baseline functional status.

CONCLUSIONS The NYHA functional classification provides prognostic utility in patients with HF and moderate to severe or severe SMR. In the COAPT trial, the benefits of MitraClip implantation were consistent in patients with better or worse functional status as assessed by NYHA functional class. (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation [The COAPT Trial] [COAPT]; NCT01626079) (J Am Coll Cardiol Intv 2020;13:2317–28) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.

From [a]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York; [b]Advanced Heart Failure and Cardiac Transplantation Section, Vanderbilt Heart and Vascular Institute, Nashville, Tennessee; [c]Division of Cardiovascular Medicine, The Ohio State University College of Medicine, Columbus, Ohio; [d]Los Robles Regional Medical Center, Thousand Oaks, California; [e]Bakersfield Heart Hospital, Bakersfield, California; [f]Division of Cardiology, University of Virginia, Charlottesville, Virginia; [g]Baylor University Medical Center, Baylor Heart and Vascular Institute,

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ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

CI = confidence interval

GDMT = guideline-directed medical therapy

HF = heart failure

HFH = heart failure–related hospitalization

HR = hazard ratio

KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary

LV = left ventricular

NYHA = New York Heart Association

QOL = quality of life

SMR = secondary mitral regurgitation

TMVr = transcatheter mitral valve repair

The presence of secondary mitral regurgitation (SMR) in patients with heart failure (HF) is associated with a poor prognosis (1–4). SMR results from left ventricular (LV) remodeling and geometric dislocation of the normal spatial relationships of the papillary muscles and chordae tendineae with the mitral valve leaflets, resulting in incomplete mitral leaflet coaptation (1–3,5). In patients with HF, SMR increases the severity of LV volume overload, promotes further LV dilatation, and is associated with decreased quality of life (QOL), increased rates of hospitalization for decompensated HF, and worse survival (1–3,5). In the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial, transcatheter mitral valve repair (TMVr) with the MitraClip device (Abbott Vascular, Santa Clara, California) reduced the rate of HF-related hospitalization (HFH) and improved survival compared with guideline-directed medical therapy (GDMT) alone in patients with HF and moderate to severe or severe SMR who remained symptomatic despite maximally tolerated GDMT and cardiac resynchronization therapy as appropriate (6).

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The New York Heart Association (NYHA) functional classification, first described almost a century ago (7), remains a widely used tool for risk stratification on the basis of the burden of HF symptoms related to activities of daily life (8,9). The NYHA functional classification is broadly used in clinical practice and to determine clinical trial eligibility and indications for HF therapies (8,9). The prognostic utility of the NYHA functional classification in patients with HF and SMR has not been established. Moreover, whether the benefits of TMVr with the MitraClip are consistent in patients with HF with SMR who have greater or lesser degrees of functional limitation according to the NYHA functional classification is unknown. We therefore examined the outcomes of TMVr with the MitraClip versus GDMT alone according to baseline NYHA functional status in patients with HF and SMR in the COAPT trial.

METHODS

STUDY DESIGN. The COAPT trial was an international, open-label, multicenter, randomized trial that

Dallas, Texas; [h]Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio; [i]University of Missouri-Kansas City School of Medicine, Kansas City, Missouri; [j]Clinical Trials Center, Cardiovascular Research Foundation, New York, New York; [k]MedStar Health Research Institute, Washington, DC; [l]Georgetown University, Washington, DC; and the [m]Baylor Scott and White Heart Hospital Plano, Plano, Texas. The COAPT trial was sponsored by Abbott. Dr. Giustino has received consulting fees (advisory board) from Bristol Myers Squibb/Pfizer. 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. 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 W.L. 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 510 Kardiac Devices and Venus. Dr. Grayburn has received consulting fees from Abbott Vascular, Edwards Lifesciences, W.L. Gore, Medtronic, and 4C Medical; and has received grant support from Abbott Vascular, Boston Scientific, Cardiovalve, Edwards Lifesciences, W.L. Gore, Medtronic, and NeoChord. Dr. Kapadia holds stock options in Navigate Cardiac Structures. 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, and Boston Scientific. Dr. Weissman is associate director of an academic echocardiography core laboratory (MedStar Health Research Institute) with institutional contracts with Abbott, Neovasc, Ancora, Mitralign, Medtronic, Boston Scientific, Edwards Lifesciences, Biotronik, and LivaNova. 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 or other honoraria from Cook, Terumo, Qool Therapeutics, and Orchestra Biomed; is a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, W.L. Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Matrizyme, CardioMech; holds 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; and is principal investigator for the COAPT trial (uncompensated). Dr. Kotinkaduwa has reported that she has 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.

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TABLE 1 Baseline Characteristics According to Baseline NYHA Functional Class

	NYHA Functional Class II (n = 240)	NYHA Functional Class III (n = 322)	Ambulatory NYHA Functional Class IV (n = 51)	p Value
Age, yrs	73.0 (65.0–79.0)	75.0 (68.0–81.0)	73.0 (67.0–81.0)	0.08
Female	30.8 (74/240)	37.9 (122/322)	49.0 (25/51)	0.03
Race				
White or Caucasian	72.9 (175/240)	76.1 (245/322)	70.6 (36/51)	0.58
Black or African American	12.9 (31/240)	14.3 (46/322)	21.6 (11/51)	
Other	14.2 (34/240)	9.7 (31/322)	7.9 (3/51)	
Body mass index, kg/m^2	25.4 (23.3–28.7)	26.4 (23.0–30.3)	25.5 (23.5–31.0)	0.22
Etiology of cardiomyopathy				
Ischemic	59.2 (142/240)	60.9 (196/322)	66.7 (34/51)	0.61
Nonischemic	40.8 (98/240)	39.1 (126/322)	33.3 (17/51)	
Hypertension	76.7 (184/240)	82.9 (267/322)	82.4 (42/51)	0.17
Diabetes	33.3 (80/240)	38.2 (123/322)	49.0 (25/51)	0.09
Chronic kidney disease*	71.2 (168/236)	75.2 (236/314)	72.0 (36/50)	0.57
Chronic obstructive pulmonary disease	17.5 (42/240)	24.5 (79/322)	43.1 (22/51)	0.0003
Anemia	24.2 (58/240)	21.1 (68/322)	33.3 (17/51)	0.15
Previous stroke	10.8 (26/240)	12.1 (39/322)	13.7 (7/51)	0.81
Previous myocardial infarction	52.9 (127/240)	49.1 (158/322)	58.8 (30/51)	0.36
History of atrial fibrillation or flutter	55.0 (132/240)	55.3 (178/322)	56.9 (29/51)	0.97
Peripheral vascular disease	15.8 (38/240)	18.3 (59/322)	23.5 (12/51)	0.40
Prior coronary artery bypass grafting	38.8 (93/240)	40.7 (131/322)	43.1 (22/51)	0.81
Prior percutaneous coronary intervention	45.0 (108/240)	47.2 (152/322)	43.1 (22/51)	0.80
Prior electronic device implantation†	70.8 (170/240)	65.2 (210/322)	60.8 (31/51)	0.23
STS replacement score, %	6.0 (3.0–9.4)	7.4 (4.4–11.2)	10.0 (5.0–15.1)	<0.0001
STS repair score, %	3.5 (1.8–6.1)	4.8 (2.8–7.6)	6.4 (2.9–11.5)	<0.0001
Kansas City Cardiomyopathy Questionnaire Overall Summary score	67.4 (53.1–82.2)	43.2 (28.6–59.9)	28.9 (18.8–41.1)	<0.0001
6-min walk distance, m	304.8 (223.5–384.0)	213.4 (120.0–295.0)	131.7 (61.0–190.2)	<0.0001
Serum creatinine, mg/dl	1.5 (1.1–2.0)	1.5 (1.2–2.0)	1.6 (1.1–2.4)	0.42
Hemoglobin, g/dl	12.4 (11.3–13.4)	12.1 (11.1–13.3)	11.5 (10.2–12.7)	0.003
Brain natriuretic peptide, pg/ml	548.0 (332.0–1,051.0)	682.0 (381.0–1,410.0)	917.5 (418.0–1,708.5)	0.02
Albumin, g/dl	4.0 (3.8–4.3)	4.0 (3.6–4.2)	3.8 (3.4–4.1)	0.001

Values are median (interquartile range) or % (n/N). *Creatinine clearance <60 ml/min. †Includes cardiac resynchronization therapy and implantable cardioverter-defibrillator or pacemaker.

NYHA = New York Heart Association; STS = Society of Thoracic Surgeons.

evaluated the benefits of edge-to-edge TMVr with the MitraClip in symptomatic patients with HF and SMR (6). The COAPT trial design and principal results have been reported previously (6,10). In brief, eligible patients had ischemic or nonischemic cardiomyopathy with LV ejection fractions of 20% to 50% and LV end-systolic diameter <7 cm, had moderate to severe (grade 3+) or severe (grade 4+) SMR that was confirmed at an echocardiographic core laboratory before enrollment, and remained symptomatic (NYHA functional class II, III, or ambulatory IV) despite the use of stable maximally tolerated doses of GDMT and cardiac resynchronization therapy (if appropriate) according to clinical practice guidelines (8). The NYHA functional class for each patient was established at each site by a heart team that consisted of an HF specialist, an interventional cardiologist, and a cardiothoracic surgeon with expertise in mitral valve disease. A central eligibility committee confirmed that the patient met all the enrollment criteria and categorized the patient's expected risk for surgery-related complications or mortality. The Institutional Review Board at each participating site approved the study, and all patients provided informed, written consent to participate.

Enrolled patients were randomly assigned in a 1:1 ratio to TMVr with the MitraClip (to be performed within 14 days after randomization) plus GDMT or to GDMT alone. Clinical follow-up was performed at 1, 6, 12, 18, and 24 months and annually thereafter

TABLE 2 Baseline Core Laboratory Echocardiographic Characteristics According to Baseline NYHA Functional Class

	NYHA Functional Class II (n = 240)	NYHA Functional Class III (n = 322)	Ambulatory NYHA Functional Class IV (n = 51)	p Value
Mitral regurgitation severity				0.003
Moderate to severe (3+)	58.8 (141/240)	50.2 (161/321)	33.3 (17/51)	
Severe (4+)	41.3 (99/240)	49.8 (160/321)	66.7 (34/51)	
Left ventricular ejection fraction, %	30.0 (24.0–37.0)	30.0 (24.0–38.0)	29.5 (24.0–35.2)	0.84
Left ventricular end-systolic dimension, cm	5.5 (4.8–6.0)	5.2 (4.6–5.8)	5.2 (4.7–5.8)	0.03
Left ventricular end-diastolic dimension, cm	6.3 (5.7–6.9)	6.1 (5.6–6.6)	6.1 (5.8–6.4)	0.04
Left ventricular end-systolic volume, ml	133.5 (101.0–179.0)	120.0 (92.0–163.0)	113.5 (92.0–158.0)	0.01
Left ventricular end-systolic volume index, ml/m^2	71.5 (52.4–92.0)	63.3 (47.9–83.9)	61.9 (49.5–83.4)	0.01
Left ventricular end-diastolic volume, ml	191.5 (153.0–251.0)	174.0 (135.0–227.0)	172.0 (137.0–216.0)	0.009
Left ventricular end-diastolic volume index, ml/m^2	102.9 (82.1–128.1)	92.9 (72.8–118.7)	89.4 (74.6–116.0)	0.006
Total stroke volume*, ml	55.5 (46.0–72.0)	54.0 (40.0–69.0)	51.0 (38.0–62.0)	0.04
Effective regurgitant orifice area, cm^2	0.35 (0.31–0.46)	0.38 (0.32–0.45)	0.41 (0.36–0.53)	0.007
Regurgitant volume, ml/beat	25.5 (17.0–35.0)	23.0 (15.0–33.0)	17.0 (14.0–28.0)	0.052
Regurgitant fraction, %	37.0 (27.0–47.0)	36.0 (27.0–45.0)	31.0 (28.0–44.0)	0.71
Mitral valve orifice area, cm^2	4.9 (4.3–5.6)	4.9 (4.3–5.7)	4.8 (4.3–5.8)	0.90
Left atrial volume, ml	88.3 (68.0–106.0)	86.0 (64.0–106.0)	77.0 (60.0–98.0)	0.24
Tricuspid regurgitation				0.01
None	3.0 (7/234)	1.3 (4/314)	2.0 (1/50)	
Mild (1+)	88.0 (206/234)	77.1 (242/314)	80.0 (40/50)	
Moderate (2+)	9.0 (21/234)	19.7 (62/314)	18.0 (9/50)	
Moderate to severe (3+)	0.0 (0/234)	1.6 (5/314)	0.0 (0/50)	
Severe (4+)	0.0 (0/234)	0.3 (1/314)	0.0 (0/50)	
Right ventricular systolic pressure, mm Hg	41.5 (33.0–52.0)	44.0 (34.0–54.0)	46.0 (38.0–56.0)	0.12

Values are % (n/N) or median (interquartile range). *Calculated as left ventricular end-diastolic volume minus left ventricular end-systolic volume.
NYHA = New York Heart Association.

through 5 years. At the present time, all patients have reached the 2-year follow-up point. Periodic assessments included echocardiography, 6-min walk distance (6MWD), and QOL measures including the NYHA functional class and the Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score (on a scale of 0 to 100, with higher scores indicating better QOL and a difference of 5 points indicating a minimally significant difference) at baseline and then at 1, 6, 12, 18, and 24 months after randomization. Crossover between treatment groups was not permitted before 2 years of follow-up.

NYHA FUNCTIONAL CLASSIFICATION. NYHA functional class I includes patients with HF who are asymptomatic with activities of daily life (i.e., have no limitations with ordinary physical activities). NYHA functional class II patients have slight limitations of physical activity; patients are comfortable at rest, but ordinary physical activity results in symptoms of HF. NYHA functional class III patients have marked limitations of physical activity; patients are comfortable at rest, but less than ordinary activity causes symptoms of HF. Ambulatory NYHA functional class IV includes patients unable to carry on any physical activity without symptoms of HF or who are having symptoms of HF at rest but who are not bedridden and are not on inotropes or mechanical circulatory support (8). NYHA functional class I and nonambulatory functional class IV patients were excluded from COAPT.

ENDPOINTS. The primary outcome of interest for the present analysis was the composite of all-cause death or HFH within 24 months after randomization in time-to-first-event analyses. Secondary outcomes included all-cause death, cardiovascular death, HF-related death, all hospitalizations, cardiovascular hospitalizations, HFH, and QOL, functional, and echocardiographic assessments during follow-up. Adverse events were adjudicated by an independent events committee with the use of original source documents. Echocardiographic data were assessed by an independent core laboratory.

STATISTICAL ANALYSIS. In the present analysis we examined the outcomes of COAPT-randomized patients with NYHA functional class II versus III versus

TABLE 3 2-Year Outcomes According to Baseline NYHA Functional Class

	NYHA Functional Class II (n = 240)	NYHA Functional Class III (n = 322)	Ambulatory NYHA Functional Class IV (n = 51)	p Value
Death or hospitalization for heart failure	50.5 (119)	56.3 (175)	78.1 (39)	<0.0001
Death				
All-cause	31.7 (73)	35.4 (108)	54.8 (27)	0.001
Cardiovascular	26.3 (59)	29.1 (84)	49.2 (23)	0.001
Related to heart failure	13.2 (27)	18.6 (50)	36.9 (16)	<0.0001
Not related to heart failure	15.1 (32)	12.8 (34)	19.5 (7)	0.48
Noncardiovascular	7.3 (14)	8.9 (24)	11.0 (4)	0.53
Hospitalizations				
All-cause	69.7 (163)	76.2 (229)	88.6 (43)	<0.0001
Cardiovascular	53.3 (121)	59.9 (175)	76.1 (34)	0.0003
Related to heart failure	41.0 (91)	46.2 (133)	64.7 (28)	0.0005
Not related to heart failure	28.3 (59)	30.1 (80)	38.1 (13)	0.71
Noncardiovascular	43.4 (92)	50.8 (141)	62.4 (27)	0.003
Unplanned mitral valve intervention	3.8 (7)	6.9 (17)	9.0 (3)	0.22
MitraClip implantation	2.9 (5)	5.5 (13)	4.5 (1)	0.33
Mitral valve surgery	0.9 (2)	1.4 (4)	4.5 (2)	0.14
Stroke or transient ischemic attack	5.4 (11)	6.6 (18)	12.0 (3)	0.68
Stroke	4.9 (10)	5.2 (14)	9.3 (2)	0.96
Transient ischemic attack	0.4 (1)	1.9 (5)	2.4 (1)	0.33
Myocardial infarction	6.0 (12)	6.5 (17)	2.8 (1)	0.70
Revascularization	3.4 (7)	3.9 (10)	4.6 (2)	0.80
Percutaneous coronary intervention	3.4 (7)	3.6 (9)	2.3 (1)	0.99
Coronary artery bypass grafting	0.0 (0)	0.3 (1)	2.3 (1)	0.056
LVAD implantation or heart transplantation	8.9 (18)	5.2 (13)	2.4 (1)	0.18
LVAD implantation	7.0 (14)	2.8 (7)	2.4 (1)	0.09
Heart transplantation	2.5 (5)	2.7 (7)	0.0 (0)	0.64

Values are Kaplan-Meier estimate (%) (number of events). The p values are from log-rank test.
LVAD = left ventricular assist device; NYHA = New York Heart Association.

ambulatory IV or functional class II versus III or ambulatory IV. COAPT excluded asymptomatic patients; however, 1 NYHA functional class I patient was inadvertently randomized. For the present analysis, this patient has been included in the NYHA functional class II group. In addition, NYHA functional class was not recorded in 1 other patient; this patient was excluded from the present study population. The present analysis population thus includes 613 of the 614 randomized patients. All analyses were performed in the intention-to-treat population, which included all patients according to the group to which they were randomly assigned, regardless of the treatment received.

Categorical variables were compared using the Fisher exact test or chi-square test. Continuous variables were compared using Student's *t*-test or the Wilcoxon rank sum test for data not normally distributed. Event rates were based on Kaplan-Meier estimates in time-to-first-event analyses and were compared using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox regression models. The independent association between baseline NYHA functional class and the risk for death or HFH at 2 years was further evaluated in multivariate Cox regression models including the following covariates: age, sex, body mass index, anemia, creatinine clearance, chronic obstructive pulmonary disease, etiology of cardiomyopathy (ischemic vs. nonischemic), Society of Thoracic Surgeons mitral valve replacement score, baseline brain natriuretic peptide level, baseline LV end-diastolic volume, and baseline effective regurgitant orifice area. The significance of the differences in the treatment effect of MitraClip implantation versus GDMT according to baseline NYHA functional class was assessed in Cox regression models for the full trial population, including main effect terms (e.g., NYHA functional class and assigned treatment) and interaction terms (e.g., NYHA functional class × assigned treatment) for each outcome of interest. Number needed to treat and corresponding 95% CI were calculated for the treatment effects of MitraClip implantation versus GDMT at 2 years after randomization. Analysis of covariance was used to compare mean changes in continuous outcome measures from

TABLE 4 2-Year Outcomes According to Baseline NYHA Functional Class in the Randomized Groups

	NYHA Functional Class II			NYHA Functional Class III or Ambulatory IV			
	MitraClip (n = 130)	GDMT (n = 110)	Hazard Ratio (95% CI)	MitraClip (n = 172)	GDMT (n = 201)	Hazard Ratio (95% CI)	$p_{interaction}$
Death or hospitalization for heart failure	39.7 (51)	63.7 (68)	0.54 (0.37–0.77)	48.8 (82)	68.6 (132)	0.58 (0.44–0.77)	0.75
Death							
All-cause	24.4 (31)	40.8 (42)	0.55 (0.35–0.88)	31.1 (52)	44.4 (83)	0.68 (0.48–0.96)	0.53
Cardiovascular	20.3 (25)	33.7 (34)	0.55 (0.33–0.93)	24.6 (39)	38.3 (68)	0.62 (0.42–0.91)	0.76
Related to heart failure	8.0 (9)	19.8 (18)	0.37 (0.17–0.83)	14.4 (21)	26.9 (45)	0.50 (0.30–0.84)	
Not related to heart failure	13.4 (16)	17.5 (16)	0.76 (0.38–1.52)	11.9 (18)	15.6 (23)	0.84 (0.45–1.56)	
Noncardiovascular	5.1 (6)	10.8 (8)	0.54 (0.19–1.57)	8.5 (13)	9.9 (15)	0.96 (0.45–2.01)	0.44
Hospitalizations							
All-cause	61.7 (79)	79.4 (84)	0.69 (0.51–0.94)	74.3 (121)	81.2 (151)	0.83 (0.65–1.05)	0.38
Cardiovascular	44.1 (55)	64.7 (66)	0.60 (0.42–0.86)	55.3 (86)	67.8 (123)	0.70 (0.53–0.92)	0.52
Related to heart failure	33.0 (40)	51.3 (51)	0.57 (0.38–0.86)	36.4 (55)	59.0 (106)	0.49 (0.35–0.68)	
Not related to heart failure	25.4 (30)	31.9 (29)	0.77 (0.46–1.28)	30.4 (44)	31.7 (49)	1.03 (0.69–1.55)	
Noncardiovascular	42.2 (51)	45.0 (41)	0.95 (0.63–1.44)	51.5 (78)	52.8 (90)	0.95 (0.70–1.29)	0.97
Unplanned mitral valve intervention	0.9 (1)	8.1 (6)	0.12 (0.01–0.97)	6.2 (9)	8.4 (11)	0.89 (0.37–2.15)	0.09
MitraClip implantation	0.9 (1)	6.2 (4)	0.17 (0.02–1.50)	5.5 (8)	5.7 (6)	1.40 (0.49–4.05)	
Mitral valve surgery	0.0 (0)	1.9 (2)	–	0.6 (1)	2.8 (5)	0.23 (0.03–1.99)	
Stroke or transient ischemic attack	4.2 (5)	7.2 (6)	0.64 (0.20–2.10)	5.5 (8)	8.6 (13)	0.68 (0.28–1.65)	0.93
Stroke	4.2 (5)	6.3 (5)	0.77 (0.22–2.66)	4.3 (6)	6.6 (10)	0.66 (0.24–1.81)	
Transient ischemic attack	0.0 (0)	1.0 (1)	–	2.0 (3)	2.0 (3)	1.12 (0.23–5.54)	
Myocardial infarction	5.2 (6)	7.3 (6)	0.75 (0.24–2.34)	4.6 (7)	7.7 (11)	0.70 (0.27–1.80)	0.90
Revascularization	1.6 (2)	6.0 (5)	0.30 (0.06–1.56)	3.6 (5)	4.4 (7)	0.79 (0.25–2.48)	0.36
Percutaneous coronary intervention	1.6 (2)	6.0 (5)	0.30 (0.06–1.56)	3.6 (5)	3.3 (5)	1.09 (0.32–3.77)	
Coronary artery bypass grafting	0.0 (0)	0.0 (0)	–	0.0 (0)	1.1 (2)	–	
LVAD implantation or heart transplantation	6.4 (7)	11.7 (11)	0.47 (0.18–1.22)	1.6 (2)	7.9 (12)	0.18 (0.04–0.79)	0.28
LVAD implantation	5.6 (6)	8.6 (8)	0.56 (0.19–1.61)	0.0 (0)	5.3 (8)	–	
Heart transplantation	0.9 (1)	4.7 (4)	0.19 (0.02–1.69)	1.6 (2)	3.1 (5)	0.43 (0.08–2.24)	

Values are Kaplan-Meier estimate (%) (number of events), unless otherwise specified.
CI = confidence interval; GDMT = guideline-directed medical therapy; other abbreviations as in Table 3.

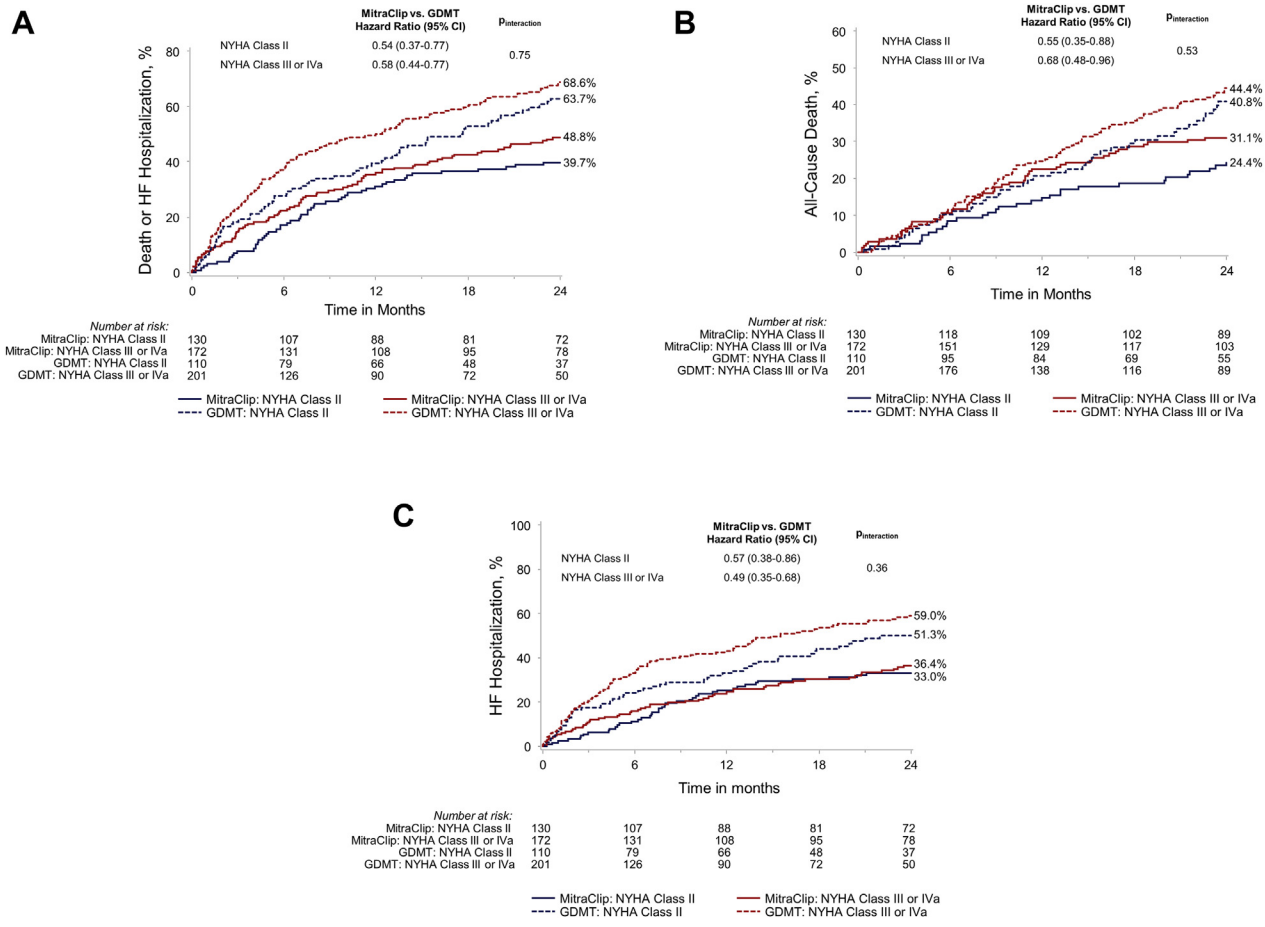
baseline to follow-up between groups. A 2-sided p value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENTS AND NYHA FUNCTIONAL CLASS. Among 613 patients randomized to TMVr with the MitraClip or GDMT, 240 (39.2%) were in NYHA functional class II, 322 (52.5%) were in NYHA functional class III, and 51 (8.3%) were in ambulatory NYHA functional class IV. Baseline characteristics in patients in NYHA functional class II versus functional class III versus ambulatory functional class IV are reported in Table 1. Patients with higher NYHA functional class were more frequently women and had a higher prevalence of chronic obstructive pulmonary disease and higher estimated surgical risk. Also, patients with higher NYHA functional class had progressively lower (i.e., worse) KCCQ-OS scores and shorter 6MWDs. Brain natriuretic peptide levels were also progressively higher in patients with greater NYHA functional class. Baseline echocardiographic characteristics are reported in Table 2. Severe (4+) MR was more prevalent with greater NYHA functional class (41.3% in NYHA functional class II, 49.8% in NYHA functional class III, and 66.7% in ambulatory NYHA functional class IV; p = 0.003); conversely, patients with lower NYHA functional class had larger LV volumes. Moderate or greater tricuspid regurgitation was more prevalent in patients with NYHA functional class III or ambulatory functional class IV than functional class II.

Among patients randomized to MitraClip implantation, the number of clips implanted, the reduction in the severity of MR, and in-hospital length of stay were independent of NYHA functional class (Supplemental Table 1). Medication use through 2-year follow-up by baseline NYHA functional class is reported in Supplemental Table 2.

FIGURE 1 Rates of Adverse Events at 2 Years in Patients Treated With MitraClip or GDMT Alone According to Baseline NYHA Functional Class

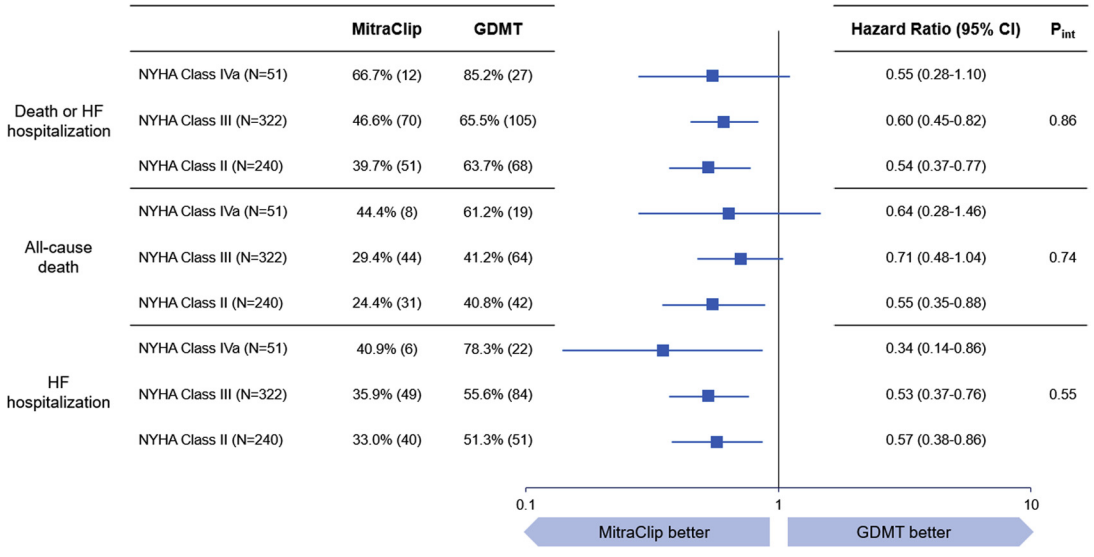


Kaplan-Meier time-to-first event curves in patients randomized to MitraClip plus guideline-directed medical therapy (GDMT) or GDMT alone by baseline New York Heart Association (NYHA) functional class. **(A)** Death or heart failure (HF) hospitalization by NYHA functional class II versus functional class III or IV, **(B)** all-cause death by NYHA functional class II versus functional class III or IV, and **(C)** HF-related hospitalization by NYHA functional class II versus functional class III or IV. CI = confidence interval.

RELATIONSHIP BETWEEN NYHA FUNCTIONAL CLASS AND CLINICAL AND HEALTH STATUS OUTCOMES. Event rates at 2 years according to baseline NYHA functional class are reported in **Table 3** and Supplemental Figure 1. The 2-year rates of adverse events were progressively greater with increasing NYHA functional class (NYHA functional class II vs. functional class III vs. ambulatory functional class IV), including death or HFH (50.5% vs. 56.3% vs. 78.1%; $p < 0.0001$), death (31.7% vs. 35.4% vs. 54.8%; $p = 0.001$), and HFH (41.0% vs. 46.2% vs. 64.7%; $p = 0.0005$). Following multivariate adjustment for baseline clinical variables, higher NYHA functional class was independently associated with greater 2-year risk for death or HFH (per increase in NYHA functional class, adjusted HR: 1.28; 95% CI: 1.04 to 1.57; $p = 0.02$) (Supplemental Table 3). Patients with higher NYHA functional class at baseline had worse KCCQ-OS scores and 6MWDs at all time points over 2 years (Supplemental Table 4).

MitraClip IMPLANTATION VERSUS GDMT BY NYHA FUNCTIONAL CLASS. Outcomes at 2 years for MitraClip implantation versus GDMT alone according to baseline NYHA functional class are reported in **Table 4 and Figures 1 and 2**. At 2 years, MitraClip placement compared with GDMT alone was associated with lower rates of death or HFH consistently in patients in NYHA functional class II (39.7% vs. 63.7%; HR: 0.54; 95% CI: 0.37 to 0.77; number needed to treat = 4.2;

FIGURE 2 Effect of MitraClip Versus GDMT According to Baseline NYHA Functional Class



Abbreviations as in Figure 1.

95% CI: 2.7 to 8.7), NYHA functional class III (46.6% vs. 65.5%; HR: 0.60; 95% CI: 0.45 to 0.82; number needed to treat = 5.3; 95% CI: 3.4 to 12.7), and ambulatory NYHA functional class IV (66.7% vs. 85.2%; HR: 0.55; 95% CI: 0.28 to 1.10; number needed to treat = 5.4; 95% CI: 2.3 to 14.7, $p_{interaction} = 0.86$). The MitraClip also reduced the 2-year rates of all-cause death, cardiovascular death, HF-related death, all hospitalizations, cardiovascular hospitalizations, and HFH consistently across NYHA functional class (Table 4).

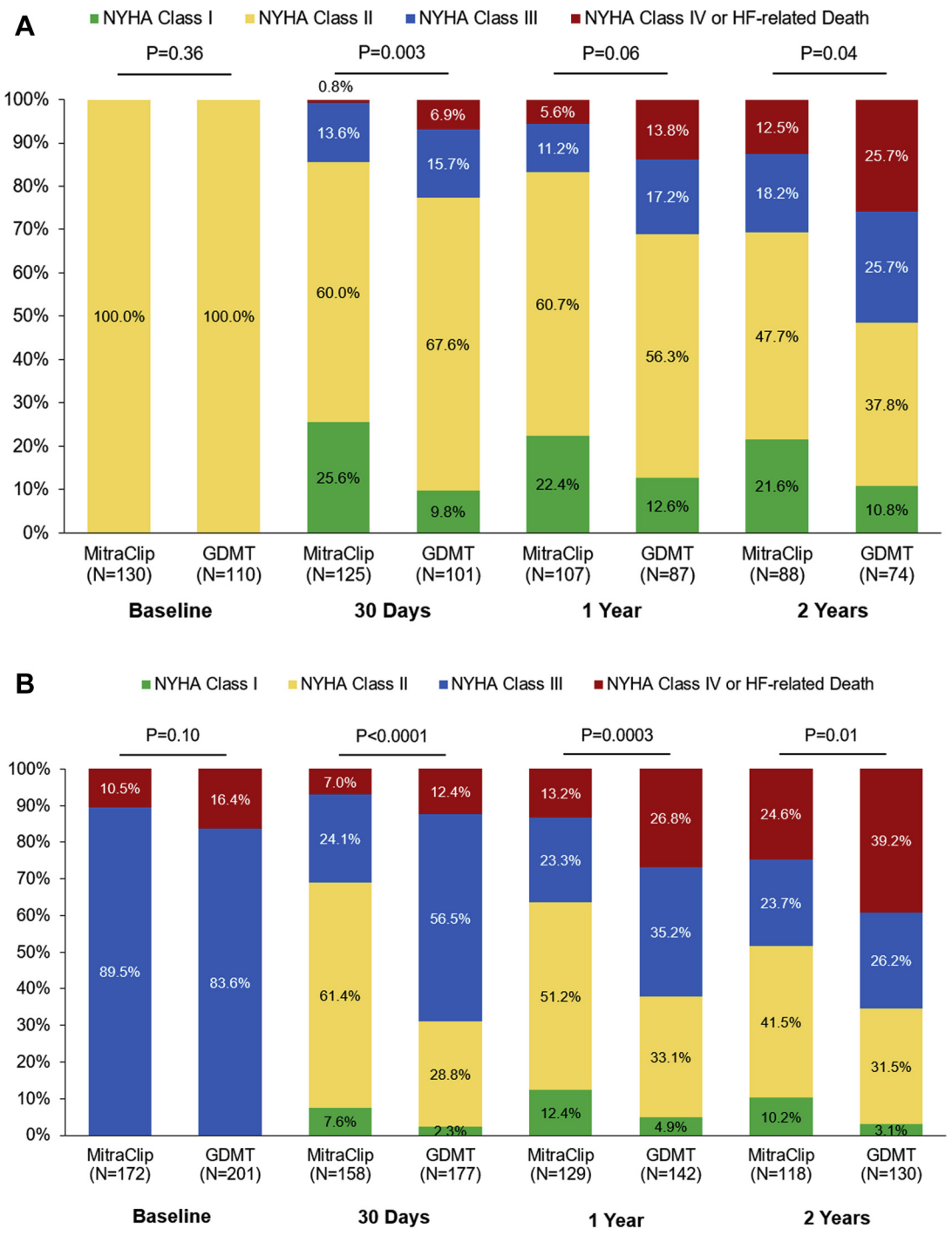
Changes in health status by baseline NYHA functional class are reported in Figure 3 and Supplemental Table 5. At 2 years, more patients treated with GDMT alone were in NYHA functional class III or IV or had experienced HF-related death than those treated with the MitraClip, irrespective of baseline functional class (Figure 3). MitraClip treatment resulted in better KCCQ-OS scores at all time points, irrespective of baseline functional status, with larger absolute improvements observed in those in NYHA functional class III or ambulatory IV at baseline (Supplemental Table 5). MitraClip placement resulted in improved 6MWD compared with GDMT at 2 years among patients with NYHA functional class III or ambulatory IV at baseline (Supplemental Table 5). The severity of SMR was consistently reduced at all time points with MitraClip treatment irrespective of baseline NYHA functional class (Supplemental Table 6).

DISCUSSION

The major findings of the present analysis from the COAPT trial, in which we examined the effect of MitraClip implantation plus GDMT versus GDMT alone in patients with HF and moderate to severe or severe SMR according to baseline NYHA functional classification, are summarized in the Central Illustration. Patients in higher NYHA functional classes had a progressively higher risk profile, had more severe SMR, were at higher risk for death and HFH, and had worse QOL and reduced exercise capacity. Reduction in the severity of SMR with the MitraClip resulted in consistent and sustained clinical benefits in patients in NYHA functional classes II, III, and ambulatory IV, including substantial reductions in the rates of death and HFH and improvements in health status outcomes over 2 years.

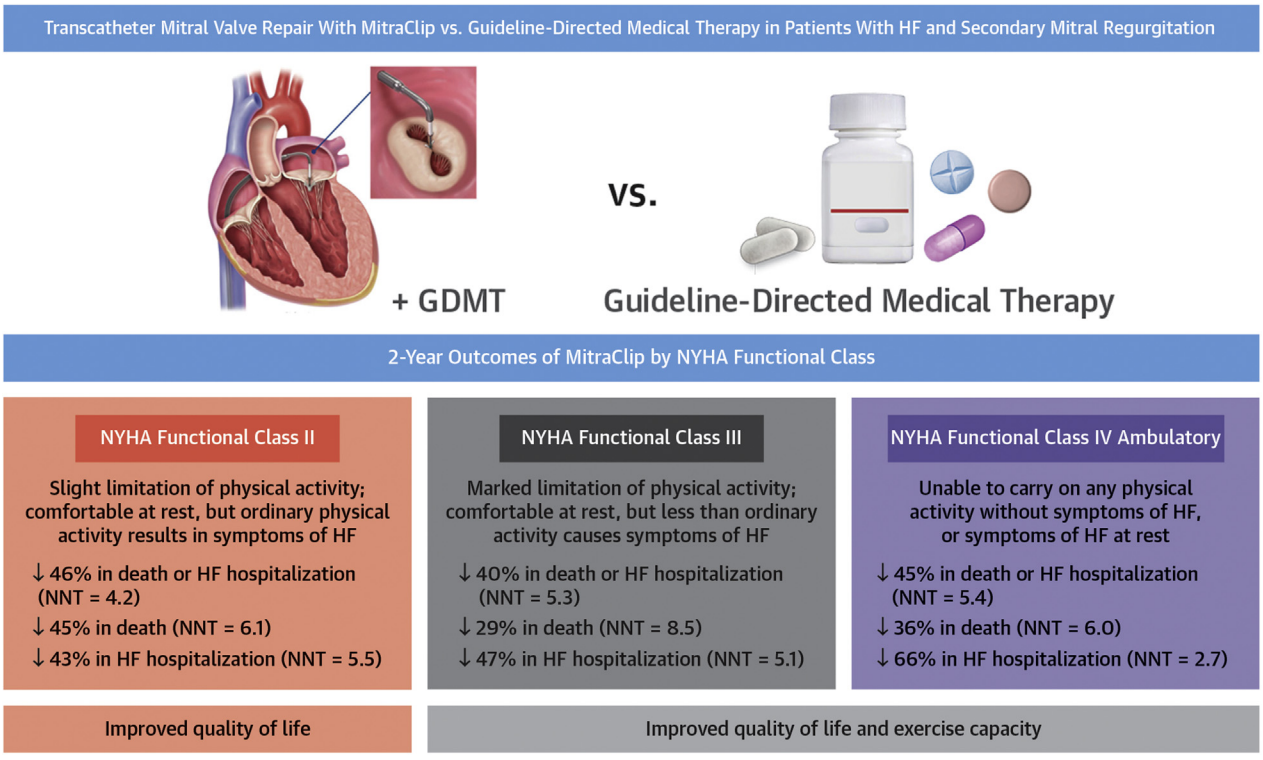
The NYHA functional classification is a simple risk stratification tool based on the burden of HF-related symptoms that has been used in clinical practice for almost a century (7,9). Although it is widely recognized that the NYHA functional classification is subjective and has high interobserver variability (9), its use is endorsed in both American and European clinical practice guidelines, and it is routinely implemented for prognostication, as a criterion for trial enrollment, and to determine eligibility for HF therapies (8,9,11). Thus, evaluating the effects of device-based therapies

FIGURE 3 **Changes in Functional Status Within 2 Years by Baseline NYHA Functional Class**



(A) In patients with baseline NYHA functional class II. **(B)** In patients with baseline NYHA functional class III or IV. Patients who experienced HF-related death were included in the analysis and assigned to NYHA functional class IV. Abbreviations as in Figure 1.

CENTRAL ILLUSTRATION **Baseline New York Heart Association Functional Class and 2-Year Outcomes After Transcatheter Mitral Valve Repair With MitraClip**



Giustino, G. et al. J Am Coll Cardiol Intv. 2020;13(20):2317–28.

GDMT = guideline-directed medical therapy; HF = heart failure; NNT = number needed to treat; NYHA = New York Heart Association.

for HF across the range of NYHA functional classification is important to support guideline recommendations and to inform clinical decision making and reimbursement criteria. However, there is high heterogeneity in risk discrimination based solely on NYHA functional classification among patients with HF with both low and preserved ejection fractions, and its prognostic role in patients with SMR has not been well characterized (9).

In the present analysis from the COAPT trial, patients in higher (i.e., worse) NYHA functional classes treated with GDMT alone displayed a greater risk profile, had more severe SMR, and had higher rates of adverse clinical events and worse health status outcomes during 2-year follow-up. A graded prognostic relationship was observed from NYHA functional class II to III to ambulatory IV. The association between higher NYHA functional class and increased risk for death and HFH persisted following multivariate adjustment for numerous demographic, clinical, laboratory, and echocardiographic parameters, confirming the prognostic utility of this simple, low-cost assessment in patients with HF with LV ejection fractions ≤50% and moderate to severe or severe SMR. Treatment of SMR with the MitraClip in combination with GDMT led to substantial reductions in death and HFH compared with GDMT alone, irrespective of baseline NYHA functional class. Thus, as the relative improvement in clinical outcomes was consistent across NYHA functional class, in general the greatest absolute improvements will occur in those patients in higher NYHA functional classes who are most impaired at baseline. Importantly, the significant reductions in death and HFH with the MitraClip were paralleled by substantial improvements in QOL assessed by the KCCQ-OS score at every time point measured through 2-year follow-up in all NYHA functional classes. Exercise capacity evaluated by 6MWD was improved over 2 years, principally among the more limited NYHA functional class III and ambulatory IV patients.

Of note, treatment of severe SMR resulted in substantial clinical benefits even in less symptomatic

patients with HF (NYHA functional class II). Thus, all patients with non-stage D HF with severe SMR otherwise meeting COAPT criteria should undergo MitraClip treatment for improvement in prognosis and QOL, even if only mildly symptomatic. Moreover, although not directly tested in COAPT, it is plausible that by mitigating the pathophysiological effects of SMR on LV maladaptive remodeling and progression toward end-stage HF, TMVr could be beneficial in patients who are asymptomatic. Randomized trials are thus warranted to evaluate the role of TMVr in treating asymptomatic patients with SMR.

Interestingly, patients in lower NYHA functional classes had larger LV dimensions but less severe SMR. The prevalence of female sex was lower in patients in lower NYHA functional classes, which may in part explain the differences in LV dimensions across groups. Despite smaller LV dimensions, patients in higher NYHA functional classes had more severe SMR as assessed by effective regurgitant orifice area. Thus, patients with more severe SMR and smaller LV volumes were more prone to develop severe symptoms (higher NYHA functional class) compared with patients with less SMR and larger LV volumes, emphasizing the importance of SMR severity to symptom status in HF.

STUDY LIMITATIONS. Key entry criteria of the COAPT trial required that patients with HF had to remain symptomatic despite maximally tolerated GDMT, including cardiac resynchronization therapy or coronary revascularization as indicated (6). Therefore, the benefits described in the present analysis apply to symptomatic patients (NYHA functional class II, III, or ambulatory IV) and cannot be generalized to asymptomatic patients or those not treated with optimal GDMT. COAPT also excluded patients with NYHA functional class IV HF who were nonambulatory or required advanced therapies. As such, these findings may not apply to patients with end-stage HF and subjects dependent on inotropic support or mechanical circulatory support devices. The results demonstrating improvement with TMVr across all NYHA functional classes enrolled are specific to the MitraClip device. Future studies are required to establish whether emerging TMVr and mitral valve replacement technologies are as safe and effective. In this regard, the risk-benefit profiles of different devices may vary for lower risk, less symptomatic patients (NYHA functional class II) compared with higher risk, more symptomatic patients (NYHA functional classes III and ambulatory IV). Finally, patients in higher NYHA functional classes had a higher prevalence of chronic obstructive pulmonary disease, which is a major noncardiac cause of dyspnea and death. We cannot therefore exclude that some of the functional limitations and adverse outcomes among patients in ambulatory NYHA functional class IV were due to chronic obstructive pulmonary disease, although the graded prognostic risk of NYHA functional class persisted after multivariate adjustment for differences in baseline characteristics, including chronic obstructive pulmonary disease.

CONCLUSIONS

Among selected patients with HF and moderate to severe or severe SMR who remained symptomatic despite the use of maximally tolerated doses of GDMT, cardiac resynchronization therapy, or revascularization as appropriate, higher baseline NYHA functional class was strongly associated with a greater risk for adverse events and worse health status outcomes during 2-year follow-up. Reduction in the severity of SMR with the MitraClip device resulted in lower rates of death and HFH, as well as improved health status outcomes, with benefits evident in patients in NYHA functional classes II, III, and ambulatory IV at baseline.

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.

PERSPECTIVES

WHAT IS KNOWN? The NYHA functional classification is endorsed in both American and European HF guidelines to risk-stratify patients with HF, characterize the burden of HF-related symptoms, and select appropriate HF therapies.

WHAT IS NEW? In the COAPT trial, among patients with HF and moderate to severe or severe SMR who remained symptomatic despite the use of maximal doses of GDMT and cardiac resynchronization therapy as appropriate, TMVr with the MitraClip was associated with significantly improved 2-year clinical and health status outcomes in patients in NYHA functional classes II, III, and ambulatory IV at baseline.

WHAT IS NEXT? Further studies are warranted to evaluate the effectiveness of TMVr in asymptomatic patients and those with end-stage HF with severe SMR, as well as the potential utility of emerging TMVr and mitral valve replacement technologies.

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KEY WORDS heart failure, medical therapy, MitraClip, NYHA functional class, secondary mitral regurgitation

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