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CLINICAL RESEARCH

Sex-Specific Outcomes of Transcatheter Mitral-Valve Repair and Medical Therapy for Mitral Regurgitation in Heart Failure

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ABSTRACT

OBJECTIVES This study sought to assess the sex-specific outcomes in patients with heart failure (HF) with 3+ and 4+ secondary mitral regurgitation (SMR) treated with transcatheter mitral valve repair (TMVr) plus guideline-directed medical therapy (GDMT) versus GDMT alone in the COAPT trial.

BACKGROUND The impact of sex in patients with HF and severe SMR treated with TMVr with the MitraClip compared with GDMT alone is unknown.

METHODS Patients were randomized 1:1 to TMVr versus GDMT alone. Two-year outcomes were examined according to sex.

RESULTS Among 614 patients, 221 (36.0%) were women. Women were younger than men and had fewer comorbidities, but reduced quality of life and functional capacity at baseline. In a joint frailty model accounting for the competing risk of death, the 2-year cumulative incidence of the primary endpoint of all HF hospitalizations (HFH) was higher in men compared with women treated with GDMT alone. However, the relative reduction in HFHs with TMVr was greater in men (HR: 0.43; 95% CI: 0.34-0.54) than women (HR: 0.78; 95% CI: 0.57-1.05) ($P_{interaction} = 0.002$). A significant interaction between TMVr versus GDMT alone treatment and time was present for all HFHs in women (HR: 0.57; 95% CI: 0.39-0.84, and HR: 1.39; 95% CI: 0.83-2.33 between 0-1 year and 1-2 years after randomization, respectively, $P_{interaction} = 0.007$) but not in men (HR: 0.48; 95% CI: 0.36-0.64, and HR: 0.33; 95% CI: 0.21-0.51; $P_{interaction} = 0.16$). Female sex was independently associated with a lower adjusted risk of death at 2 years (HR: 0.64; 95% CI: 0.46-0.90; $P = 0.011$). TMVr consistently reduced 2-year mortality compared with GDMT alone, irrespective of sex ($P_{interaction} = 0.99$).

CONCLUSIONS In the COAPT trial, TMVr with the MitraClip resulted in improved clinical outcomes compared with GDMT alone, irrespective of sex. However, the impact of TMVr in reducing HFH was less pronounced in women compared with men beyond the first year after treatment. (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation [The COAPT Tria] [COAPT]; NCT01626079) (J Am Coll Cardiol HF 2021;9:674–683) © 2021 by the American College of Cardiology Foundation.

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Heart failure (HF) is a highly prevalent condition that affects both sexes equally (1), although the age-adjusted HF incidence is higher in men as they have shorter survival compared with women (2–5). Moreover, recent evidence suggests that men with HF suffer more frequent HF hospitalizations (HFH) (2), yet women with HF have a lower quality of life and more significant functional impairment (1). Among patients with HF, the development of secondary mitral regurgitation (SMR) in the setting of left-ventricular (LV) dysfunction is associated with poor long-term prognosis (6,7). The randomized COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial demonstrated that selected patients with HF and moderate-to-severe or severe SMR treated with transcatheter mitral valve repair (TMVr) with the MitraClip (Abbott) and concomitant guideline-directed medical therapy (GDMT) had significantly lower rates of HFH and death at 2 years compared with GDMT alone (8). Nevertheless, little is known about the impact of sex on long-term outcomes with either GDMT or TMVr in patients with HF and severe SMR. In the current study, we aimed to examine the baseline clinical characteristics and procedural and cardiovascular outcomes in women compared with men with SMR managed with TMVr versus GDMT alone in the COAPT trial.

METHODS

STUDY DESIGN AND ENDPOINTS. The COAPT trial design has been published previously (9). In brief, COAPT (NCT01626079) was a multicenter, randomized, controlled, open-label trial of TMVr with the MitraClip device in patients with HF and moderate-to-severe (3+) or severe (4+) SMR who remained symptomatic despite maximally tolerated GDMT. Patients had LV ejection fraction (LVEF) between 20% and 50%, LV end-systolic diameter ≤70 mm, and absence of severe pulmonary hypertension (defined as pulmonary artery systolic pressure >70 mm Hg despite vasodilator therapy) or moderate or severe right-ventricular failure. Patients were randomized 1:1 to receive TMVr plus GDMT or GDMT alone. The primary effectiveness endpoint of the COAPT trial was the cumulative incidence of all HFH within 24 months. Secondary outcomes included the individual endpoints of all-cause death and the composite outcome of death or HFH at 2 years. Crossover was not permitted before 2 years of follow-up. The protocol was approved by the investigational review board at each participating center, and all patients provided written informed consent. Follow-up is ongoing through 5 years and is currently complete for all patients at 2 years.

STATISTICAL METHODS. For this study, outcomes were analyzed according to sex. All analyses were performed with data from the time of randomization 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. Data are summarized using descriptive statistics, presented as proportions (%, count/sample size) or mean ± SD. Categorical variables were compared by the chi-square test or Fisher exact test, and continuous variables were compared by the Wilcoxon rank-sum test. An analysis of covariance model was used to compare mean changes in continuous variables from baseline to follow-up between groups. All HFHs were displayed as a cumulative incidence function and compared in a joint frailty model to account for correlated events and the competing risk of death. Time-to-first-event rates were estimated using the Kaplan-Meier method, with comparisons made using the log-rank test. Multivariable analyses were performed using Cox regression and the Anderson-Gill model for recurrent events and included the following predefined clinically relevant covariates: treatment modality (TMVr plus GDMT vs GDMT alone), sex, race (Caucasian vs non-Caucasian), age, diabetes mellitus, nonischemic (vs ischemic) cardiomyopathy, history of major arrhythmias, previous myocardial infarction, previous coronary artery disease, previous coronary artery bypass grafting or percutaneous coronary intervention, and chronic kidney disease. All P values were 2-sided, and $P < 0.05$ was considered statistically significant. All analyses were performed with SAS version 9.4 (SAS Institute).

ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

GDMT = guideline-directed medical therapy

HF = heart failure

HFH = heart failure hospitalization

KCCQ = Kansas City Cardiomyopathy Questionnaire

LV = left ventricular

LVEF = left-ventricular ejection fraction

SMR = secondary mitral regurgitation

TMVr = transcatheter mitral valve repair

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 Author Center.

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TABLE 1 Baseline Characteristics According to Sex

	Women (n = 221)	Men (n = 393)	*P* Value
Age, y	69.5 ± 12.8	73.8 ± 9.8	<0.0001
Race			0.0002
White or Caucasian	69.7 (154/221)	77.1 (303/393)	0.04
Black or African American	22.2 (49/221)	9.9 (39/393)	<0.0001
Hispanic or Latino	5.0 (11/221)	7.4 (29/393)	0.25
Asian	2.7 (6/221)	3.1 (12/393)	0.81
Pacific Islander	0.5 (1/221)	0.0 (0/393)	0.18
Other	0.0 (0/221)	2.5 (10/393)	0.02
Etiology of cardiomyopathy			
Ischemic	36.7 (81/221)	74.3 (292/393)	<0.0001
Nonischemic	63.3 (140/221)	25.7 (101/393)	<0.0001
Previous stroke or transient ischemic attack			
Stroke	11.8 (26/221)	11.7 (46/393)	0.98
Transient ischemic attack	6.8 (15/221)	7.1 (28/393)	0.88
Previous myocardial infarction	36.7 (81/221)	59.8 (235/393)	<0.0001
Coronary artery disease	52.5 (116/221)	84.0 (330/393)	<0.0001
Hypertension	77.8 (172/221)	81.9 (322/393)	0.22
Hypercholesterolemia	43.9 (97/221)	59.0 (232/393)	0.0003
Chronic obstructive pulmonary disease	21.7 (48/221)	24.2 (95/393)	0.49
Arrhythmia event history	53.4 (118/221)	72.3 (284/393)	<0.0001
Ventricular fibrillation	3.6 (8/221)	8.7 (34/393)	0.02
Ventricular tachycardia	19.0 (42/221)	26.2 (103/393)	0.04
Atrial fibrillation or flutter	42.1 (93/221)	62.6 (246/393)	<0.0001
Diabetes	38.9 (86/221)	36.4 (143/393)	0.53
Peripheral vascular disease	12.7 (28/221)	20.6 (81/393)	0.01
Renal disease	50.2 (111/221)	60.6 (238/393)	0.01
History of anemia	26.2 (58/221)	21.9 (86/393)	0.22
History of bleeding disorder	5.9 (13/221)	8.1 (32/393)	0.30
STS replacement or repair score ≥8%	51.1 (113/221)	50.5 (197/390)	0.88
Body mass index, kg/m^2	27.6 ± 7.2	26.7 ± 4.9	0.07
Previous cardiac interventions			
Coronary artery bypass grafting	20.4 (45/221)	51.4 (202/393)	<0.0001
Percutaneous coronary intervention	30.3 (67/221)	55.0 (216/393)	<0.0001
Device implantation	64.3 (142/221)	68.4 (269/393)	0.29
ICD	30.3 (67/221)	31.8 (125/393)	0.70
Resynchronization (CRT-D or CRT-P)	34.4 (76/221)	37.7 (148/393)	0.42
Previous cardiac valve interventions			
Aortic valve interventions	2.3 (5/221)	4.8 (19/393)	0.11
Mitral valve interventions	0.0 (0/221)	0.3 (1/393)	0.45
NYHA functional class			0.06
I	0.0 (0/221)	0.3 (1/392)	0.45
II	33.5 (74/221)	42.1 (165/392)	0.04
III	55.2 (122/221)	51.0 (200/392)	0.32
IV	11.3 (25/221)	6.6 (26/392)	0.04
III or IV	66.5 (147/221)	57.7 (226/392)	0.03
KCCQ score	49.6 ± 23.6	53.9 ± 22.6	0.03
6-min walk distance, m	213.9 ± 120.9	257.5 ± 122.8	<0.0001

Values are mean ± SD or % (n/N).

CRT-D = cardiac resynchronization therapy-defibrillator; CRT-P = cardiac resynchronization therapy-pacemaker; ICD = implantable cardioverter-defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

RESULTS

BASELINE AND PROCEDURAL CHARACTERISTICS. Among 614 patients, 221 (36.0%) were women (including 97 and 124 randomized to the device vs control group, respectively) and 393 (64.0%) were men (including 197 and 196 randomized to the device vs control group, respectively). Baseline characteristics differed significantly between women and men (Table 1). Women were younger and more frequently non-Caucasian, more frequently had nonischemic cardiomyopathy, and less frequently had histories of coronary artery disease, myocardial infarction, previous coronary revascularization, atrial or ventricular arrhythmias, renal dysfunction, and hypercholesterolemia. Women more frequently had New York Heart Association functional class III or IV symptoms compared with men and lower baseline Kansas City Cardiomyopathy Questionnaire (KCCQ) scores and 6-min walk distance (6MWD).

Echocardiographic characteristics at baseline are shown in Table 2. The severity of SMR was similar in men and women. LV end-systolic and end-diastolic volume indices were smaller in women compared with men at baseline, although the LVEF did not differ between sexes. Women had lower right-ventricular systolic pressures but more frequently had moderate-to-severe or severe tricuspid regurgitation.

Procedural characteristics among patients randomized to TMVr are shown in Table 3. Number of MitraClip devices implanted and procedure duration were lower in women compared with men. Site-reported reduction MR was similar in both groups. The postprocedural duration of hospitalization was longer in women than men.

Medication use at baseline and at 24-month follow-up is presented in Table 4. Aspirin and statins were less frequently used in women compared with men at both time periods. Oral anticoagulants were less frequently used in women compared with men at baseline.

CLINICAL OUTCOMES. The 2-year cumulative incidences of HFHs according to sex and randomization treatment are shown in the Central Illustration. Among patients treated with GDMT alone, men had 197 total HFHs per 269 patient-years of follow-up (73.1% HFH rate per year), whereas women had 102 total HFHs per 185 patient-years of follow-up (55.1% HFH rate per year). Among patients treated with TMVr, men had 98 total HFHs per 322 patient-years of follow-up (30.5% HFH rate per year), whereas women had 71 HFHs per 168 patient-years of follow-up (42.4% HFH rate per year). In a joint frailty model accounting for the competing risk of death, the 2-year cumulative incidence of the primary endpoint of recurrent HF hospitalizations (HFH) was higher in

men compared with women in the GDMT-alone group and similar between sexes in the TMVr group; a significant interaction was present between sex and treatment modality for all HFH at 2 years ($P_{interaction}$ = 0.002). After adjusting for clinically relevant covariates, a significant interaction persisted between sex and treatment modality for the primary outcome of all HFH at 2 years (adjusted $P_{interaction}$ = 0.009). In sensitivity analyses, a significant interaction between time from treatment and TMVr versus GDMT-alone treatment was present for all HFH in women (HR: 0.57; 95% CI: 0.39-0.84, and HR: 1.39; 95% CI: 0.83-2.33 between 0-1 year and 1-2 years after randomization, respectively; $P_{interaction}$ = 0.007) but not in men (HR: 0.48; 95% CI: 0.36-0.64 vs HR: 0.33; 95% CI: 0.21-0.51; $P_{interaction}$ = 0.16). Further, there were no significant interactions between type of cardiomyopathy and treatment modality on the risk of recurrent HFH in women ($P_{interaction}$ = 0.65) or men ($P_{interaction}$ = 0.98).

Unadjusted 2-year clinical outcomes based on time-to-first-event analyses are shown in Table 5. There were no significant interactions between sex and treatment modality for the 2-year rates of HF-related or other hospitalizations, cardiovascular (CV) or all-cause death, or other outcomes. Of note, following adjustment for differences in baseline covariates, female sex was not independently associated with a difference in the 2-year risk for the time to first HFH (HR: 0.84; 95% CI: 0.63-1.13; P = 0.25), but was independently associated with a lower risk of death (HR: 0.64; 95% CI: 0.46-0.90; P = 0.011). No significant interactions between sex and treatment modality were observed for the 2-year adjusted rates of time-to-first HFH (adjusted $P_{interaction}$ = 0.81) or all-cause death (adjusted $P_{interaction}$ = 0.50). Similarly, there were no significant interactions between type of cardiomyopathy and treatment modality on the risk of death in women ($P_{interaction}$ = 0.48) or men ($P_{interaction}$ = 0.73).

QUALITY OF LIFE AND FUNCTIONAL OUTCOMES. As shown in Table 6, treatment with MitraClip compared with GDMT alone led to consistent improvements from baseline to 1 year in quality of life as evaluated by the KCCQ in both women and men. Similarly, the change in functional capacity from baseline to 1 year as evaluated by 6MWD was superior in MitraClip-treated patients compared with those treated with GDMT alone, irrespective of sex.

LONG-TERM REDUCTION IN MITRAL REGURGITATION. As shown in Figure 1, by echocardiographic core laboratory analysis, TMVr reduced the severity of SMR from 3+ or 4+ at baseline to ≤2+ through 2-year follow-up compared with GDMT alone, consistently in men and women ($P_{interaction}$ >0.05 at all time points).

TABLE 2 Baseline Echocardiographic Characteristics According to Sex

	Women (n = 221)	Men (n = 393)	*P* Value
Mitral regurgitation			0.63
3+ (moderate to severe)	50.9 (112/220)	52.9 (208/393)	
4+ (severe)	49.1 (108/220)	47.1 (185/393)	
LV ejection fraction, %	31.6 ± 9.7	31.1 ± 9.1	0.57
LV end-systolic dimension, cm	5.1 ± 0.9	5.4 ± 0.8	0.0005
LV end-diastolic dimension, cm	6.0 ± 0.7	6.3 ± 0.7	<0.0001
LV end-systolic diameter index, mL/m^2	2.9 ± 0.6	2.7 ± 0.5	<0.0001
LV end-systolic volume, mL	118.7 ± 56.0	143.8 ± 57.5	<0.0001
LV end-diastolic volume, mL	169.9 ± 68.1	205.6 ± 69.5	<0.0001
LV end-systolic volume index, mL/m^2	67.6 ± 30.6	73.0 ± 28.1	0.03
LV end-diastolic volume index, mL/m^2	96.7 ± 35.9	104.1 ± 33.2	0.01
Regurgitant fraction, %	36.7 ± 16.7	36.3 ± 13.5	0.84
Right-ventricular systolic pressure, mm Hg	42.1 ± 14.1	45.5 ± 13.3	0.006
Left atrial volume, mL	80.0 ± 35.7	97.8 ± 42.2	<0.0001
Tricuspid regurgitation			
0 (none)	3.3 (7/214)	1.3 (5/385)	0.10
1+ (mild)	77.6 (166/214)	83.9 (323/385)	0.055
2+ (moderate)	16.8 (36/214)	14.5 (56/385)	0.46
3+ (moderate to severe) or 4+ (severe)	2.3 (5/214)	0.3 (1/385)	0.01

Values are mean ± SD or % (n/N).
LV = left ventricle.

DISCUSSION

In the current substudy from the randomized COAPT trial, we assessed the impact of sex on clinical outcomes following TMVr with the MitraClip plus GDMT

TABLE 3 Procedural Characteristics in the Device Group According to Sex

	Women (n = 96)	Men (n = 197)	*P* Value
Number of MitraClip devices implanted	1.5 ± 0.6	1.8 ± 0.7	0.006
0	2.1 (2/96)	2.0 (4/197)	0.98
1	46.9 (45/96)	31.0 (61/197)	0.008
2	46.9 (45/96)	56.9 (112/197)	0.11
3	4.2 (4/96)	9.6 (19/197)	0.10
4	0.0 (0/96)	0.5 (1/197)	0.48
Procedure duration, min	143.6 ± 75.0	175.7 ± 124.8	0.02
Device procedure duration, min	106.2 ± 56.8	125.1 ± 65.7	0.02
Device duration, min	64.8 ± 42.7	91.6 ± 93.0	0.008
Total fluoroscopy duration, min	31.4 ± 27.9	35.0 ± 20.7	0.23
Site-reported post procedure SMR			0.29
≤1+ (none to mild)	75.0 (66/88)	68.4 (130/190)	0.26
2+ (moderate)	17.0 (15/88)	25.8 (49/190)	0.11
≤2+ (none to moderate)	92.0 (81/88)	94.2 (179/190)	0.50
≥3+ (moderate to severe)	8.0 (7/88)	5.8 (11/190)	0.50
Length of hospital stay, days	2.9 ± 3.0	2.3 ± 1.8	0.02

Values are mean ± SD or % (n/N).
SMR = secondary mitral regurgitation.

TABLE 4 Medications According to Sex

	Women	Men	*P* Value
Baseline	n = 221	n = 393	
ACEi, ARB, or ARNi	68.8 (152)	65.9 (259)	0.47
ACEi/ARB	65.6 (145)	62.1 (244)	0.38
ARNi	3.2 (7)	3.8 (15)	0.68
Aldosterone antagonist	50.7 (112)	50.1 (197)	0.90
Beta blockers	89.1 (197)	90.8 (357)	0.50
Nitrate	8.6 (19)	6.4 (25)	0.30
Hydralazine	19.0 (42)	16.0 (63)	0.35
Nitrate plus hydralazine	5.9 (13)	5.1 (20)	0.68
Diuretic	88.7 (196)	89.6 (352)	0.74
Chronic oral anticoagulant, any	36.2 (80)	47.3 (186)	0.008
Warfarin	24.0 (53)	32.8 (129)	0.02
Direct-acting oral anticoagulant	12.2 (27)	14.8 (58)	0.38
Aspirin	52.0 (115)	66.7 (262)	0.0004
P2Y12 receptor inhibitor, any	19.9 (44)	26.2 (103)	0.08
Statin	50.2 (111)	68.2 (268)	<0.0001
24 mo	n = 140	n = 220	
ACEi, ARB, or ARNi	70.7 (99)	65.9 (145)	0.34
ACEi/ARB	55.7 (78)	49.5 (109)	0.25
ARNi	15.7 (22)	17.7 (39)	0.62
Aldosterone antagonist	52.9 (74)	47.3 (104)	0.30
Beta blockers	87.1 (122)	90.9 (200)	0.26
Nitrate	7.9 (11)	6.4 (14)	0.59
Hydralazine	12.1 (17)	15.0 (33)	0.44
Nitrate plus hydralazine	5.7 (8)	4.1 (9)	0.48
Diuretic	90.0 (126)	90.0 (198)	1.00
Chronic oral anticoagulant, any	45.0 (63)	51.8 (114)	0.21
Warfarin	25.0 (35)	34.5 (76)	0.056
Direct-acting oral anticoagulant	20.0 (28)	18.2 (40)	0.67
Aspirin	52.9 (74)	66.4 (146)	0.01
P2Y12 receptor inhibitor, any	16.4 (23)	25.5 (56)	0.04
Statin	45.7 (64)	70.5 (155)	<0.0001

Values are % (n).

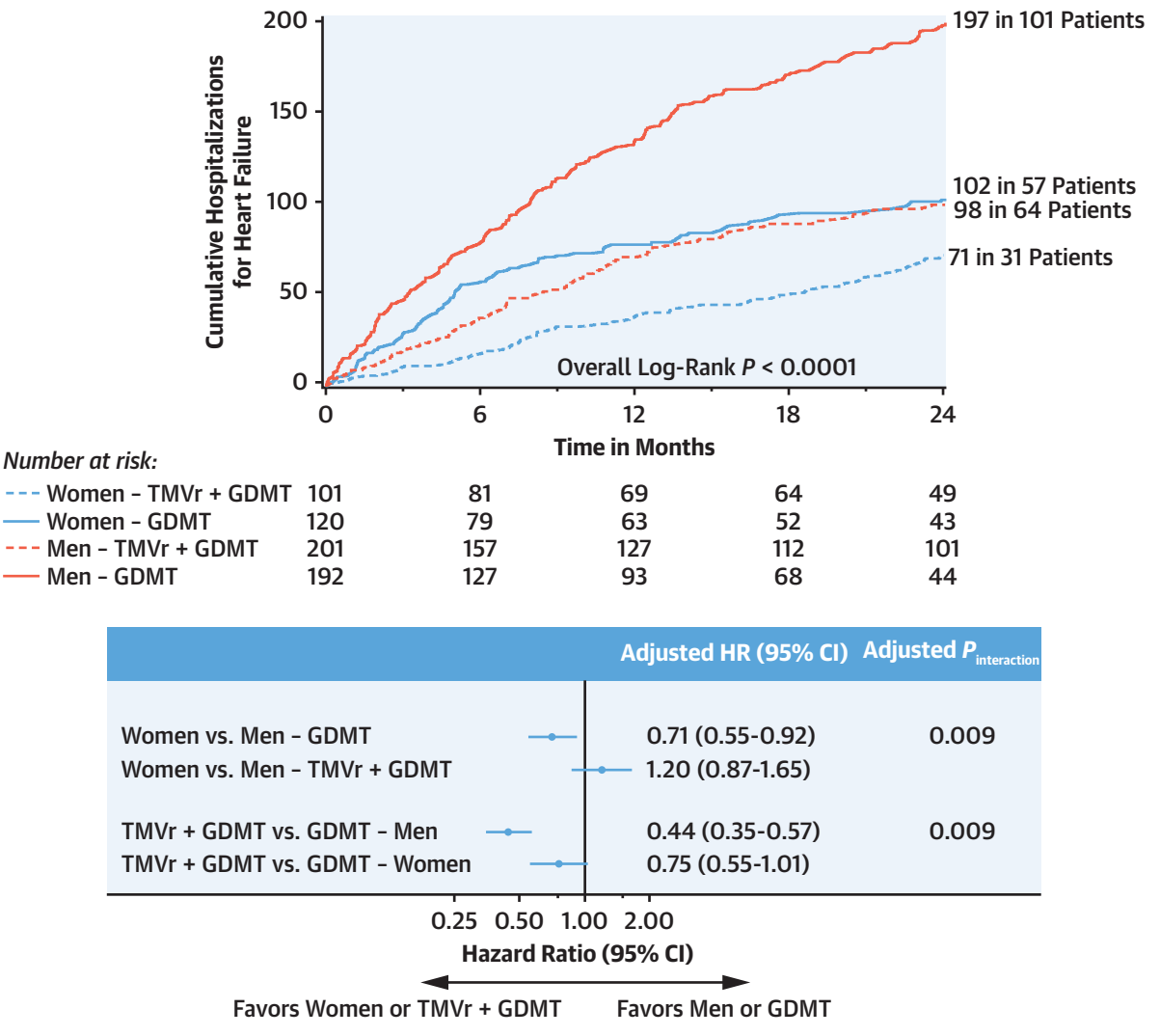
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor neprilysin inhibitor.

versus GDMT alone in patients with HF and LV dysfunction and moderate-to-severe or severe SMR. The major findings from this study are that, despite being younger and having fewer comorbidities, women nonetheless had greater HF symptoms and poorer quality of life and functional capacity at baseline than men; women had a lower cumulative incidence of total HFHs at 2 years compared with men when managed with GDMT alone; conversely, the relative reduction in all HFHs with TMVr treatment compared with GDMT alone was less in women than men, a finding attributable to a lack of reduction in HFHs with TMVr between 1 and 2 years after randomization in women but not in men; female sex was an independent predictor of a lower risk of death, although the impact of TMVr in reducing mortality was consistent in men and women; the improvement in quality of life and functional capacity with TMVr treatment was also consistent in men and women.

HF is associated with significant morbidity and mortality and has a dramatic impact on patient wellness and health care expenditures in the Western world (5,10,11). In recent years, differences in the incidence and baseline characteristics between men and women with HF have been emphasized, including sex-specific responses to pharmacological and device therapies (2,3,12). Women have been reported to have a more pronounced response to beta blockers (13,14) and cardiac-resynchronization therapy (15) than men, whereas a neutral effect of sex has been observed with angiotensin converting enzyme inhibitors and aldosterone antagonists (12).

The development of severe SMR connotes a poor prognosis in patients with HF (1,2), and recent reports have indicated a higher incidence of SMR in men with HF compared with women (16). However, to our knowledge, no previous study has examined the sex-specific effects of SMR and its treatment on long-term prognosis in HF. The current analysis from the randomized COAPT trial demonstrates that the outcomes of both sexes were substantially improved after TMVr with the MitraClip compared with GDMT alone. Procedural success rates were high, and device-related complications were infrequent, and did not differ between sexes, confirming previous reports of TMVr safety irrespective of sex (17–19). Mortality was substantially and consistently reduced in both men and women after MitraClip treatment, and QOL and functional outcomes were improved irrespective of sex. However, sex-specific outcomes were noted in the rates of total HFHs and the response of this outcome to treatment with GDMT versus TMVr. Among patients treated with GDMT alone, men had more HFHs during follow-up than women. Fortuitously, the relative effect of TMVr with the MitraClip in reducing HFHs compared with GDMT alone was more pronounced in men than in women. This effect was explained by a strong temporal interaction in effectiveness. The rate of HFHs within the first year after randomization were reduced to a similar degree in both men and women. Between years 1 and 2 after randomization, however, treatment with the MitraClip continued to afford a marked reduction in HFHs in men but not in women. These interactions were highly significant, suggesting more than play of chance. Of note, these effects were not evidenced in the more rudimentary time-to-first-event analyses, signifying that considering recurrent events (and adjusting for the competing risk of death) is necessary to comprehensively evaluate therapies for HF.

CENTRAL ILLUSTRATION **Cumulative Incidence of Heart Failure Hospitalization According to Treatment Group and Sex**



Kosmidou, I. et al. J Am Coll Cardiol HF. 2021;9(9):674–683.

The **top panel** shows the cumulative incidence of heart failure hospitalization in women versus men who were randomized to transcatheter mitral valve repair (TMVr) with the MitraClip plus guideline-directed medical therapy (GDMT) versus GDMT alone. In patients treated with GDMT alone, the 2-y cumulative incidence of heart failure hospitalizations was higher in men compared with women, whereas it was lower in men compared with women in those treated with TMVr + GDMT. The **bottom panel** shows the hazards for recurrent heart-failure hospitalization events with interaction testing between sex and treatment. The relative reduction in all heart- failure hospitalizations with TMVr + GDMT compared with GDMT alone was less in women than men.

Several potential mechanisms may explain these sex-specific differences in HFHs. First, the efficacy and durability in the amelioration of severe SMR at 1 and 2 years was similar in men and women. Thus, other explanations for the loss in effectiveness of TMVr in reducing HFHs after the first year in women must be sought. Examination of the cumulative incidence curves among GDMT-alone-treated patients shows that, after the first year, there were relatively few HFHs in women compared with men. This may, in part, be because of the better comorbidity profile in women and perhaps other unmeasured factors such as differences in adherence to medication. Second, the observed sex-specific differences in late HFHs may be related, in part, to differences in cardiac structure and remodeling in

TABLE 5 Unadjusted Clinical Outcomes at 2 Years According to Sex and Treatment Assignment

	Women (n = 221)			Men (n = 393)			
	TMVr + GDMT (n = 97)	GDMT Alone (n = 124)	HR (95% CI)	TMVr + GDMT (n = 197)	GDMT Alone (n = 196)	HR (95% CI)	$P_{interaction}$
Death or HF hospitalization	41.8 (41)	58.0 (68)	0.61 (0.41-0.89)	46.4 (92)	72.8 (133)	0.52 (0.40-0.68)	0.63
CV death or HF hospitalization	40.3 (39)	55.6 (64)	0.61 (0.41-0.91)	42.8 (82)	68.8 (123)	0.51 (0.38-0.67)	0.52
Death							
All-cause	22.9 (22)	31.6 (37)	0.67 (0.39-1.13)	30.8 (61)	50.4 (88)	0.58 (0.42-0.80)	0.70
Cardiovascular	18.3 (17)	27.3 (31)	0.61 (0.34-1.11)	25.0 (47)	42.8 (71)	0.55 (0.38-0.80)	0.81
Related to HF	11.8 (10)	21.0 (23)	0.48 (0.23-1.01)	11.5 (20)	26.9 (40)	0.42 (0.24-0.71)	0.78
Not related to HF	7.4 (7)	8.0 (8)	0.99 (0.36-2.72)	15.2 (27)	21.7 (31)	0.73 (0.43-1.22)	0.63
Non-cardiovascular	5.6 (5)	6.0 (6)	0.94 (0.29-3.07)	7.8 (14)	13.4 (17)	0.69 (0.34-1.40)	0.68
Hospitalization							
All-cause	71.9 (70)	75.8 (88)	0.87 (0.64-1.20)	67.0 (130)	84.0 (148)	0.70 (0.55-0.88)	0.27
Cardiovascular	48.1 (46)	58.9 (67)	0.73 (0.50-1.06)	51.4 (95)	72.4 (123)	0.60 (0.46-0.78)	0.47
Related to HF	33.9 (31)	51.3 (57)	0.54 (0.35-0.84)	35.3 (64)	59.7 (101)	0.49 (0.36-0.67)	0.72
Not related to HF	25.8 (24)	29.7 (31)	0.91 (0.53-1.54)	29.4 (50)	33.3 (47)	0.91 (0.61-1.36)	0.94
Noncardiovascular	52.3 (48)	48.3 (53)	1.05 (0.71-1.55)	44.8 (81)	52.5 (79)	0.86 (0.63-1.18)	0.48
Stroke or TIA	4.5 (4)	10.3 (11)	0.41 (0.13-1.28)	5.1 (9)	6.9 (8)	0.97 (0.37-2.52)	0.23
Myocardial infarction	4.4 (4)	6.4 (6)	0.75 (0.21-2.65)	5.1 (9)	8.2 (11)	0.70 (0.29-1.70)	0.94
Mitral valve intervention	5.5 (5)	7.5 (7)	0.81 (0.26-2.55)	2.9 (5)	10.3 (11)	0.35 (0.12-1.02)	0.34
MitraClip	4.5 (4)	4.9 (4)	1.12 (0.28-4.49)	2.9 (5)	8.1 (7)	0.52 (0.17-1.66)	0.45
Mitral valve surgery	1.1 (1)	2.6 (3)	0.39 (0.04-3.77)	0.0 (0)	2.5 (4)	–	0.99
PCI or CABG	1.1 (1)	2.1 (2)	0.55 (0.05-6.11)	3.5 (6)	6.9 (10)	0.52 (0.19-1.43)	0.95
New CRT	2.3 (2)	2.8 (3)	0.75 (0.13-4.52)	2.9 (5)	3.4 (5)	0.88 (0.25-3.05)	0.88
Major bleeding	7.2 (7)	0.8 (1)	8.56 (1.05-69.55)	6.2 (12)	1.1 (2)	5.84 (1.31-26.08)	0.76
LVAD or heart transplant	0.0 (0)	10.2 (10)	–	5.8 (9)	8.6 (13)	0.57 (0.24-1.34)	0.99
Primary safety outcome[a]	2.0 (2)	0.0 (0)	–	6.8 (11)	0.0 (0)	–	–

Rates presented are time-to-first event Kaplan-Meier estimates, shown as % (n), unless otherwise indicated. [a]Device-related complications including single-leaflet device attachment, device embolization, endocarditis, or mitral stenosis requiring mitral valve surgery, LVAD, heart transplantation, or any other device-related event requiring nonelective cardiovascular surgery.

CABG = coronary artery bypass grafting; CRT = cardiac resynchronization therapy; CV = cardiovascular; HF = heart failure; LVAD = left ventricular assist device; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

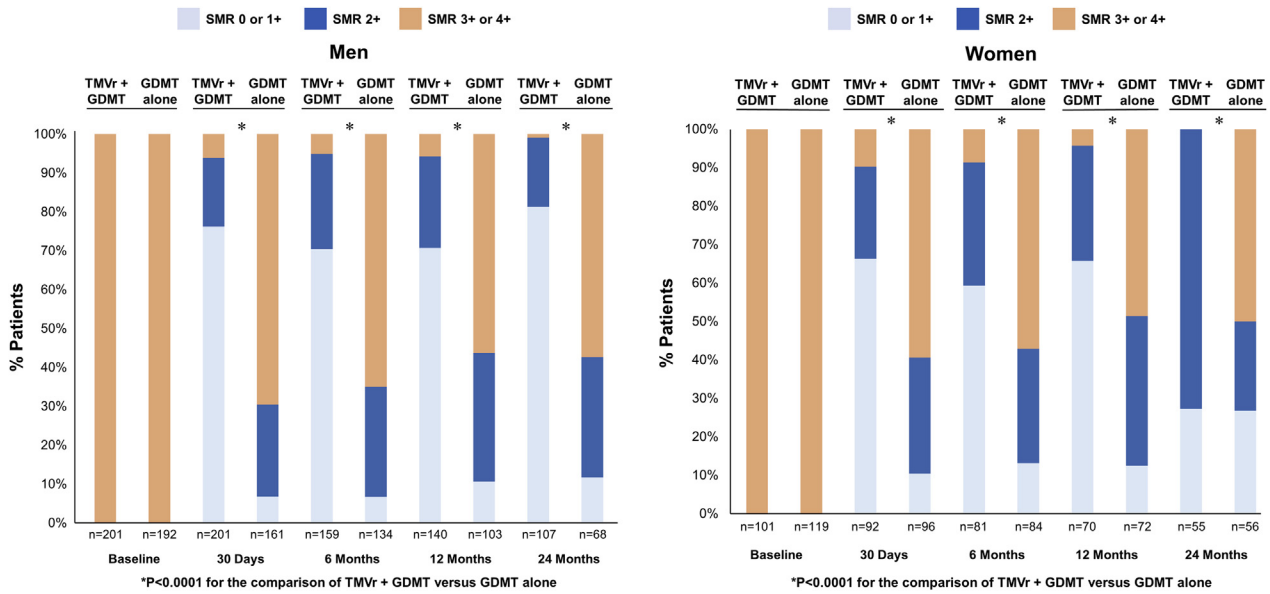
men compared with women (20,21). The larger LV systolic and diastolic volumes in men compared with women in the current study, evident even when indexed to body surface area, may explain the longer-term ongoing responses to chronic reductions in regurgitant volume in men. Further, in the current study, women more commonly had non-ischemic cardiomyopathy compared with men, consistent with previous reports (4); nevertheless, in interaction testing, the type of cardiomyopathy did

TABLE 6 1-Year Changes in Quality of Life and Exercise Capacity According to Treatment Assignment and Sex

	Women			Men			
	TMVr + GDMT	GDMT Alone	Difference (95% CI)	TMVr + GDMT	GDMT Alone	Difference (95% CI)	$P_{interaction}$
KCCQ overall summary score							
Baseline	50.2 ± 23.7 (75)	52.5 ± 23.6 (74)	-2.3 (-9.9 to 5.4)	57.3 ± 21.3 (144)	56.9 ± 22.7 (114)	0.4 (-5.0 to 5.8)	0.56
12 months	71.8 ± 22.6 (75)	59.1 ± 23.5 (74)	12.7 (5.30 to 20.2)	71.8 ± 22.1 (144)	60.9 ± 25.3 (114)	10.9 (5.1 to 16.7)	0.70
Change from baseline to 12 months	21.6 ± 24.6 (75)	6.6 ± 22.9 (74)	–	14.5 ± 25.5 (144)	4.0 ± 25.5 (114)	–	–
Least square mean change from baseline to 12 months [SE] (n)	18.9 [2.7] (75)	5.2 [2.5] (74)	13.7 (6.8 to 20.6)	14.6 [1.8] (144)	3.9 [2.1] (114)	10.7 (5.5 to 16.0)	0.49
6-min walk distance, meters							
Baseline	242.5 ± 118.1 (63)	247.0 ± 126.6 (69)	-4.4 (-46.7 to 37.8)	291.4 ± 119.2 (128)	276.2 ± 121.5 (97)	15.2 (-16.7 to 47.1)	0.46
12 months	277.3 ± 123.6 (63)	260.6 ± 139.1 (69)	16.7 (-28.8 to 62.2)	323.5 ± 110.6 (130)	276.0 ± 129.2 (98)	47.5 (16.1 to 78.8)	0.24
Change from baseline to 12 months	34.7 ± 94.4 (63)	13.6 ± 128.5 (69)	–	33.4 ± 102.5 (128)	-0.3 ± 104.6 (97)	–	–
Least square mean change from baseline to 12 months [SE] (n)	33.9 [13.3] (63)	14.3 [12.7] (69)	19.5 (-14.0 to 53.0)	35.9 [8.2] (128)	-3.6 [9.5] (97)	39.3 (13.4 to 65.2)	0.36

Values are mean ± SD (n), unless otherwise indicated.

FIGURE 1 Mitral Regurgitation Severity at Baseline and During Follow-Up in Men and Women



*$P < 0.05$; †$P < 0.01$; and ‡$P < 0.001$ for the comparison of secondary mitral regurgitation (SMR) severity (≤2+ vs ≥3+) at each follow-up period for patients randomized to transcatheter mitral valve repair (TMVr) with the MitraClip plus guideline-directed medical therapy (GDMT) versus GDMT alone. TMVr with GDMT resulted in significant reduction in SMR severity in both women and men at all time points following randomization. The reduction in severity of SMR, and its durability over time with TMVr, were consistent in men and women ($P_{interaction}$ >0.05 for all time points).

not affect sex-related differences on clinical outcomes, thus suggesting alternate mechanisms underlying the observed sex-specific differences. Third, there may be an inherent variable sex-specific response to pharmacological and device therapies, as previously described (22,23), which may relate to unmeasured confounders or other unexplored differences in biology.

Notwithstanding these differences in HFH outcomes, despite the younger age, fewer comorbidities, and smaller indexed LV volumes in women compared with men, women had more advanced signs and symptoms of HF at baseline, in agreement with previous reports (24,25). Nevertheless, substantial and clinically meaningful improvements in quality-of-life and functional capacity were observed following TMVr with the MitraClip irrespective of sex. Thus MitraClip thus provides both survival and symptomatic benefits in both men and women with HF and severe SMR.

STUDY LIMITATIONS. Although a prespecified substudy, outcomes in individual subgroups are inherently underpowered and should be considered hypothesis generating. Randomization was not stratified according to sex. Although the sex-specific outcomes were consistent in unadjusted and covariate-adjusted analyses, the presence of unmeasured confounders cannot be excluded. Precisely grading the severity of SMR after MitraClip treatment can be challenging (26), and we cannot exclude modest long-term differences in ≤1+ vs 2+ SMR in men versus women. The implications of any such differences are uncertain. Longer-term follow-up from the current study is required to determine if the observed temporal-related differences in HFHs between men and women continues over time or whether any new interactions become apparent.

CONCLUSIONS

In the COAPT trial, among patients with HF and severe SMR treated with maximally tolerated GDMT, TMVr with the MitraClip provided a substantial and consistent reduction in mortality and HFH and improvement in quality of life and functional capacity in both men and women compared with GDMT alone. However, the impact of TMVr in reducing HFH was less pronounced in women compared with men beyond the first year after treatment, in part because of fewer HFH events in women treated with GDMT alone after 1 year.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In the COAPT trial, men and women with heart failure and moderate-to-severe or severe SMR treated with the MitraClip had significantly reduced 2-year rates of death and heart failure hospitalization and improved quality-of-life and functional capacity compared with guideline-directed medical therapy alone. The reduction in all heart failure hospitalizations following MitraClip treatment was higher in men compared with women beyond 1 year of treatment. Patients with heart failure and severe SMR should be assessed for eligibility for transcatheter mitral valve repair with the MitraClip, irrespective of sex.

TRANSLATIONAL OUTLOOK: Future studies are required to address the long-term clinical and cardiac remodeling responses after MitraClip treatment in women and men with heart failure.

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