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ORIGINAL INVESTIGATIONS

Hospitalizations and Mortality in Patients With Secondary Mitral Regurgitation and Heart Failure

The COAPT Trial

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ABSTRACT

BACKGROUND The impact of transcatheter edge-to-edge repair (TEER) on the rate and prognostic impact of hospitalizations in patients with heart failure (HF) and severe secondary mitral regurgitation is unknown.

OBJECTIVES This study sought to evaluate the effect of the MitraClip percutaneous edge-to edge repair system on fatal and nonfatal hospitalizations and their relationship with mortality in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial.

METHODS Patients with HF (n = 614) with severe secondary mitral regurgitation were randomized to TEER plus guideline-directed medical therapy (GDMT) versus GDMT alone. Hospitalizations were classified as fatal if death occurred during that hospitalization or nonfatal if the patient was discharged alive.

RESULTS At 2 years, TEER treatment, compared with GDMT alone, resulted in lower time-to-first-event rates of any heart failure hospitalization (HFH) (34.8% vs 56.4%; HR: 0.51; 95% CI: 0.39-0.66) and fatal HFH (6.5% vs 12.6%; HR: 0.47; 95% CI: 0.26-0.85). TEER also resulted in lower rates of all-cause nonfatal and fatal hospitalizations. During the 2-year follow-up period, patients who underwent TEER spent an average of 2 more months alive and out of the hospital than did patients treated with GDMT alone (581 ± 27 days vs 519 ± 26 days; $P = 0.002$). All HFHs (adjusted HR: 6.37; 95% CI: 4.63-8.78) and nonfatal HFHs (adjusted HR: 1.78; 95% CI: 1.27-2.49) were consistently independently associated with increased 2-year mortality in both the TEER and GDMT groups ($P_{interaction} = 0.34$ and 0.39, respectively).

CONCLUSIONS In the COAPT trial, compared with GDMT alone, patients with HF and severe secondary mitral regurgitation undergoing TEER with the percutaneous edge-to edge repair system had lower 2-year rates of fatal and nonfatal all-cause hospitalizations and HFH and spent more time alive and out of the hospital. HFHs were strongly associated with mortality, irrespective of treatment. (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation [The COAPT Trial] and COAPT CAS [COAPT]; NCT01626079) (J Am Coll Cardiol 2022;80:1857–1868) © 2022 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CV = cardiovascular

GDMT = guideline-directed medical therapy

HF = heart failure

HFH = heart failure hospitalization

KCCQ = Kansas City Cardiomyopathy Questionnaire

MR = mitral regurgitation

QOL = quality of life

SMR = secondary mitral regurgitation

TEER = transcatheter edge-to-edge repair

Patients with heart failure (HF) and secondary mitral regurgitation (SMR), compared with patients without SMR, have increased risks of hospitalization and mortality.[1-4] Hospitalizations in patients with HF have been associated with increased health care costs, poor quality of life (QOL), and greater morbidity and mortality.[5] Transcatheter edge-to-edge repair (TEER) of the mitral valve with the MitraClip (Abbott) has been shown to lower the rate of heart failure hospitalizations (HFHs) and improve survival compared to guideline-directed medical therapy (GDMT) alone in selected patients with HF and severe SMR.[6-8] However, the predictors of HFH after TEER have been incompletely characterized, and the impact of TEER with the percutaneous edge-to-edge repair system on the prognostic impact of hospitalizations in patients with HF and severe SMR is unknown.

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We therefore sought to characterize the effects of treatment with TEER plus GDMT vs GDMT alone on fatal and nonfatal all-cause and cause-specific (HF-related, cardiovascular [CV]-related, and non-CV-related) hospitalizations in patients with HF and moderate-to-severe or severe MR enrolled in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial. Additionally, we investigated whether the reduction in the severity of SMR with a percutaneous edge-to-edge repair system modulates the subsequent effect of nonfatal hospitalizations on mortality.

METHODS

STUDY DESIGN. The COAPT trial was an international, open-label, multicenter, randomized trial that evaluated the effect of TEER with a percutaneous edge-to-edge repair system plus GDMT vs GDMT alone in patients who are symptomatic with HF and SMR.[9] The COAPT trial design and principal results were previously reported.[9] In brief, 614 patients at 78 sites in the United States and Canada were randomized 1:1 to TEER plus GDMT (n = 302) or GDMT alone (n = 312). Inclusion criteria included: 1) ischemic or nonischemic cardiomyopathy with a site-assessed left ventricular ejection fraction of 20% to 50%; 2) moderate-to-severe (3+) or severe (4+) SMR, as confirmed by an echocardiographic core laboratory using a multiparametric integrative approach as per American Society of Echocardiography recommendations[10]; and 3) New York Heart Association functional class II-IVa (ambulatory) symptoms despite a stable, maximally tolerated GDMT regimen and cardiac resynchronization therapy, if appropriate, as confirmed by a central eligibility committee. Patients were excluded if the LV end-systolic dimension was >7 cm, for severe pulmonary hypertension, severe tricuspid regurgitation, or moderate or severe right ventricular dysfunction. The trial was approved by the institutional review committee at each site, and all subjects provided written informed consent.

Transthoracic echocardiography was performed in all patients at baseline; at discharge (TEER group only); at 30 days, and 6, 12, 18, and 24 months; and then annually through 5 years. QOL was assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score at baseline; 30 days; and 6, 12, and 24 months. Clinical follow-up is ongoing through 5 years. At the present time, all patients have completed the 2-year follow-up. All echocardiograms were read at an independent core laboratory (MedStar Health Research Institute), and clinical events, including the causes of unplanned hospitalizations, were adjudicated by an independent clinical events committee (Cardiovascular Research Foundation) after review of original source documents.

STUDY ENDPOINTS. Endpoints of interest in the present analysis included all-cause hospitalizations, CV-related hospitalizations, HFHs, non-CV-related hospitalizations, and all-cause mortality. Each hospitalization was classified as fatal if the patient died

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during that index hospitalization or as nonfatal if the patient was discharged alive. HFH was defined as hospital admission or emergency department stay for >24 hours meeting the following criteria: 1) presence of increased signs and/or symptoms of HF; and 2) administration of intravenous HF therapy (eg, diuretic agents, inotropes, and/or vasodilators). Overnight stays at nursing home, physical rehabilitation, or extended-care facilities, including hospice, did not meet the protocol definition of hospitalization.

STATISTICAL ANALYSIS. All analyses were performed in the intention-to-treat population, including outcomes through 2 years postrandomization. Mean ± SD for normally distributed data and median (IQR) for non-normally distributed data were used to summarize continuous measures, and between-group measures were compared using the nonparametric Kruskal-Wallis test. Categorical variables were summarized by proportions, and comparisons between treatment groups were reported from a chi-square test or from Fisher exact test when the Cochran rule was not met. For time-to-first-event analyses, event rates were estimated by the Kaplan-Meier method and were compared to the log-rank statistic. A 2-sample Student's *t*-test was used to test the differences in days alive and out of the hospital between the TEER and GDMT groups. The association between hospitalization events and subsequent all-cause mortality was examined using time-adjusted Cox regression models that included hospitalizations as a time-adjusted covariate. Additional baseline covariates included in the multivariable models (chosen for their prior established relationships to outcomes in patients with HF) were age, sex, body mass index, creatinine clearance, B-type natriuretic peptide (BNP), ischemic vs nonischemic cardiomyopathy, history of atrial fibrillation or flutter, New York Heart Association functional class, and baseline severity of MR. We evaluated the association of each type of hospitalization event with 2-year all-cause mortality. Furthermore, the association between hospitalization and mortality was evaluated separately in the TEER and GDMT groups. Interaction testing was performed to assess the heterogeneity of the effect of hospitalization on mortality according to the randomized treatment. Independent predictors of all-cause and cause-specific hospitalizations were also evaluated using multivariable Cox regression models, entering the randomized assignment to TEER vs GDMT as well as all baseline variables that were significantly different ($P < 0.05$) on univariate analyses. A 2-sided *P* value <0.05 was considered statistically significant for all tests. Statistical analyses were performed with SAS version 9.3 (SAS Institute).

TABLE 1 Baseline Characteristics According to Hospitalization Status During 2-Year Follow-Up

	Any Hospitalization (n = 436)	No Hospitalization (n = 178)	*P* Value
Age, y	74.0 (67.0–81.0)	73.0 (65.0–80.0)	0.21
Female	158 (36.2)	63 (35.4)	0.84
Race			
White or Caucasian	329 (75.5)	128 (71.9)	0.32
Black or African American	62 (14.2)	26 (14.6)	
Other	45 (10.3)	24 (13.5)	
BMI, kg/m^2	25.8 (22.8–29.7)	26.0 (23.4–29.1)	0.93
Etiology of cardiomyopathy			
Ischemic	268 (61.5)	105 (59.0)	0.57
Nonischemic	168 (38.5)	73 (41)	
Hypertension	353 (81.0)	141 (79.2)	0.62
Diabetes	168 (38.5)	61 (34.3)	0.32
Chronic kidney disease[a]	322 (75.9)	119/177 (67.2)	0.03
Chronic obstructive pulmonary disease	108 (24.8)	35 (19.7)	0.17
Anemia	109 (25.0)	35 (19.7)	0.16
Previous stroke or TIA	70 (16.1)	35 (19.7)	0.28
Previous myocardial infarction	127/240 (52.9)	158/322 (49.1)	0.36
History of atrial fibrillation or flutter	261(59.9)	78 (43.8)	0.0003
Peripheral vascular disease	77 (17.7)	32 (18.0)	0.93
Prior coronary artery bypass graft	182 (41.7)	65 (36.5)	0.23
Prior percutaneous coronary intervention	202 (46.3)	81 (45.5)	0.85
Prior electronic device implantation[b]	286 (65.6)	125 (70.2)	0.27
STS replacement score, %	7.5 (4.2–11.3)	6.1 (3.2–9.7)	0.004
STS repair score, %	4.8 (2.6–7.7)	3.9 (1.8–6.9)	0.01
NYHA functional class III or IV	272/435 (62.5)	101 (56.7)	0.18
KCCQ Overall Summary score	50.4 (32.8–68.8)	55.2 (37.5–72.4)	0.06
6MWD, m	231.3 (135.0–321.9)	265.1 (167.6–367.3)	0.001
Serum creatinine, mg/dL	1.5 (1.2–2.1)	1.4 (1.1–1.8)	0.0009
Hemoglobin, g/dL	12.0 (10.8–13.1)	12.7 (11.6–14.0)	<0.0001
BNP, pg/mL	736.0 (389.5–1,336.5)	462.0 (288.0–1,079.0)	0.006
Albumin, g/dL	4.0 (3.7–4.2)	4.0 (3.7–4.3)	0.14

Values are median (IQR), n (%), or n/N (%). [a]Creatinine clearance <60 mL/min. [b]Includes cardiac resynchronization therapy and implantable cardioverter-defibrillator/pacemaker.

6MWD = 6-minute walking distance; BMI = body mass index; BNP = B-type natriuretic peptide; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

RESULTS

BASELINE CHARACTERISTICS. Among the 614 patients randomized in COAPT, 436 (71.0%) had 1 or more unplanned hospitalizations during follow-up. As shown in Table 1, patients who experienced any hospitalization during the 2-year follow-up had a greater prevalence of chronic kidney disease and history of atrial fibrillation or flutter, higher Society of Thoracic Surgeons scores, and higher BNP levels at baseline. Patients who were hospitalized also had

TABLE 2 Baseline Core Laboratory Echocardiographic Characteristics According to Hospitalization Status During 2-Year Follow-Up

	Hospitalization (n = 436)	No Hospitalization (n = 177)	*P* Value
Mitral regurgitation severity			0.005
Moderate-to-severe (3+)	212 (48.6)	108 (61.0)	
Severe (4+)	224 (51.4)	69 (39.0)	
LVEF, %	30.0 (24.0-37.0)	31.0 (25.0-36.0)	0.69
LVESD, cm	5.3 (4.6-5.9)	5.4 (4.8-5.9)	0.28
LVEDD, cm	6.1 (5.6-6.7)	6.2 (5.7-6.6)	0.55
LVESV, mL	124.0 (94.0-169.0)	123.0 (95.0-158.0)	0.64
LVEDV, mL	181.0 (140.0-232.0)	180.0 (140.0-225.0)	0.56
Total stroke volume,[a] mL	55.0 (41.0-71.0)	53.0 (42.0-68.0)	0.72
Mitral valve orifice area, cm^2	4.9 (4.4-5.7)	4.8 (4.2-5.6)	0.08
EROA, cm^2	0.38 (0.32-0.46)	0.36 (0.31-0.44)	0.14
Left atrial volume, mL	87.0 (66.0-105.0)	85.0 (63.8-107.0)	0.54
Tricuspid regurgitation			0.05
None	6/426 (1.4)	6/173 (3.5)	0.10
Mild (1+)	343/426 (80.5)	146/173 (84.4)	0.27
Moderate (2+)	72/426 (16.9)	20/173 (11.6)	0.10
Moderate to severe (3+)	5/426 (1.2)	0/173 (0.0)	0.15
Severe (4+)	0/426 (0.0)	1/173 (0.6)	0.12
RVSP, mm Hg	45.0 (35.0-54.7)	40.0 (33.0-51.0)	0.004

Values are n (%), median (IQR), or n/N (%). [a]Calculated as LVEDV − LVESV.

EROA = effective regurgitant orifice area; LVEDD = left ventricular end-diastolic dimension; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; LVESV = left ventricular end-systolic volume; RVSP = right ventricular systolic pressure.

lower KCCQ scores and 6-minute walking distances. As reported in **Table 2**, patients who were hospitalized were more likely to have more severe MR and tricuspid regurgitation at baseline and higher right ventricular systolic pressures. Baseline characteristics by hospitalization status in the TEER plus GDMT group and the GDMT group are reported separately in Supplemental Tables 1 and 2. Procedural outcomes after TEER treatment were unrelated to subsequent hospitalizations (Supplemental Table 3).

RATES OF HOSPITALIZATION. The median time to first hospitalization was 253 days (IQR: 115-453 days) in the TEER group and 240 days (IQR: 107-437 days) in the GDMT group ($P = 0.37$). As shown in **Table 3**, patients randomized to TEER had lower 2-year rates of all-cause and CV hospitalizations, driven by a 49% reduction in HFHs. There were no differences in the rates of CV hospitalizations not related to HF and non-CV hospitalizations between the TEER and GDMT groups. The total numbers (including recurrent events) and incidence rate of hospitalizations by cause in each group are shown in **Table 4** and Supplemental Figure 1, and time-to-first-event curves of fatal and nonfatal hospitalizations according to randomization arm and hospitalization type are shown in **Figure 1**. TEER plus GDMT resulted in significantly lower rates of fatal and nonfatal HF-related and overall CV hospitalizations and fatal all-cause hospitalizations compared with GDMT alone. Treatment with the percutaneous edge-to-edge repair system did not reduce the incidence of either fatal or nonfatal CV hospitalizations not related to HF or hospitalizations caused by non-CV causes. During the 2-year follow-up, patients treated with TEER spent, on average, 2 more months alive and out of the hospital than patients treated with GDMT alone did (581 ± 27 days vs 519 ± 26 days; $P = 0.002$) (**Figure 2**). The mean number of days dead during the 2-year follow-up period was 121 ± 221 days in the TEER group and 155 ± 231 days in the GDMT group ($P = 0.052$). The mean number of days hospitalized was 11 ± 20 vs 14 ± 19 in the TEER and GDMT groups, respectively ($P = 0.06$).

HOSPITALIZATIONS AND MORTALITY. For each successive hospitalization, the risk of in-hospital death progressively rose (eg, the rate of in-hospital death for a third hospitalization was greater than for a second hospitalization, which was greater than for a first hospitalization), both in patients who were TEER-treated and those who were GDMT-treated (Supplemental Table 4). The duration of each successive hospitalization also increased (Supplemental Table 5).

Kaplan-Meier curves for time to death following a first hospitalization after randomization by type are shown in Supplemental Figure 2. In multivariable-adjusted models, the risk of subsequent mortality within 2 years was significantly higher in patients who were hospitalized vs those who were not, both for all-cause hospitalizations and each cause-specific hospitalization (**Figure 3A**, Supplemental Table 6). The effect of each hospitalization type on mortality was consistent between the TEER plus GDMT and GDMT-alone groups, without significant interactions. When restricting the analysis to only nonfatal hospitalizations (**Figure 3B**, Supplemental Table 6), all-cause, HF-related, and CV-related hospitalizations remained consistently associated with increased 2-year mortality, with both TEER plus GDMT and GDMT alone treatments. Nonfatal, non-CV-related hospitalizations were not associated with a higher risk of 2-year mortality.

PREDICTORS OF HOSPITALIZATION. After multivariable adjustment, TEER treatment was associated with significantly lower risks of all-cause, CV-related, and HF-related hospitalizations compared to GDMT alone (**Table 5**). Higher BNP levels, lower KCCQ scores, 4+ vs 3+ MR, higher right ventricular systolic pressures, higher Society of Thoracic Surgeons scores, and history of atrial fibrillation or flutter were also

associated with increased rates of all-cause, CV-related, and HF-related hospitalizations. Finally, an increase in left atrial size between baseline and 30 days was independently associated with a higher risk of all-cause, HF-related, and CV-related hospitalizations between 30 days and 2 years (Supplemental Table 7).

DISCUSSION

As summarized in the **Central Illustration**, the main findings from the present analysis from the COAPT trial, in which we examined the rates and implications of fatal and nonfatal hospitalizations within the 2-year follow-up period in patients with HF and severe SMR, are as follows:

1. First and recurrent hospitalizations were frequent in both groups, and mortality rates were high after hospitalizations.
2. Nonfatal all-cause, CV-related, and HF-related hospitalizations (but not non-CV-related hospitalizations) were strongly associated with subsequent mortality.
3. Compared with GDMT alone, TEER with the percutaneous edge-to-edge repair system plus GDMT resulted in lower rates of both fatal and nonfatal all-cause hospitalizations, driven by a marked reduction in HFHs and, within the 2-year follow-up, resulted in an approximately 2-month increase in time alive and out of the hospital; however, TEER did not affect the relationship between nonfatal hospitalizations and mortality.
4. In addition to treatment with the percutaneous edge-to-edge repair system, several clinical, echocardiographic, and laboratory variables independently predicted the risk of subsequent hospitalization in this high-risk patient cohort.

Patients with HF and SMR are at increased risk for both fatal and nonfatal CV events.[4] Nonfatal events, including hospitalizations, have been associated with increased health care costs, reduced QOL, and mortality in patients with chronic HF.[5] In the COAPT trial, among patients with HF and moderate-to-severe or severe SMR who remained symptomatic despite maximally tolerated GDMT, first and recurrent hospitalizations during the 2-year follow-up in patients treated with GDMT alone were common, with approximately 10% of all hospitalizations resulting in death before hospital discharge. As described later, even in patients who survived their hospitalizations and were discharged, subsequent mortality was substantially increased. TEER with a percutaneous edge-to-edge repair system resulted in fewer total events and reduced time-to-first-event rates of all-cause, HFH, and CV-related hospitalizations (but not non-CV-related hospitalizations) compared with GDMT alone, with the greatest effect on reducing HFHs. Furthermore, TEER reduced both the incident rate of fatal and nonfatal CV-related and HF-related hospitalizations.

There is an increasing appreciation of the value of patient-centered outcomes such as symptoms, functional status, QOL, and overall disease morbidity burden. Days alive out of the hospital accounts for both the number and duration of multiple hospitalizations, as well as mortality.[11] In the present analysis, TEER with a percutaneous edge-to-edge repair system resulted in a mean per patient benefit of ~2 months of additional life free from hospitalization within 2 years after treatment compared with GDMT alone, complementing the previously reported improvements in New York Heart Association functional

TABLE 3 2-Year Hospitalization Rates According to Treatment Assignment

Hospitalization Type	TEER + GDMT (n = 302)	GDMT alone (n = 312)	HR (95% CI)	*P* Value
All-cause	200 (68.6)	236 (80.7)	0.76 (0.63-0.92)	0.004
CV	141 (50.2)	190 (66.8)	0.65 (0.52-0.80)	<0.0001
Related to HF	95 (34.8)	158 (56.4)	0.51 (0.39-0.66)	<0.0001
Not related to HF	74 (28.1)	78 (31.7)	0.92 (0.67-1.26)	0.60
Non-CV	129 (47.3)	132 (50.4)	0.93 (0.73-1.18)	0.54

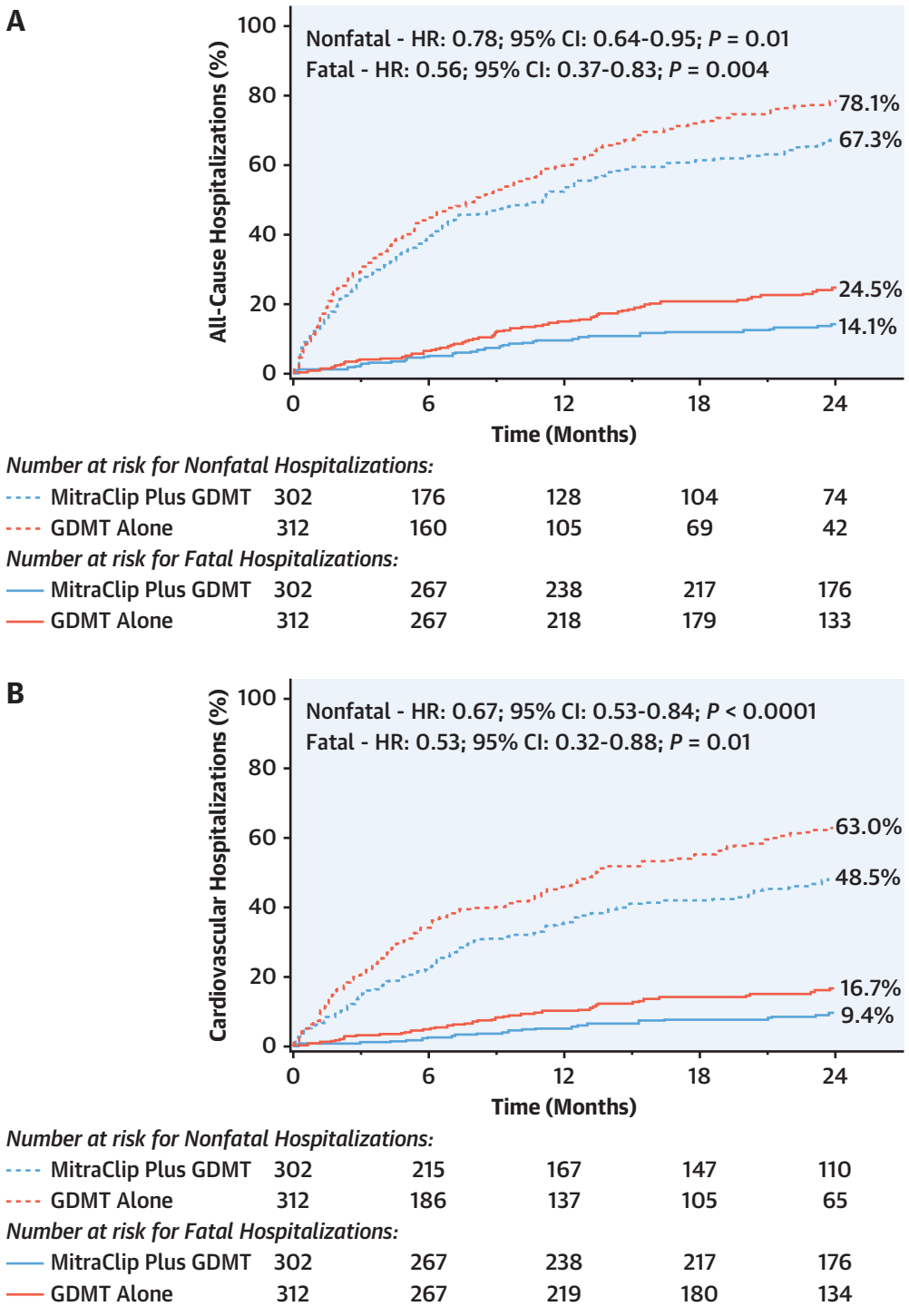
Event rates are number of events (Kaplan-Meier estimates [%]). *P* values determined by log-rank test.
CV = cardiovascular; GDMT = guideline-directed medical therapy; HF = heart failure.

TABLE 4 Total Hospitalizations During 2-Year Follow-Up by Type and Treatment

Hospitalization Type	TEER + GDMT (n)	Incidence Rate per 100 Person-Years (%)	GDMT Alone (n)	Incidence Rate per 100 Person-Years (%)	*P* Value
All-cause	496	102.3	643	143.3	<0.00001
Fatal	38	7.8	65	14.5	0.002
Nonfatal	458	94.5	578	128.8	<0.00001
CV-related	266	54.9	395	88.0	<0.00001
Fatal	24	5.0	43	9.6	0.008
Nonfatal	242	49.9	352	78.4	<0.00001
HF-related	169	34.9	296	66.0	<0.00001
Fatal	16	3.3	33	3.3	0.007
Nonfatal	153	31.6	263	31.6	<0.00001
CV-non-HF-related	97	20.0	99	22.1	0.50
Fatal	8	01.7	10	02.2	0.53
Nonfatal	89	18.4	89	19.8	0.61
Non-CV-related	230	47.5	248	55.3	0.10
Fatal	14	02.9	22	2.9	0.12
Nonfatal	216	44.6	226	50.4	0.20

Abbreviations as in Table 3.

FIGURE 1 Time to First Fatal and Nonfatal Hospitalizations



Kaplan-Meier time-to-first event curves in patients randomized to transcatheter edge-to-edge repair plus guideline-directed medical therapy (GDMT) (device) or GDMT (control) for: **(A)** all-cause hospitalization, **(B)** cardiovascular hospitalization, **(C)** heart failure hospitalization, and **(D)** noncardiovascular hospitalization. **Dotted lines** indicate nonfatal hospitalization and **solid lines** indicate fatal hospitalization.

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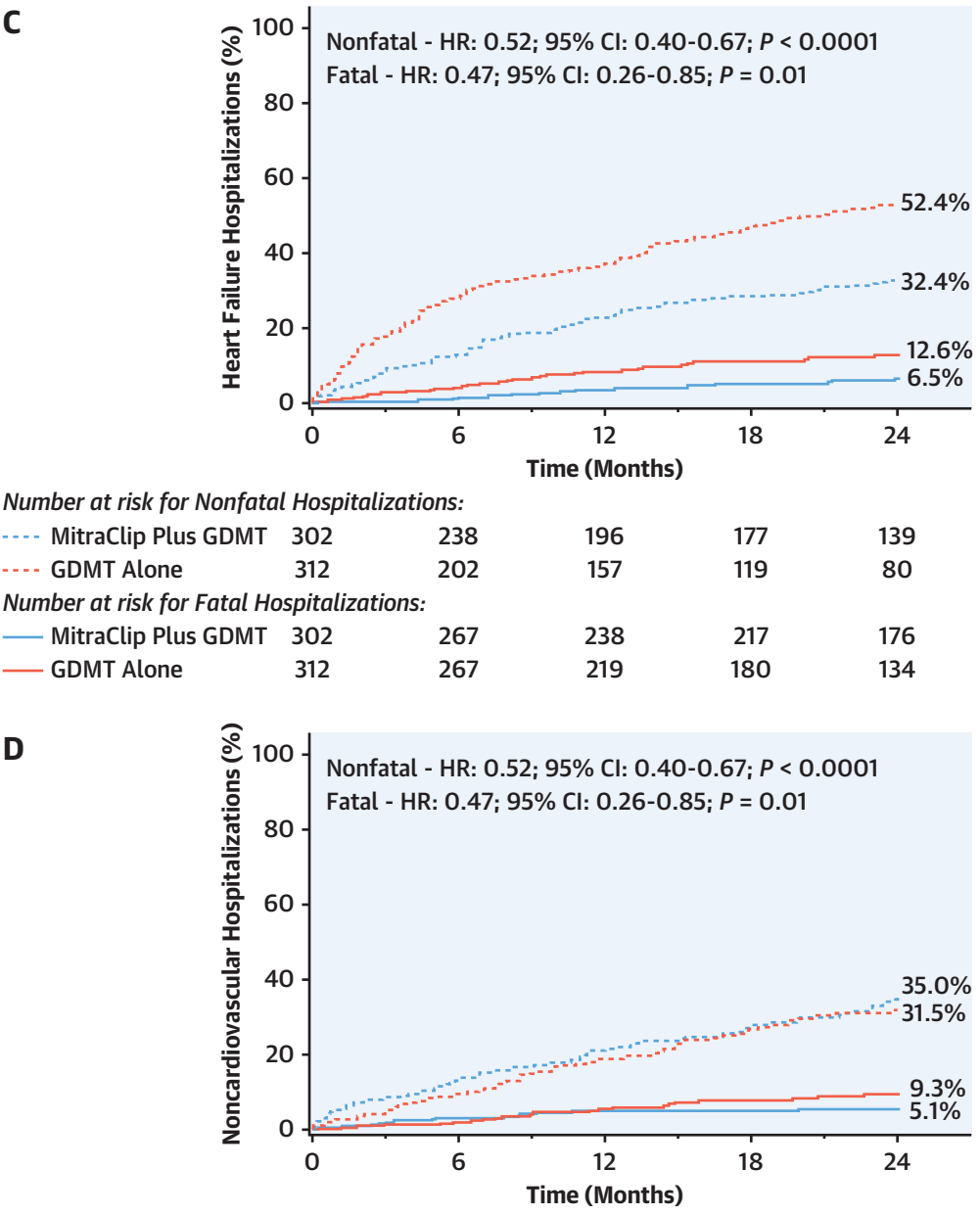
FIGURE 1 Continued



class, 6-minute walk distance, and KCCQ scores with TEER.[8]

Nonfatal all-cause, CV-related, and HF-related hospitalizations in the COAPT trial were strongly associated with an increased risk of subsequent mortality during the 2-year follow-up. Conversely, nonfatal non-CV-related hospitalizations did not have a significant effect on survival. These data

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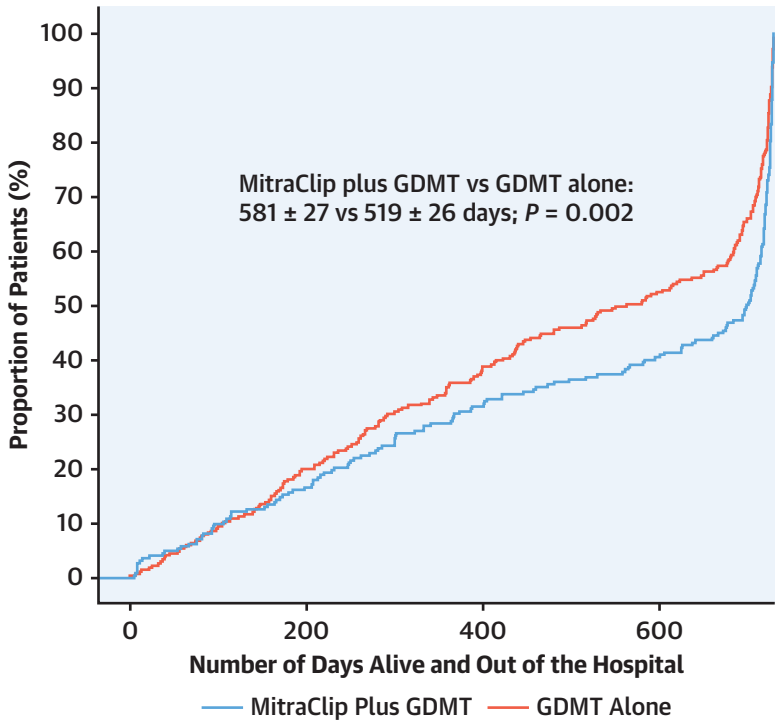
FIGURE 2 Days Alive and Out of the Hospital in the COAPT Trial



Cumulative frequency distribution curves of days alive and out of the hospital in the transcatheter edge-to-edge repair plus guideline-directed medical therapy (GDMT) and GDMT alone groups. The median number of days alive and out of the hospital was 721 days (IQR: 446-731 days) in the transcatheter edge-to-edge repair plus GDMT group and 681 days (IQR: 289-726 days) in the GDMT alone group.
COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation.

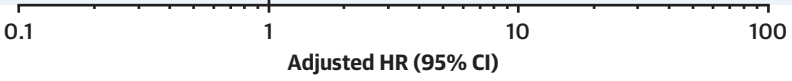
confirm and extend the findings from other HF cohorts. In the CHARM (Candesartan in Heart Failure: Reduction in Mortality and Morbidity) trial, nonfatal HFHs were independently associated with an increased risk of mortality in patients with symptomatic HF and reduced or preserved left ventricular ejection fraction randomized to placebo or candesartan.[5] In a study from the U.S. Department of Defense network that included 51,286 patients with a first HFH, repeat HFHs were associated with an increased risk of mortality, an effect that was amplified with the number of hospitalizations.[12] We observed similar findings in the present analysis, in which each sequential hospitalization was associated with a greater rate of in-hospital death in both patients treated with TEER and those treated with GDMT alone.

The lower rates of hospitalizations with TEER emerged within the first 30 days after treatment, whereas the survival benefit became apparent beyond 1 year of follow-up and presumably was a delayed effect of ameliorating chronic volume overload after reducing MR.[8] However, although the percutaneous edge-to-edge repair system, compared with GDMT alone, mitigated the incidence of future hospitalizations, it did not affect the adjusted risk of nonfatal hospitalizations on subsequent mortality. These data are concordant with our prior report that HFH rates and survival are improved by SMR reduction, regardless of whether this is achieved by TEER or GDMT.[13] Thus, irrespective of the presence of SMR, optimally treated patients with HF who require hospitalization are a high-risk group, with a more than 6-fold adjusted increase in mortality within the next 2 years, including a 78% increased hazard of mortality, even when they survive the hospitalization event. Further measures are needed to reduce the overall disease burden from HF, especially in patients requiring frequent hospitalizations. At a minimum, intensification of GDMT is warranted, with the use of neprilysin inhibitors[14] and sodium-glucose cotransporter-2 inhibitors,[15] cardiac resynchronization,[16] and

FIGURE 3 Association Between Hospitalization and Subsequent Mortality Within 2 Years

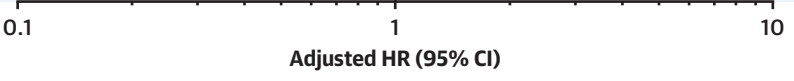
A

Endpoint	Group	Adjusted HR (95% CI)	$P_{interaction}$
All-cause hospitalization	Overall (N = 422)	9.59 (6.04–15.22)	
	MitraClip (N = 194)	9.44 (4.88–18.24)	0.95
	GDMT (N = 228)	9.71 (5.29–17.84)	
Heart failure-related hospitalization	Overall (N = 243)	6.37 (4.63–8.78)	
	MitraClip (N = 92)	7.36 (4.64–11.68)	0.39
	GDMT (N = 151)	5.64 (3.70–8.60)	
Cardiovascular-related hospitalization	Overall (N = 318)	6.94 (4.87–9.88)	
	MitraClip (N = 138)	7.44 (4.47–12.38)	0.71
	GDMT (N = 180)	6.55 (4.13–10.38)	
Noncardiovascular-related hospitalization	Overall (N = 252)	2.20 (1.61–3.01)	
	MitraClip (N = 124)	2.64 (1.66–4.20)	0.31
	GDMT (N = 128)	1.94 (1.30–2.89)	



B

Endpoint	Group	Adjusted HR (95% CI)	$P_{interaction}$
All-cause hospitalization	Overall (N = 422)	1.54 (1.05–2.26)	
	MitraClip (N = 194)	1.50 (0.85–2.65)	0.37
	GDMT (N = 228)	1.29 (0.76–2.20)	
Heart failure-related hospitalization	Overall (N = 243)	1.78 (1.27–2.49)	
	MitraClip (N = 92)	1.94 (1.15–3.29)	0.34
	GDMT (N = 151)	1.61 (1.05–2.47)	
Cardiovascular-related hospitalization	Overall (N = 318)	1.50 (1.08–2.08)	
	MitraClip (N = 138)	1.58 (0.96–2.59)	0.34
	GDMT (N = 180)	1.35 (0.88–2.08)	
Noncardiovascular-related hospitalization	Overall (N = 252)	0.93 (0.65–1.33)	
	MitraClip (N = 124)	0.88 (0.52–1.50)	0.82
	GDMT (N = 128)	0.85 (0.52–1.40)	



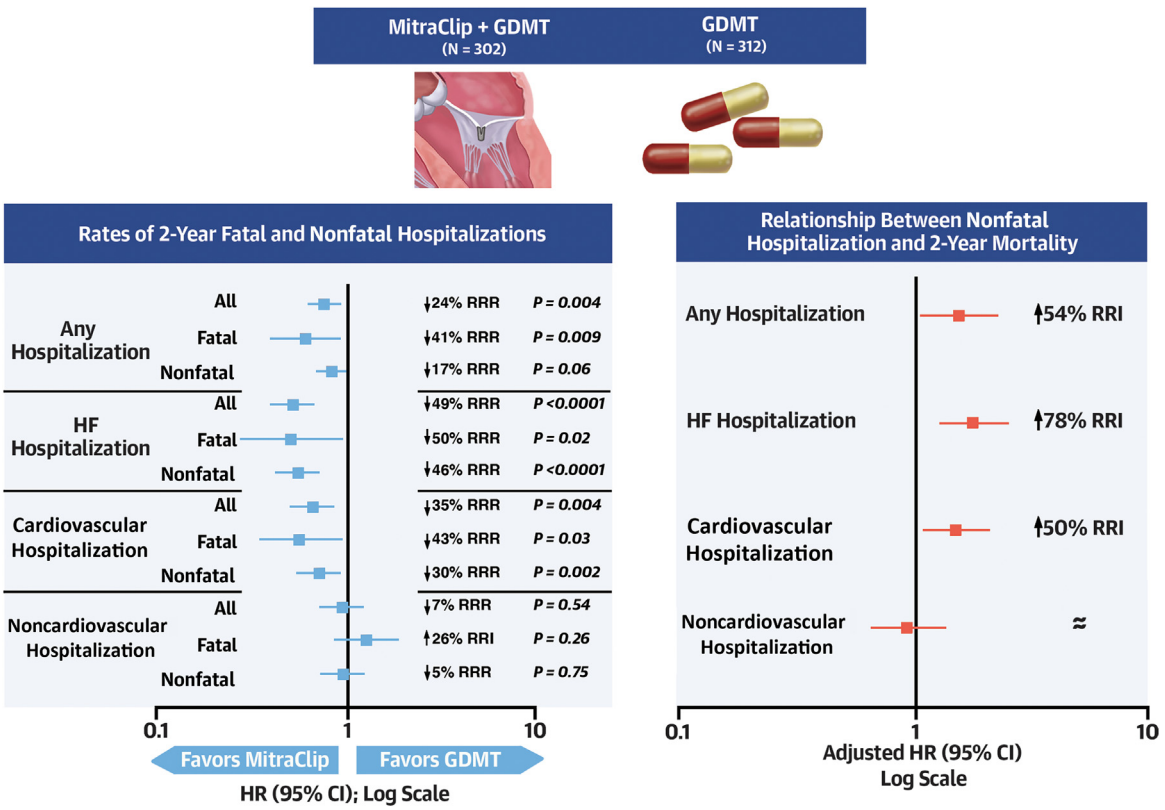
(A) Following all hospitalizations and **(B)** following nonfatal hospitalizations only. The following covariates were included in the adjusted models: age; sex; body mass index; creatinine clearance; B-type natriuretic peptide; ischemic vs nonischemic cardiomyopathy; history of atrial fibrillation or flutter; New York Heart Association functional class III or IV; and baseline severity of mitral regurgitation. The hospitalization event was modeled as a time-adjusted covariate. GDMT = guideline-directed medical therapy.

TABLE 5 Independent Predictors of Hospitalizations

	All Hospitalizations		HFH		CV Hospitalizations		Non-CV Hospitalizations	
	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
TEER vs GDMT alone	0.68 (0.55-0.85)	0.0008	0.43 (0.32-0.58)	<0.0001	0.58 (0.45-0.75)	<0.0001	1.02 (0.77-1.36)	0.89
MR severity, 4+ vs 3+	1.40 (1.11-1.77)	0.004	1.52 (1.13-2.05)	0.006	1.47 (1.13-1.92)	0.004	1.27 (0.95-1.71)	0.11
BNP, per 100 pg/mL	1.02 (1.01-1.03)	0.002	1.02 (1.01-1.03)	0.0002	1.02 (1.01-1.03)	0.001	1.01 (1.00-1.03)	0.057
Baseline KCCQ, per 10 points	0.93 (0.88-0.98)	0.009	0.92 (0.86-0.98)	0.015	0.94 (0.89-1.00)	0.047	0.91 (0.84-0.98)	0.01
Baseline 6MWD, per 10 m	0.99 (0.98-1.00)	0.054	–	–	–	–	0.99 (0.98-1.01)	0.36
RVSP, per 10 mm Hg	–	–	1.14 (1.02-1.27)	0.017	1.11 (1.01-1.22)	0.034	–	–
STS score, per 10% increase	1.30 (1.01-1.69)	0.045	–	–	–	–	1.67 (1.23-2.27)	0.001
History of atrial fibrillation or flutter	1.78 (1.40-2.26)	<0.0001	1.76 (1.29-2.40)	0.0004	1.56 (1.19-2.06)	0.001	1.47 (1.09-2.00)	0.01

Dashes indicate that the variable was not an independent predictor of the outcome.
HFH = heart failure hospitalization; MR = mitral regurgitation; other abbreviations as in Tables 1, 2, and 3.

CENTRAL ILLUSTRATION Independent Predictors and Implications of Hospitalizations and Mortality



Giustino G, et al. J Am Coll Cardiol. 2022;80(20):1857–1868.

Among patients with heart failure (HF) and moderate-to-severe or severe secondary mitral regurgitation who were enrolled in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial, treatment with transcatheter edge-to-edge repair reduced both fatal and nonfatal HF-related and all cardiovascular (CV) hospitalizations compared to guideline-directed medical therapy (GDMT) alone. Patients surviving a CV-related or HF-related hospitalization were at increased risk for subsequent mortality within the 2-year follow-up period. Nonfatal hospitalizations were a powerful independent predictor of subsequent mortality, an effect that did not differ between patients treated with transcatheter edge-to-edge repair plus GDMT vs GDMT alone. GDMT = guideline-directed medical therapy; RRI = relative risk increase; RRR = relative risk reduction.

revascularization[17]; if indicated, consideration of additional device-based interventions (eg, tricuspid valve-directed interventions[18]); and timely referral for advanced HF therapies if these measures are inadequate.

In addition to TEER treatment, several clinical variables (prior hospitalizations, lower KCCQ scores, history of atrial fibrillation or flutter, and non-ischemic cardiomyopathy), echocardiographic measures (more severe baseline SMR, higher right ventricular systolic pressure), and laboratory measures (higher BNP levels) that are routinely assessed independently predicted the risk of all-cause, CV-related, and HF-related hospitalizations. Although some of these variables have been previously reported in other cohorts of patients with HF,[4-19] the present findings in patients with HF and SMR prove the utility of these variables for future risk prediction and stratification of patients with HF after TEER.

STUDY LIMITATIONS. First, 2 years is a relatively short follow-up duration. Long-term follow-up (ongoing through 5 years) is necessary to fully characterize the late effects of hospitalizations on the subsequent risk of mortality and the utility of TEER in preventing these events. Second, the associations between nonfatal hospitalizations and subsequent death are subject to residual confounding. Third, the present findings are applicable to a selected patient population, according to the entry criteria of the COAPT trial;[8] the generalizability of the present results to other HF cohorts, with or without SMR, who are either more or less ill than those in the present study is uncertain. Fourth, few patients in the COAPT trial were treated with neprilysin inhibitors, and sodium-glucose cotransporter-2 inhibitors were not used during the course of this study. Although these agents may have improved the prognosis of the patients enrolled, they likely would not have affected the underlying relationship between hospitalizations and mortality. Finally, although all hospitalization events and their causes were adjudicated by a central events committee, the exact mechanisms and possible contributing causes leading to hospitalizations were not captured.

CONCLUSIONS

Among selected patients with HF and moderate-to-severe or severe SMR who remained symptomatic despite maximally tolerated GDMT, hospitalizations during follow-up were frequent and were strongly associated with both in-hospital and subsequent mortality. TEER plus GDMT compared with GDMT alone substantially reduced HF-related, CV-related, and all-cause hospitalizations, both fatal and nonfatal, but did not modify the association between nonfatal hospitalization events and subsequent death. Further pharmacologic and device-based treatments directed at the mechanisms that contribute to hospitalizations are needed to improve survival in this high-risk HF population.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The COAPT trial was sponsored by Abbott. Dr Giustino has received consulting fees (Advisory Board) from Bristol Myers Squibb/Pfizer. Dr Kapadia has received stock options from Navigate Cardiac Structures, Inc. Dr Kar has received consulting fees and served on the advisory board of Boston Scientific; has received consulting fees/stock equity from Valcare; and has received consulting fees from W.L. Gore and Medtronic. Dr Abraham has received research grant support from Abbott Vascular; and has received consulting fees from Abbott Vascular. Dr Lindenfeld has received research grant support from AstraZeneca; and has received consulting fees from Abbott Vascular, AstraZeneca, CVRx, Edwards Lifesciences, Impulse Dynamics, Boehringer Ingelheim, and V-Wave. Dr Lim has received research grant support from Abbott, Edwards, Medtronic, and Gore; has served as a consultant to Abbott, Edwards, Keystone Heart, Pipeline, Siemens, Valgen, and Venus; has served on the advisory boards of Ancora and Venus; and holds equity in 510Kardiac 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 Cohen has received research grant support from Abbott, Medtronic, Edwards Lifesciences, and Boston Scientific; and has received consulting fees from Abbott, Medtronic, Edwards Lifesciences, and Boston Scientific. Dr Asch has institutional contracts with Abbott, Neovasc, Ancora, Mitralign, Medtronic, Boston Scientific, Edwards Lifesciences, Biotronik, and Livanova. Dr Mack has served as coprimary investigator of the PARTNER Trial for Edwards Lifesciences and of COAPT trial for Abbott; and served as study chair for the APOLLO trial for Medtronic. Dr Stone has received speaker honoraria from Medtronic, Pulnovo, Infraredx; has served as a consultant to Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Vectorious, Miracor, Neovasc, Abiomed, Ancora, Elucid Bio, Occlutech, CorFlow, Apollo Therapeutics, Impulse Dynamics, Vascular Dynamics, Shockwave, V-Wave, Cardiomech, Gore, and Amgen; and has received equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Xenter; his employer, Mount Sinai Hospital, has received research support from Abbott, Abiomed, Bioventrix, Cardiovascular Systems Inc, Phillips, Biosense-Webster, Shockwave, Vascular Dynamics, and V-wave; and his daughter is an employee at Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Transcatheter edge-to-edge mitral valve repair with the MitraClip reduces both fatal and nonfatal hospitalizations and increases days alive out of the hospital compared to GDMT alone.

TRANSLATIONAL OUTLOOK: Further interventions are needed to reduce the burden of hospitalizations among patients with severe SMR and HF.

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KEY WORDS guideline-directed medical therapy, in-hospital mortality, mitral valve insufficiency, transcatheter mitral valve repair

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