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ORIGINAL RESEARCH

Incidence, Predictors, and Outcomes Associated With Worsening Renal Function in Patients With Heart Failure and Secondary Mitral Regurgitation: The COAPT Trial

Jeremy Kong, MD; Jonathan G. Zaroff, MD; Andrew P. Ambrosy, MD; Jesse K. Fitzpatrick, MD; Ivy A. Ku, MD; Jacob M. Mishell, MD; Lak N. Kotinkaduwa, PhD; Björn Redfors, MD, PhD; Nirat Beohar, MD; Gorav Ailawadi, MD; JoAnn Lindenfeld, MD; William T. Abraham, MD; Michael J. Mack, MD; Saibal Kar, MD; D. Scott Lim, MD; Brian K. Whisenant, MD; Gregg W. Stone, MD

BACKGROUND: The incidence and implications of worsening renal function (WRF) after mitral valve transcatheter edge-to-edge repair (TEER) in patients with heart failure (HF) are unknown. Therefore, the aim of this study was to determine the proportion of patients with HF and secondary mitral regurgitation who develop persistent WRF within 30 days following TEER, and whether this development portends a worse prognosis.

METHODS AND RESULTS: In the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial, 614 patients with HF and severe secondary mitral regurgitation were randomized to TEER with the MitraClip plus guideline-directed medical therapy (GDMT) versus GDMT alone. WRF was defined as serum creatinine increase ≥1.5× or ≥0.3 mg/dL from baseline persisting to day 30 or requiring renal replacement therapy. All-cause death and HF hospitalization rates between 30 days and 2 years were compared in patients with and without WRF. WRF at 30 days was present in 11.3% of patients (9.7% in the TEER plus GDMT group and 13.1% in the GDMT alone group; P=0.23). WRF was associated with all-cause death (hazard ratio [HR], 1.98 [95% CI, 1.3–3.03]; P=0.001) but not HF hospitalization (HR, 1.47 [95% CI, 0.97–2.24]; P=0.07) between 30 days and 2 years. Compared with GDMT alone, TEER reduced both death and HF hospitalization consistently in patients with and without WRF ($P_{interaction}$=0.53 and 0.57, respectively).

CONCLUSIONS: Among patients with HF and severe secondary mitral regurgitation, the incidence of WRF at 30 days was not increased after TEER compared with GDMT alone. WRF was associated with greater 2-year mortality but did not attenuate the treatment benefits of TEER in reducing death and HF hospitalization compared with GDMT alone.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01626079.

Key Words: acute kidney injury ■ heart failure ■ MitraClip ■ mitral valve edge-to-edge repair ■ secondary mitral regurgitation ■ worsening renal function

Heart failure (HF) is increasing with a current estimated incidence of more than 6.2 million people in the United States.[1] The number of patients suffering from HF with reduced ejection fraction is roughly equal to that of those suffering from HF with preserved ejection fraction.[1] Secondary mitral regurgitation (SMR) is

Correspondence to: Gregg W. Stone, MD, Mount Sinai Medical Center, 1 Gustave L. Levy Place, New York, NY 10029. Email: gregg.stone@mountsinai.org

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CLINICAL PERSPECTIVE

What Is New?

- MitraClip treatment was shown to reduce the 2-year incidence of new-onset end-stage renal disease and the need for dialysis.
- Acute kidney injury may be transient, and the incidence of persistent worsening renal function within 30 days after transcatheter edge-to-edge repair for secondary mitral regurgitation is unknown.
- The incidence and implications of worsening renal function after mitral valve transcatheter edge-to-edge repair in patients with heart failure are unknown.

What Are the Clinical Implications?

- Transcatheter edge-to-edge repair treatment compared with guideline-directed medical therapy alone reduced the rates of death and heart failure hospitalization between 30 days and 2 years consistently in patients in whom 30-day worsening renal function did not develop.
- Transcatheter edge-to-edge repair treatment did not increase the risk of worsening renal function but did not improve chronic renal function over time.

Nonstandard Abbreviations and Acronyms

AKI	acute kidney injury
GDMT	guideline-directed medical therapy
HFH	heart failure hospitalizations
SMR	secondary mitral regurgitation
TEER	transcatheter edge-to-edge repair
WRF	worsening renal function

commonly present in patients with HF and adverse cardiac remodeling.[2] The excess volume overload from SMR further impairs functional status and quality of life and increases the rates of hospitalization and mortality despite appropriate guideline-directed medical therapy (GDMT) and cardiac resynchronization therapy.[3–5] The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial evaluated the role of mitral valve transcatheter edge-to-edge repair (TEER) with the MitraClip system that approximates the anterior and posterior mitral leaflets. The MitraClip device safely reduced SMR in high-risk patients with HF in this trial and reduced the rates of death and HF hospitalization (HFH) within 24 months compared with ongoing treatment with GDMT alone.[6]

In a prior report from COAPT, MitraClip device treatment was shown to reduce the 2-year incidence of new-onset end-stage renal disease (ESRD) and the need for dialysis.[7] However, the rate and implications of acute kidney injury (AKI) were not examined. Although the MitraClip system does not require contrast for proper deployment, a prior study reported an approximate 30% rate of postprocedural AKI in 163 MitraClip-treated patients (63.8% of whom had SMR).[8] Postprocedural AKI portended worse clinical outcomes in this study.[8,9] Similarly, tricuspid edge-to-edge repair, another contrast-free procedure, has also been associated with an increased risk of post-procedural AKI and worse clinical outcomes.[10] However, AKI may be transient, and the incidence of persistent worsening renal function (WRF) within 30 days after TEER for SMR is unknown. Finally, prior studies have not had a concurrent control group, and thus it is unclear whether WRF is a consequence of the TEER procedure or progressive HF.

The objectives of the present analysis of the COAPT trial were therefore to (1) determine the proportion of patients with HF and SMR who develop persistent WRF after TEER; (2) evaluate whether the TEER procedure is associated with WRF; (3) identify risk factors that are associated with the development of WRF after TEER; and (4) assess whether patients who develop persistent WRF after TEER have subsequently worse clinical outcomes.

METHODS

Study Overview

The study design[11] and principal results[12] of the COAPT trial (NCT01626079) have been previously published. Briefly, COAPT was a multicenter, randomized, controlled, parallel-group, open-label trial of TEER with the MitraClip device in patients with HF of ischemic or nonischemic cause, left ventricular ejection fraction 20% to 50%, and moderate-to-severe (3+) or severe (4+) SMR who remained symptomatic (New York Heart Association functional class II, III, or ambulatory IV) despite maximally tolerated GDMT and cardiac resynchronization therapy as appropriate. Selected exclusion criteria included chronic obstructive pulmonary disease requiring home oxygen, valvular heart disease requiring intervention, cerebrovascular accident within 30 days of enrollment, American College of Cardiology/American Heart Association Stage D HF, Modified Rankin Scale score ≥4 disability, left ventricular end-systolic dimension >7 cm, severe pulmonary hypertension or symptomatic moderate or severe right ventricular dysfunction, and life expectancy <12 months because of noncardiac conditions. The study complies with the

Declaration of Helsinki and was approved by the institutional review board at each participating center. All patients provided written informed consent. The sponsor participated in site selection and provided funding to the Cardiovascular Research Foundation (New York, NY) for data analysis. The authors had full access to all data in the study and accept responsibility for the article's integrity, the data analysis, and the decision to publish. The data from this study may be made available to support additional studies; such requests should be made to the COAPT publications committee (coapt@crf.org).

A total of 614 patients were randomized to TEER plus GDMT versus GDMT alone. Serum creatinine was measured at the local hospital laboratory at baseline, at the time of discharge in TEER-treated patients, and at 30 days and 6, 12, 18, and 24 months following randomization. At 2 years, patients in the GDMT alone group were allowed to "crossover" and receive the MitraClip device; follow-up for the present report was thus truncated at 2 years to preserve intention-to-treat. Clinical follow-up is ongoing through 5 years.

Worsening Renal Function and Clinical Outcomes

Based on prior studies,[13–15] WRF was defined as a persistent increase in serum creatinine from baseline to 30 days by ≥1.5× or ≥0.3 mg/dL or that required renal replacement therapy. The estimated glomerular filtration rate (eGFR) was determined by the Modification of Diet in Renal Disease formula.[16] The clinical end points of interest for the present analysis were the 2-year rates of all-cause death and HFH. HFH was defined as admission for at least 24 hours in patients with clinical signs or symptoms of HF that resulted in intravenous therapy, mechanical or surgical interventions, or ultrafiltration for worsening HF. All end points were adjudicated by an independent clinical events committee.

Statistical Analysis

Analyses were performed from the time of randomization in the intention-to-treat population. Demographic and clinical variables of interest are reported for the WRF and no WRF groups. Categorical variables are presented as frequency (percentage) and were compared with the chi-square or Fisher's exact test. Continuous variables are presented as mean±SD and were compared with *t* test or the Wilcoxon rank-sum test for nonnormally distributed data. Baseline and interval serum creatinine and eGFR data during 2-year follow-up are presented in the 2 treatment groups and were compared at each time period.

Univariable logistic regression models were created to examine whether TEER and other clinical, echocardiographic, and laboratory factors (covariates shown in Table 1) were associated with 30-day WRF. The variables hypertension, diabetes, renal disease, previous transient ischemic attack, coronary artery disease, implantable cardioverter-defibrillator, estimated glomerular filtration rate, combined factor for BNP/NTproBNP (B-type natriuretic peptide/N-terminal pro-B-type natriuretic peptide), and left ventricular end-diastolic volume index, which showed *P* values <0.20 in univariable logistic models were included in a multivariable logistic regression model to identify covariates independently associated with WRF. To assess whether patients who developed 30-day WRF after TEER and GDMT alone had worse clinical outcomes compared with those who did not develop postprocedural WRF, cumulative event rates from 30 days through 2 years were estimated according to the Kaplan–Meier method. The difference in clinical outcomes between the WRF and no WRF groups were assessed with the log-rank test, and the hazard ratio (HR) and associated 95% CIs were calculated using Cox proportional hazard models. An interaction analysis was performed to assess whether the development of WRF modified the relative outcomes of TEER plus GDMT versus GDMT alone for subsequent death and HFH. A 2-sided *P* value of <0.05 was considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients and Worsening Renal Function

As shown in Figure 1, after excluding patients with ESRD at baseline, those with missing baseline or 30-day creatinine values and those who died within 30 days, 504 patients remained in the analysis data set. This group included 245 patients randomized to GDMT alone and 259 patients randomized to TEER plus GDMT.

WRF at 30 days was present in 57 (11.3%) patients who met these criteria, including 55 (96.5%) with a qualifying creatinine increase and 2 (3.5%) with new-onset renal replacement therapy but who did not have a qualifying creatinine increase. WRF at 30 days was present in 9.7% of patients assigned to TEER plus GDMT and 13.1% of patients assigned to GDMT alone (*P*=0.23). Similarly, there were no significant differences in renal function between the randomized treatment groups at any time period through 2-year follow-up (Figure 2).

Factors Associated With Worsening Renal Function

As shown in Table 1, mean age, sex, and the proportion of patients randomized to TEER were similar in the

Table 1. Baseline Clinical Characteristics, Echocardiographic Parameters, and Laboratory Values Stratified by WRF

Characteristic	WRF (N=57)	No WRF (N=447)	*P* value
Age, y	73.9±8.6	71.9±11.6	0.21
Sex, male	57.9 (33/57)	64.9 (290/447)	0.30
Race, White	78.9 (45/57)	70.7 (316/447)	0.19
Hypertension	91.2 (52/57)	79.2 (354/447)	0.03
Diabetes	50.9 (29/57)	34.7 (155/447)	0.02
Renal disease	71.9 (41/57)	51.9 (232/447)	0.004
Previous transient ischemic attack	14.0 (8/57)	6.7 (30/447)	0.05
Coronary artery disease	89.5 (51/57)	69.4 (310/447)	0.002
Ischemic cardiomyopathy	64.9 (37/57)	59.3 (265/447)	0.41
New York Heart Association class			
I	0 (0/56)	0.2 (1/447)	0.72
II	37.5 (21/56)	40.5 (181/447)	0.67
III	48.2 (27/56)	52.3 (234/447)	0.56
IV	14.3 (8/56)	6.9 (31/447)	0.053
Heart failure hospitalization within 12 mo	61.4 (35/57)	57.3 (256/447)	0.55
Guideline-directed medical therapy			
Angiotensin converting-enzyme inhibitor, angiotensin receptor blocker, angiotensin receptor-neprilysin inhibitor	63.2 (36/57)	69.6 (311/447)	0.32
Aldosterone antagonist	47.4 (27/57)	53.7 (240/447)	0.37
Beta-blockers	93.0 (53/57)	91.1 (407/447)	0.63
Diuretic	94.7 (54/57)	92.8 (415/447)	0.60
Prior device implantation			
Implantable cardioverter-defibrillator	14.0 (8/57)	35.3 (158/447)	0.001
Cardiac resynchronization therapy	45.6 (26/57)	36.2 (162/447)	0.17
Vital signs			
Systolic blood pressure, mm Hg	113.5±14.5	110.6±16.5	0.21
Heart rate, bpm	75.7±13.3	74.1±12.3	0.34
Laboratory findings			
Estimated glomerular filtration rate, mL/min per 1.73 m^2	41.6±15.3	48.3±20.6	0.02
≤60 mL/min per 1.73 m^2	89.5 (51/57)	75.2 (336/447)	0.02
BNP or NT-proBNP converted, pg/mL*	1106.0±1339.8	823.2±994.9	0.057
Echocardiographic core laboratory findings			
Severity of mitral regurgitation at baseline			
Moderate-to-severe, grade 3+	56.1 (32/57)	51.8 (231/446)	0.54
Severe, grade 4+	43.9 (25/57)	48.2 (215/446)	0.54
Effective regurgitant orifice area, cm^2	0.39±0.12	0.41±0.15	0.45
Left ventricular ejection fraction, %	31.9±9.7	31.0±9.4	0.55
≤40%	81.5 (44/54)	82.3 (323/417)	0.89
Left ventricular end-systolic volume index, mL/m^2	66.6±27.4	71.9±29.5	0.21
Left ventricular end-diastolic volume index, mL/m^2	95.8±31.3	102.3±34.7	0.19
Right ventricular systolic pressure, mmHg	45.8±13.6	43.6±13.7	0.31
Left atrial volume, mL	92.2±42.6	90.5±37.4	0.76
Right ventricular fractional area contraction	32.9±9.1	31.7±9.0	0.43
Hospital length of stay, d	3.0±3.2	2.4±2.1	0.25

Data are presented as mean±SD or % (n/N). *If only NT-proBNP was available, it was divided by 7 for conversion to BNP equivalents. bpm indicates beats per minute; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP; and WRF, worsening renal function.

30-day WRF and no WRF groups. Patients with WRF had a higher prevalence of co-morbidities including diabetes, hypertension, coronary artery disease (CAD), and anemia. Baseline echocardiographic measures, including baseline left ventricular ejection fraction, were not associated with 30-day WRF. Patients who

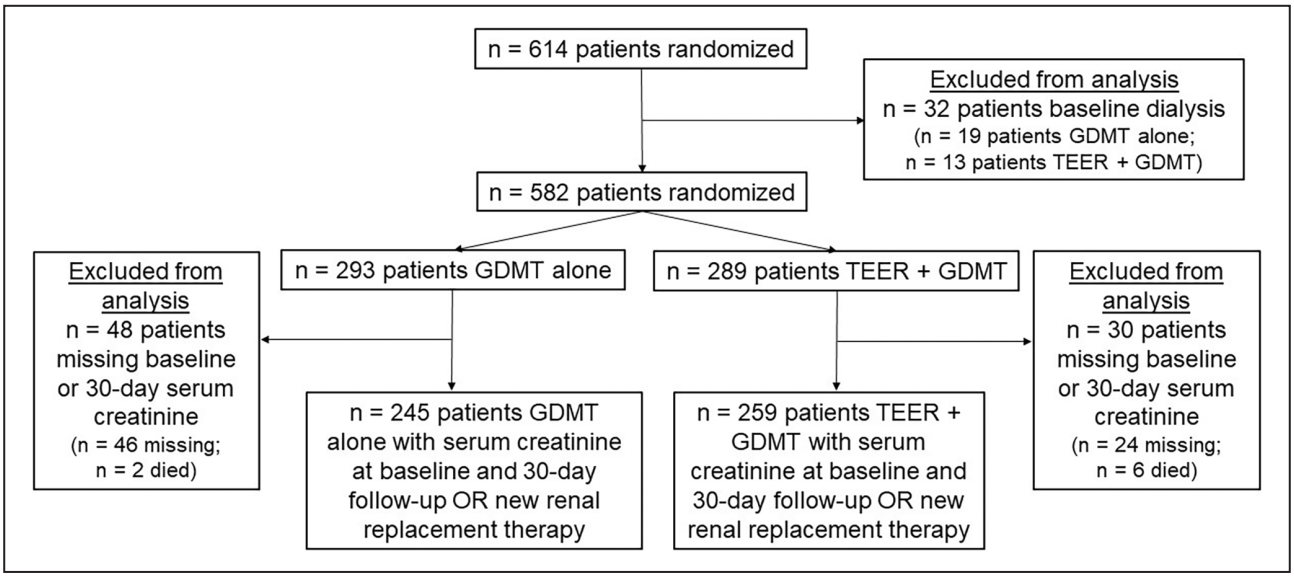

Figure 1. Flow chart for patient selection in the present study.
GDMT indicates guideline-directed medical therapy; and TEER, transcatheter edge-to-edge repair.

developed WRF had a lower baseline eGFR (41.6±15.3 versus 48.3±20.6 mL/min per 1.73 m^2; P=0.02) compared with those without WRF. By multivariable analysis, the only independent predictors of WRF development were the presence of CAD and the absence of an implantable cardiac defibrillator (ICD; Table 2).

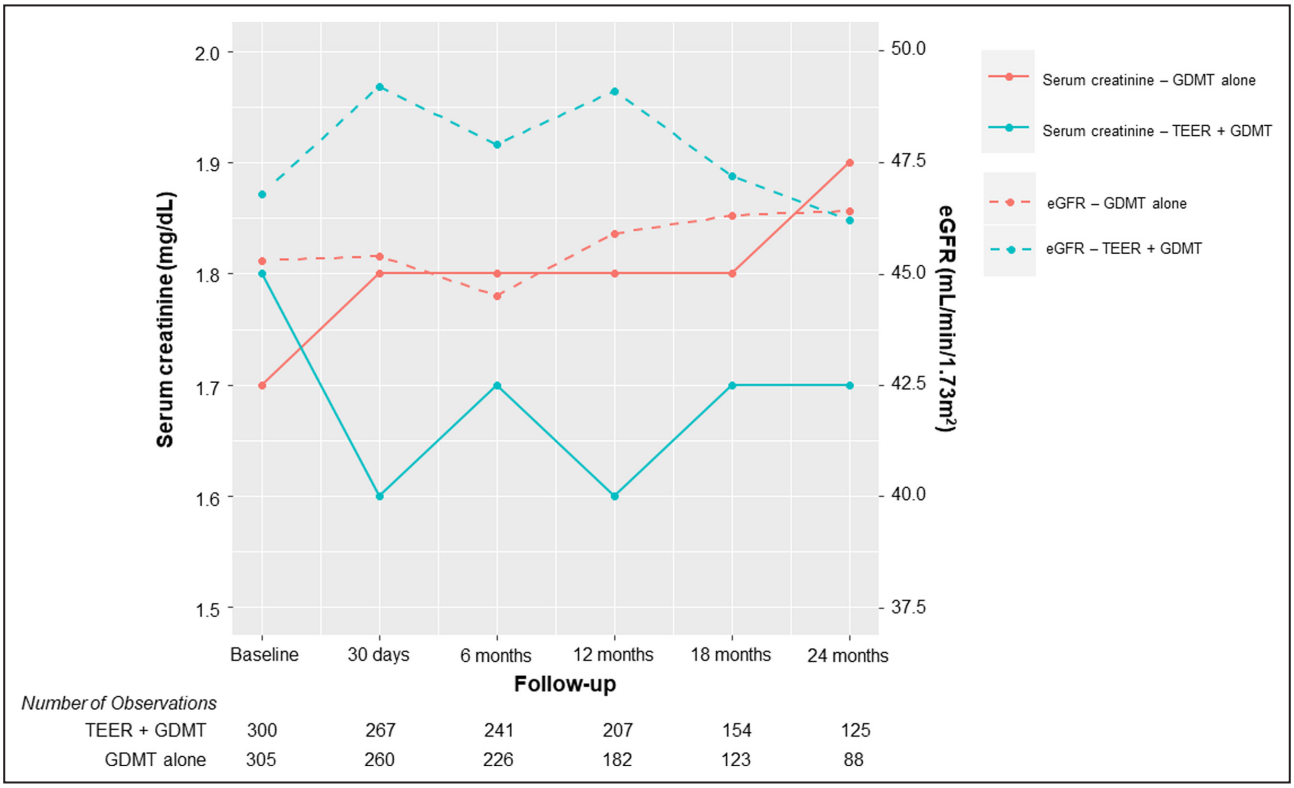

Figure 2. Serum creatinine and estimated glomerular filtration rate at follow-up intervals.
eGFR indicates estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; and TEER, transcatheter edge-to-edge repair.

Table 2. Multivariable Logistic Model of Predictors of Worsening Renal Function at 30 Days

Clinical factor	Odds ratio (95% CI)	*P* value
Hypertension	1.71 (0.60–4.86)	0.32
Diabetes	1.55 (0.84–2.87)	0.16
History of chronic renal disease	1.93 (0.91–4.09)	0.09
Coronary artery disease	3.02 (1.22–7.44)	0.017
Implantable cardioverter-defibrillator	0.32 (0.14–0.77)	0.01
Estimated glomerular filtration rate per 10 mL/min per 1.73 m^2 at baseline	1.03 (0.85–1.26)	0.74

Area under the curve value (95% CI): 0.74 (0.68–0.81), *P* value <0.0001.

Outcomes Stratified by Worsening Renal Function and Treatment

eGFR values in the WRF group remained lower compared with those in the group without WRF throughout the 2-year follow-up (Figure 3). Patients who developed WRF within 30 days had increased mortality between 30 days and 2 years compared with those who did not develop WRF (49.3% versus 29.2%; HR, 1.98 [95% CI, 1.30–3.03]; *P*=0.001) (Figure 4A). The difference in HFH between 30 days and 2 years in patients with versus without 30-day WRF was not statistically significant (54.2% versus 42.0%; HR, 1.47 [95% CI, 0.97–2.24]; *P* value=0.07; Figure 4B). The composite outcome of all-cause death or HFH between 30 days and 2 years was increased in the WRF group compared with the no WRF group (66.0% versus 50.3%; HR, 1.57 [95% CI, 1.09–2.27]; *P*=0.02; Figure 4C). Assignment to TEER plus GDMT compared with GDMT alone reduced the incidence of all-cause death ($P_{interaction}$=0.53) and HFH ($P_{interaction}$=0.57) between 30 days and 2 years consistently in patients with and without 30-day WRF (Figure 5).

DISCUSSION

The present analysis demonstrates that persistent WRF at 30-days post randomization was present in patients with HF and moderate-to-severe or severe SMR enrolled in the COAPT trial, being present in

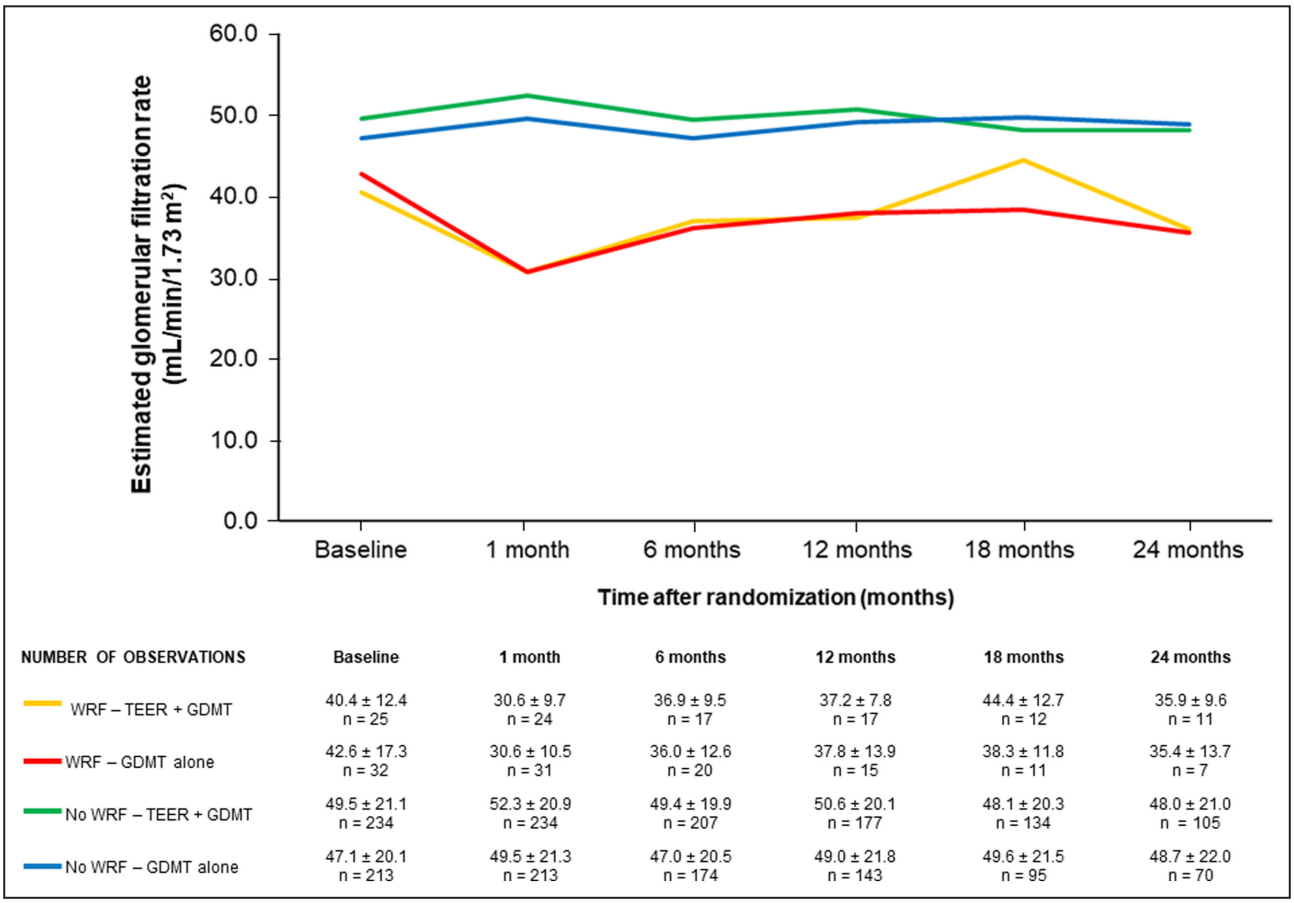

Figure 3. Estimated glomerular filtration rate by worsening renal function.
Estimated glomerular filtration rate at baseline, 30 days, 6 months, 1 year, 18 months, and 2 years in patients who developed WRF at 30 days compared with those who did not. There was no significant interaction between treatment group and WRF ($P_{interaction}$-value=0.69). GDMT indicates guideline-directed medical therapy; TEER, mitral valve transcatheter edge-to-edge repair; and WRF, worsening renal function.

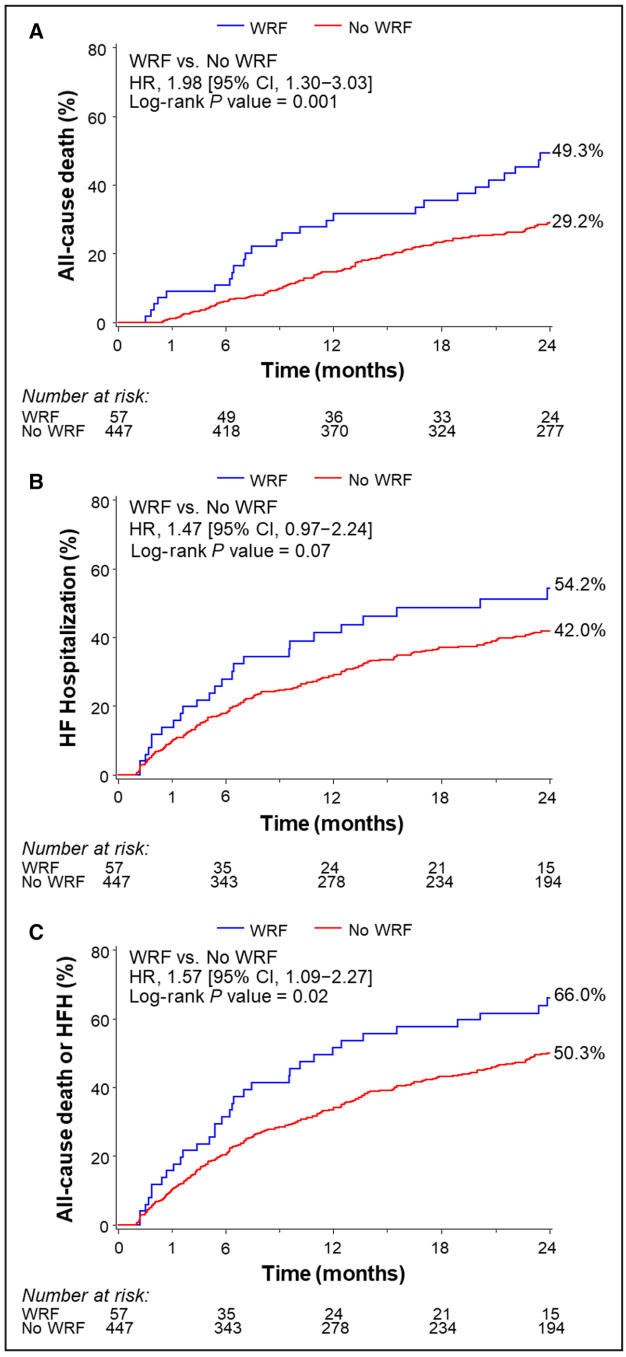

Figure 4. Worsening renal function and event rates.
Event rates for all-cause death (**A**), HF hospitalization (**B**), and the composite of all-cause death or HF hospitalization (**C**) between 30 days and 2 years in patients who developed WRF and those who did not. The composite outcome of all-cause death and HF hospitalization was increased in patients who developed WRF compared with those who did not, driven by the increased mortality between the 2 groups. HF indicates heart failure; HFH, heart failure hospitalization; HR, hazard ratio; and WRF, worsening renal function.

approximately 1 in 9 patients. The incidence of 30-day WRF was not increased after TEER plus GDMT compared with GDMT alone. Identifying patients at risk for WRF was difficult; only prior CAD and the absence of an ICD were independent predictors of WRF. Persistent WRF at 30 days was an independent predictor of increased all-cause mortality between 30 days and 2 years but not HFH. Finally, the clinical benefits of TEER plus GDMT versus GDMT alone in reducing both mortality and HFH during 2-year follow-up were consistent in patients with and without WRF.

WRF at 30 days was present in 9.7% of patients assigned to TEER plus GDMT compared with 13.1% of patients assigned to GDMT alone. The observation that TEER was not associated with a higher WRF incidence suggests that complications from general anesthesia or fluid shifts from the TEER procedure do not result in persistent renal injury. However, the development of WRF within 30 days was associated with persistently lower eGFR values through 2-year follow-up. These findings are consistent with those from the Spanish MitraClip registry, in which AKI was observed in ~15% of TEER-treated patients, and the occurrence of which was associated with a persistent deterioration in eGFR at 1-year follow-up.[9]

Of note, despite the salutary benefits of the MitraClip in improving exercise capacity and clinical outcomes, chronic renal function was not improved in patients treated with TEER compared with GDMT alone. This finding is also at odds with our prior report demonstrating that TEER reduced the development of ESRD and the need for new renal replacement therapy during 2-year follow-up.[7] These observations may have been concordant had the sample size been larger. It may also be that established chronic kidney disease is not substantially improved in the average patient by TEER, although halting the progression of severe left ventricular dysfunction with TEER may prevent progression to ESRD. We also cannot exclude the impact of survivorship bias on these observations given the substantially lower mortality with TEER in the COAPT trial.

Few independent predictors of 30-day WRF were identified. CAD was associated with an increased risk of WRF whereas the presence of an ICD was associated with a protective effect. The relationship between CAD and renal dysfunction has been well established.[17] Changes in plasma composition, angiotensin II-mediated alterations, and endothelial lipoprotein composition due to progressive renal disease amplify subsequent inflammatory events.[17] Alterations in renal perfusion, both arterial and venous, can also increase the risk of WRF. As previously noted by Mullens et al., venous congestion rather than cardiac output impairment is the most important hemodynamic factor driving WRF in advanced decompensated HF.[14] The relationship between ICD use and freedom from WRF is less explainable and may represent a surrogate for the higher quality of care these patients received.[18] The association observed between ICD and WRF could

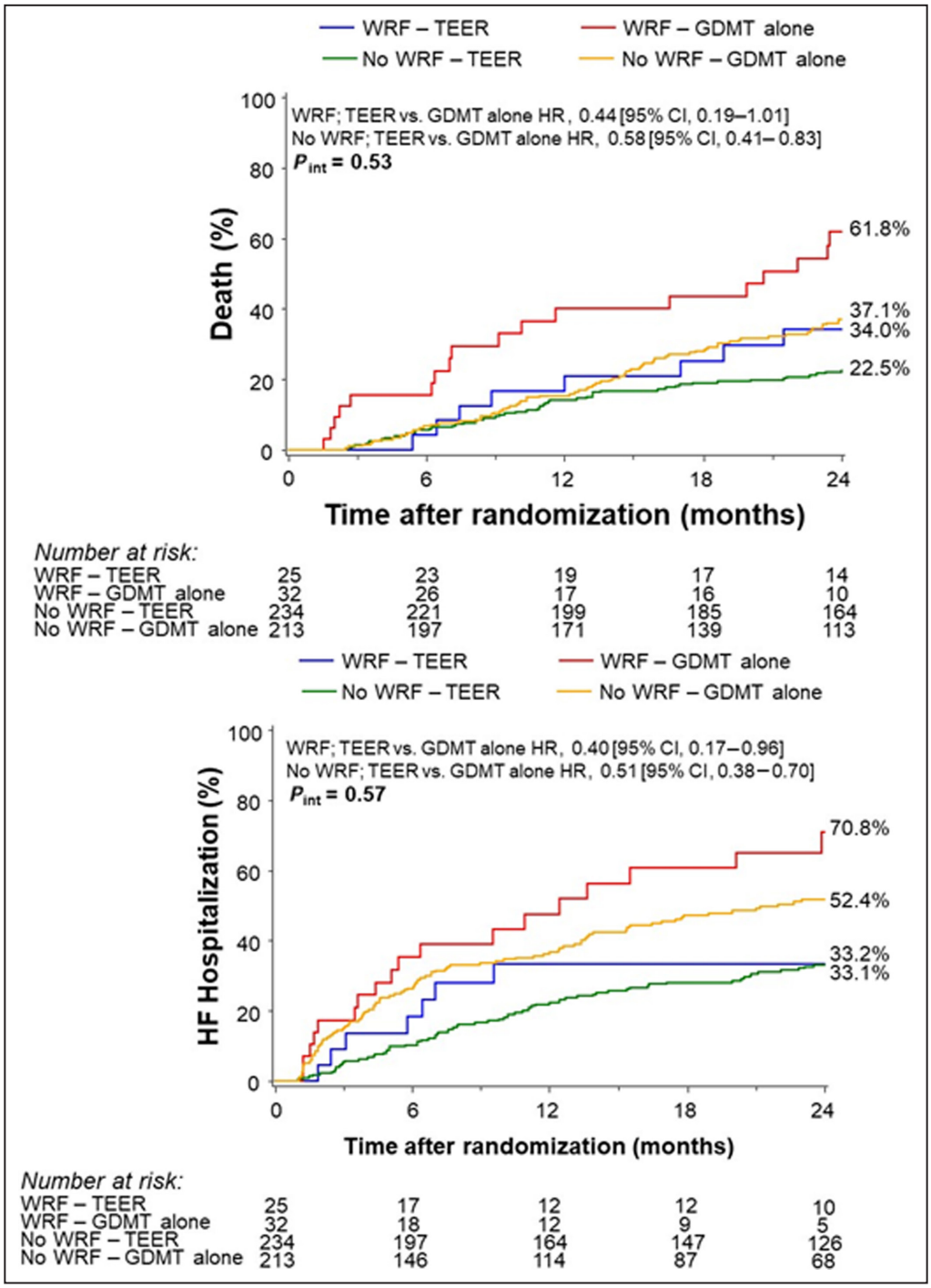

Figure 5. Clinical outcomes by worsening renal function and treatment group.
Cumulative rates of all-cause death and HF hospitalization between 30 days and 2 years in patients randomized to TEER plus GDMT vs GDMT alone. TEER treatment compared with GDMT alone reduced the rates of death and HF hospitalization between 30 days and 2 years consistently in patients in whom 30-day WRF did not develop. GDMT indicates guideline-directed medical therapy; HF, heart failure; HR, hazard ratio; TEER, transcatheter edge-to-edge repair; and WRF, worsening renal function.

potentially be influenced by unmeasurable factors that were not accounted for in the analysis. No echocardiographic factors were independently associated with the development of WRF within 30 days.

We previously reported from COAPT that baseline renal dysfunction was a significant predictor of the 2-year rate of all-cause death or HFH, with TEER improving prognosis at all levels of baseline eGFR.[7] The

present study extends these findings by demonstrating that patients who developed WRF had subsequently worse clinical outcomes compared with those who did not, including higher mortality and a numerical excess of HFHs. Importantly, however, TEER provided consistent reductions in mortality and HFH between 30 days and 2 years both in patients with and without 30-day WRF compared with GDMT alone. Collectively, these studies demonstrate that TEER should not be withheld in otherwise appropriate patients with HF solely on the grounds of baseline renal dysfunction or the perceived risk of WRF, and that if WRF does develop it does not signify loss of the beneficial effects from TEER. Thus, patients with moderate-to-severe or severe SMR who meet COAPT trial criteria can safely be offered TEER, which may provide clinical benefits such as reduced mortality, lower HFH rates and mitigation of severe left ventricular dysfunction progression, which may in turn reduce ESRD development.

There are limitations of the present study. Our findings cannot necessarily be generalized to patients with HF and severe SMR who do not otherwise meet enrollment criteria for the COAPT trial. The frequency of WRF at 30 days in COAPT was modest (1 in 9 patients), and a larger study may have identified additional risk factors for WRF or shown a significant relationship between WRF and subsequent HFH. Moreover, the prognostic utility of our definition of persistent WRF for mortality requires external validation, especially as prior definitions of AKI have had prognostic limitations in patients with acute HF.[19] The combination of serum creatinine and serum cystatin C may be more accurate than either marker alone for calculating eGFR.[20] Future TEER studies might benefit from closer monitoring of renal function within the first 30 days of intervention. This may help identify which patients will develop WRF even before postprocedure day 30 and could assist in guiding interim clinical management (although mortality was infrequent in the first 30 days after randomization).[12]

CONCLUSIONS

In the COAPT trial, among patients with HF and moderate-to-severe or severe SMR who remained symptomatic despite maximally tolerated GDMT, WRF was present in approximately 1 in 9 patients at 30 days following randomization and was associated with increased mortality through 2-year follow-up. TEER treatment did not increase the risk of WRF but did not improve chronic renal function over time (despite reducing the incidence of new-onset ESRD and the need for renal replacement therapy during follow-up).[7] Moreover, TEER reduced mortality and HFH consistently in patients with and without WRF. Hence, TEER use should be considered in appropriately selected candidates regardless of baseline renal dysfunction[7] or their propensity for developing WRF. Future research is necessary to identify reliable risk factors for WRF given the recent approval of several classes of GDMT that have demonstrated cardioprotective and renoprotective effects.[21–23]

ARTICLE INFORMATION

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Affiliations

Kaiser Permanente Department of Cardiology, San Francisco, CA (J.K., J.G.Z., A.P.A., J.K.F., I.A.K., J.M.M.); Division of Research, Kaiser Permanente Northern California, Oakland, CA (A.P.A.); Clinical Trials Center Cardiovascular Research Foundation, New York City, NY (L.N.K., B.R.); NewYork-Presbyterian Hospital/Columbia University Medical Center, New York, NY (B.R.); Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden (B.R.); Mount Sinai Medical Center Columbia University Division of Cardiology, Miami Beach, FL (N.B.); Department of Cardiac Surgery, University of Michigan, Ann Arbor, MI (G.A.); Vanderbilt University Division of Cardiology, Nashville, TN (J.L.); Division of Cardiovascular Medicine, The Ohio State University, Columbus, OH (W.T.A.); Baylor Scott and White Healthcare, Dallas, TX (M.J.M.); Cardiovascular Institute, Los Robles Health System, Thousand Oaks, CA (S.K.); Division of Cardiology, University of Virginia, Charlottesville, VA (D.S.L.); Intermountain Medical Center, Murray, UT (B.K.W.); and (G.W.S.), The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY.

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Disclosures

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