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ORIGINAL RESEARCH

Coronary Chronic Total Occlusions Affect Long-Term Prognosis in Heart Failure With Mildly Reduced Ejection Fraction

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BACKGROUND: This study investigates the prevalence and prognostic impact of coronary chronic total occlusions (CTO) in patients with heart failure with mildly reduced ejection fraction (HFmrEF). Although coronary artery disease represents the leading cause of HFmrEF, data about CTO in this population are rare.

METHODS: All consecutive patients with HFmrEF (ie, left ventricular ejection fraction 41%–49% with signs and/or symptoms of heart failure) undergoing invasive coronary angiography from 2016 to 2022 were included retrospectively. Patients with at least 1 CTO were compared with patients with no CTO, further risk stratification was performed according to the extend of coronary artery disease. The primary end point was long-term all-cause mortality at 30 months (ie, median follow-up). Secondary end points comprised the risks of major adverse cardiac and cerebrovascular events, as well as heart failure-related and cardiac rehospitalization at 30 months. Furthermore, the association of percutaneous coronary intervention with long-term outcomes was investigated.

RESULTS: Seventy-one percent of patients with HFmrEF (1545/2184, primary cohort) underwent invasive coronary angiography. In patients undergoing invasive coronary angiography during index hospitalization, the rate of coronary artery disease was 81% (836/1037, final cohort), and at least 1 CTO was present in 17% (n=141). The presence of a CTO was associated with the highest rate of the primary end point (33%) compared with non-CTO (19%), single-vessel (12%) and multivessel coronary artery disease (21%) in HFmrEF (*P*=0.001). Accordingly, HFmrEF patients with CTO had the highest rates of long-term major adverse cardiac and cerebrovascular events compared with patients without CTO (60% versus 32%, *P*=0.001). Successful CTO-percutaneous coronary intervention was associated with improved long-term survival (21% versus 38%; hazard ratio, 0.49 [95% CI, 0.24–0.99]; *P*=0.046).

CONCLUSIONS: Coronary CTO are common in patients with HFmrEF and significantly impair long-term prognosis.

REGISTRATION: URL: https://www.clinicaltrials.gov; unique identifier: NCT0560339.

Key Words: chronic total occlusion (CTO) ■ coronary artery disease ■ heart failure with mildly reduced ejection fraction (HFmrEF) ■ percutaneous coronary intervention

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CLINICAL PERSPECTIVE

What Is New?

- Among 836 patients with coronary artery disease with heart failure with mildly reduced ejection fraction, coronary chronic total occlusions (CTO) were identified in 17%, with patients with CTO accompanied by a higher burden of comorbidities including diabetes, prior coronary artery disease, myocardial infarction, and peripheral artery disease.
- The presence of coronary CTO was associated with higher long-term all-cause death and major adverse cardiac and cerebrovascular events, even compared with multivessel coronary artery disease, whereas successful percutaneous CTO revascularization may be associated with improved long-term survival.

What Are the Clinical Implications?

- Coronary CTO represent a key prognostic factor in heart failure with mildly reduced ejection fraction, underscoring the need for randomized trials to define optimal invasive management strategies.

Nonstandard Abbreviations and Acronyms

COMMIT-HF	Clopidogrel and Metoprolol in Myocardial Infarction Trial
CTO	chronic total occlusion
ERCTO	European Registry of Chronic Total Occlusion
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
ICA	invasive coronary angiography
MACCEs	major adverse cardiac and cerebrovascular events

Heart failure (HF) is the major cardiovascular disease syndrome causing a relevant impact on morbidity due to an increasing prevalence affecting up to 60 million individuals worldwide.[1,2] Despite advances in HF therapies, annual HF-related death remains high, at ≈30% for acute and 10% for chronic HF syndrome. It is, therefore, comparable to most common types of cancer.[3,4] International guidelines have classified HF according to left ventricular ejection fraction (LVEF) into 3 subtypes: HF with reduced (HFrEF; LVEF ≤40%), preserved (HFpEF; LVEF ≥50%), and mildly reduced ejection fraction (HFmrEF; LVEF, 41%–49%).[5] Patients with HFmrEF are common, with an overall prevalence of 20%–25%. The 1-year mortality rates for these patients are slightly lower than those with HFrEF, at 6.3% compared with 7.6%.[6–8] Therefore, a thorough differential diagnostic workup and prompt initiation of treatment are essential to potentially improve symptoms, slow disease progression, and enhance the prognosis for affected patients.

Coronary artery disease (CAD) represents a common cause of HF, specifically in up to 60% of patients with HFmrEF.[1,6,9] Coronary chronic total occlusions (CTO) represent the most complex type of CAD lesions. CTO are found in up to 25% of patients undergoing invasive coronary angiography (ICA), and this percentage increases to nearly 50% of patients after coronary artery bypass surgery (CABG).[10–13] The last ERCTO (European Registry of Chronic Total Occlusion) update reported depressed LVEF in 30% of patients undergoing percutaneous coronary intervention (PCI) of CTO.[14] As demonstrated in the randomized Euro CTO trial, CTO-PCI improved angina-related symptoms and quality of life in patients with HFpEF.[15] In line, CTO-PCI improved cardiopulmonary exercise capacity as measured by objective spiroergometric testing in patients with HFpEF.[16] Recent meta-analyses of representative observational registries, including >50 000 patients, demonstrated improved long-term survival in patients with CTO successfully treated with PCI compared with patients with CTO undergoing failed PCI and patients without CTO-PCI with HFpEF.[11,17,18] Furthermore, CTO-PCI was associated with improved survival in patients with HFpEF and patients with LVEF <30%.[19–21] It has been described that HF patients with CTO more commonly present with HF-related symptoms, such as shortness of breath and limited exercise capacity, whereas typical angina is rare.[21]

However, the presence and treatment of coronary CTO have never been investigated in detail in patients with HFmrEF. Therefore, this study aims to examine the prevalence, characteristics, and prognostic impact of coronary CTO in these patients.

METHODS

Study Patients, Design, and Data Collection

For the present study, all consecutive patients hospitalized from January 2016 to December 2022 with HFmrEF at one university medical center were included, as recently published.[22] Using the electronic hospital information system, all relevant clinical data related to the index event were documented, such as baseline characteristics, vital signs on admission, prior medical history, prior medical treatment, length of index hospital and intensive care unit stay, laboratory values, data derived from all noninvasive or invasive cardiac diagnostics and device therapies (such as echocardiographic data, ICA, and data derived from prior or newly implanted cardiac devices). Every revisit at the outpatient clinic or rehospitalization related to HF or adverse cardiac events was documented.

The present study is derived from HARMER (Heart Failure with Mildly Reduced Ejection Fraction Registry; clinicaltrials.gov identifier NCT05603390), a retrospective single-center registry including all consecutive patients with HFmrEF hospitalized at the University Medical Center Mannheim, Germany (clinicaltrials.gov identifier: NCT05603390). The registry was carried out according to the principles of the Declaration of Helsinki and approved by the Medical Ethics Committee II of the Medical Faculty Mannheim, University of Heidelberg, Germany (ethical approval code: 2022-818). The requirement for informed consent was waived related to the retrospective study design. The data set used or analyzed during the current study are available from the corresponding author upon reasonable request.

Inclusion and Exclusion Criteria

All consecutive patients being hospitalized with HFmrEF at one institution were included. All patients underwent at least 1 standardized transthoracic echocardiography at the cardiologic department at index hospitalization, where the diagnosis of HFmrEF was assessed. The diagnosis of HFmrEF was determined retrospectively according to the 2021 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic HF.[23] Accordingly, all patients had LVEF 41% to 49% and symptoms and/or signs of HF were included. The presence of elevated amino-terminal prohormone of brain natriuretic peptide levels and other evidence of structural heart disease was considered to make the diagnosis more likely. Still, it was not mandatory to diagnose HFmrEF. Heart failure pathogenesis was classified on the basis of clinical, angiographic, and echocardiographic data. Ischemic cardiomyopathy was defined by the presence of previously documented or newly diagnosed CAD, identified by ICA during the index hospitalization, and deemed sufficient to cause myocardial dysfunction. Primary nonischemic cardiomyopathy included patients without significant CAD, valvular disease, or congenital heart disease sufficient to explain the observed myocardial dysfunction. Other nonischemic pathogeneses were categorized as hypertensive cardiomyopathy, congenital heart disease, valvular heart disease, tachycardia-associated HF, tachycardia-induced cardiomyopathy, and pacemaker-induced cardiomyopathy according to current recommendations.[24]

Standardized transthoracic echocardiography was performed by cardiologists during routine clinical care following current European guidelines. All echocardiographic and angiographic examinations and reports were reassessed post hoc by 2 independent cardiologists blinded to the final data analysis. In cases of ambiguous findings or documentation, source data were reassessed on the basis of the available Digital Imaging and Communications in Medicine files. For the present analysis, patients aged <18 years; patients without a history of CAD, without evidence from documented ICA; and patients without complete follow-up data were excluded. To ensure reliable documentation of the presence of CAD and CTO and reliable comparability subgroups, patients with evidence from ICA performed >12 months before or at least 6 weeks after the index hospital admission were excluded.

Study End Points

The primary end point was long-term all-cause death. Long-term follow-up was defined as the median follow-up time at 30 months. Secondary end points were all-cause death at 12 months, as well as long-term heart failure–related rehospitalization, cardiac rehospitalization, acute myocardial infarction, stroke, revascularization, and major adverse cardiac and cerebrovascular events (MACCE).

All-cause death was documented using the electronic hospital information system, and state resident registration offices (Bureau of Mortality Statistics) were directly contacted across Germany. From a total number of 2228 patients with HFmrEF, 44 patients (2%) without data on long-term follow-up were excluded (ie, lost to follow-up). HF-related rehospitalization was defined as a rehospitalization due to worsening of HF requiring intravenous diuretic therapy. Cardiac rehospitalization was defined as rehospitalization due to a primary cardiac condition, including acute decompensation or worsening HF symptoms, acute myocardial infarction, urgent revascularization, ventricular tachyarrhythmias, and decompensated atrial arrhythmias. Planned procedures such as staged PCI, planned cardioversion for atrial fibrillation, or planned valve interventions were not counted as cardiac rehospitalization events. MACCE was defined as the composite of all-cause death, coronary revascularization, nonfatal acute myocardial infarction and nonfatal stroke.

Statistical Analysis

Quantitative data are presented as median and interquartile range, and ranges depending on the data distribution were compared using Student's *t* test for normally distributed data or the Mann–Whitney *U* test for nonparametric data. Deviation from a Gaussian distribution was tested using the Kolmogorov–Smirnov test. Qualitative data are presented as absolute and relative frequencies and compared using the χ^2 or

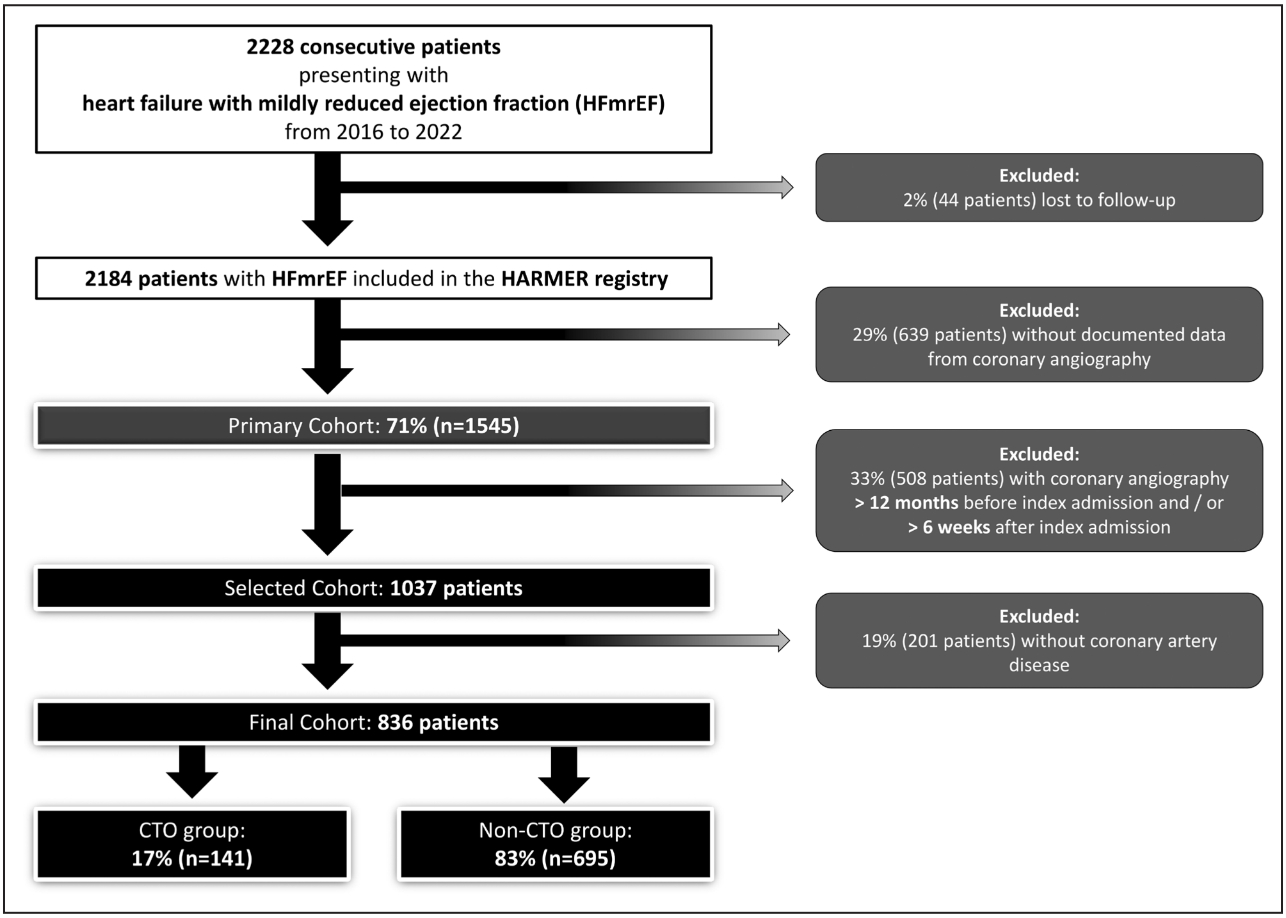

Figure 1. Flowchart cohort composition.
CTO indicates chronic total occlusion.

Fisher's exact test, as appropriate. Kaplan–Meier analyses were stratified by the presence of CTO, non-CTO, single-vessel CAD, multivessel CAD, CTO PCI, and non-CTO PCI (ie, both optimal medical treatment and non-CTO PCI included). Univariable hazard ratios (HRs) were given with 95% CI. The prognostic impact of CTO was thereafter investigated within multivariable Cox regression models using the "forward selection" option. The results of all statistical tests were considered significant for $P \leq 0.05$. SPSS software version 2511 (IBM, Armonk, NY) was used for statistics.

RESULTS

Study Population

As outlined in Figure 1, the HARMER registry retrospectively included 2184 consecutive patients hospitalized with HFmrEF. Overall, 71% of patients underwent ICA (n=1545, primary cohort), where coronary CTO were found in 14% (n=208), similar to the selected cohort (n=141/1037; Table S1). After excluding patients without CAD and patients with ICA 12 months before and 6 weeks after index hospitalization (see Figure 1), the final cohort comprised n=836 (38%) patients with HFmrEF. The rate of CTO within this final study cohort was 17% (n=141/836). Multiple CTOs were found in 25%, and the right coronary artery was the most common CTO vessel in 50% (Figure 2B).

As outlined in Table 1, age, sex, and cardiovascular risk profile were comparable between patients with CTO and patients without CTO, except for diabetes (50% versus 37%, median hemoglobin A_{1c}, 6.2%). Patients with CTO more commonly had a history of prior CAD, myocardial infarction, and CABG. On index admission, patients with CTO presented with non–ST-segment–elevation myocardial infarction (35%), ventricular tachyarrhythmias (11%), and cardiac arrest (9%), whereas patients without CTO presented more frequently with ST-segment–elevation myocardial infarction (23%). While most patients in the entire cohort presented with sinus rhythm on admission (74.5% versus 62.2%, P=0.049), patients with CTO were less likely to have atrial fibrillation (23.4% versus 34.0%, P=0.049).

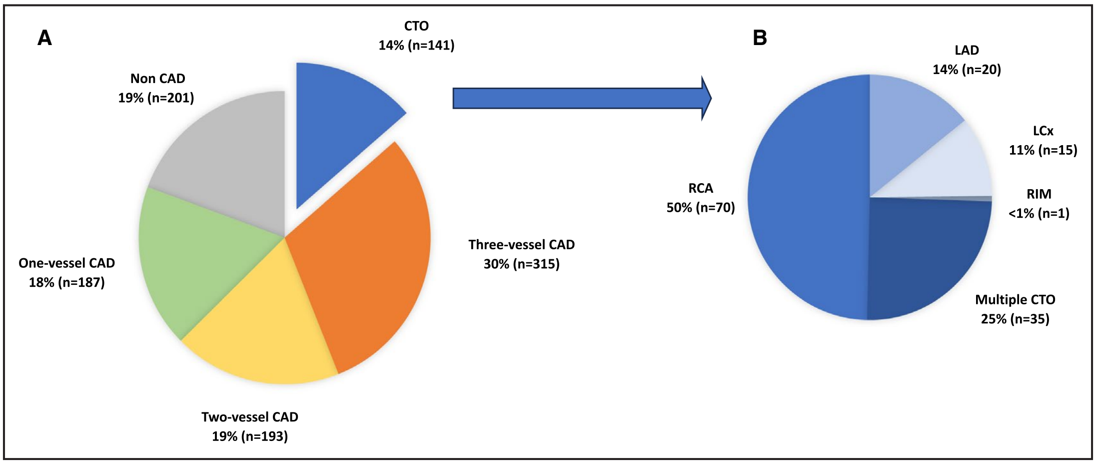

Figure 2. Distribution of the extent of CAD types.
A, Distribution in the selected study cohort (n=1037). **B**, Distribution of coronary CTO. CAD indicates coronary artery disease; CTO, chronic total occlusion; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right circumflex artery; and RIM, ramus intermedius.

Table 2 reveals no relevant differences regarding patients' symptoms according to New York Heart Association classification, heart failure pathogenesis, and most echocardiographic findings. Notably, patients with CTO had larger end-diastolic diameters of the left ventricle than non-CTO patients.

CAD and CTO Characteristics in HFmrEF

Within the analyzed study population, patients with CTO HFmrEF had higher coronary 3-vessel disease rates than patients non-CTO HFmrEF (Table 3). The right coronary artery, left circumflex artery, intermediate branch, and CABG were more frequently stenosed in patients with CTO than patients without CTO. PCI rates and target vessels were similar in both groups, besides CABG-PCI being more often performed in the CTO group.

Focusing on patients with CTO, CTO-PCI was performed in 38%. The corresponding success rate of CTO-PCI was 87% (Table 3). More than a third of patients with HFmrEF revealed complex CTO, defined as the presence of a Japan–Chronic Total Occlusion score of ≥3, accompanied by an ambiguous or blunt stump, poor distal vessel quality and CC1-type collaterals in >40%.

Prognostic Impact of a Coronary CTO in HFmrEF

Primary and secondary end points for prognosis are summarized in Table 4. In patients with HFmrEF, the presence of a coronary CTO was associated with an increasing rate of long-term all-cause death at 30 months compared with patients without CTO (33% versus 19%; HR, 1.94 [95% CI, 1.38–2.71]; *P*=0.001) (Table 4, Figure 3A). In line, patients with CTO with HFmrEF showed a 2-fold increase in all-cause death at 12 months with 23% versus 11% (*P*=0.001). Furthermore, patients with CTO and HFmrEF experienced higher rates of the secondary end points: long-term cardiac rehospitalization (46% versus 28%) and MACCE (60% versus 32%) (*P*<0.004) (Figure 3B). Notably, patients with CTO HFmrEF had similar rates of long-term HF-related rehospitalization compared with patients with HFmrEF without CTO (17% versus 15%, *P*>0.05; Table 4).

Multivariable Risk Prediction Models

As outlined in Table 5, model 1, the presence of a coronary CTO remained significantly associated with the primary end point of long-term all-cause death at 30 months (HR, 1.870 [95% CI, 1.255–2.787]; *P*=0.002) in HFmrEF even after multivariable adjustment. Similarly, CTO in patients with HFmrEF were still associated with long-term MACCE at 30 months within multivariable Cox regression models (HR, 2.147 [95% CI, 1.608–2.865]; *P*=0.001). In a further multivariable Cox regression (Table 5, model 2) adjusted for optimal medical treatment, the presence of a coronary CTO remained independently associated with an increased risk of all-cause death (HR, 1.929 [95% CI, 1.269–2.931]; *P*=0.002) and MACCE (HR, 2.201 [95% CI, 1.636–2.960]; *P*=0.001). Notably, after excluding patients presenting with ST-segment–elevation myocardial infarction, non–ST-segment–elevation myocardial infarction, cardiac arrest, or cardiogenic shock on admission, the prognostic impact of CTO on long-term all-cause death (HR, 3.185 [95% CI, 1.908–5.315]; *P*=0.001) and long-term MACCE (HR, 2.639 [95% CI, 1.774–3.924]; *P*=0.001) remained evident, when adjusted in a similar multivariable model (data not shown).

Table 1. Baseline Characteristics

	Non-CTO (n=695)	CTO (n=141)	*P* value
Age, median (IQR)	73 (64–81)	71 (62–79)	0.108
Male sex, n (%)	503 (72.4)	111 (78.7)	0.143
Body mass index, kg/m^2, median (IQR)	27.4 (24.7–31.1)	26.8 (24.3–34.0)	0.439
Cardiovascular risk factors, n (%)			
Arterial hypertension	565 (81.3)	116 (82.3)	0.905
Diabetes	257 (37.0)	70 (49.6)	0.006*
Hyperlipidemia	256 (36.8)	61 (43.3)	0.155
Smoking			
Current	168 (24.2)	43 (30.5)	0.136
Former	147 (21.2)	32 (22.7)	0.736
Family history	101 (14.5)	25 (17.7)	0.366
Medical history			
Prior coronary artery disease	349 (50.2)	87 (61.7)	0.016*
Prior myocardial infarction	198 (28.5)	59 (41.8)	0.003*
Prior PCI	266 (38.3)	66 (46.8)	0.073
Prior CABG	60 (8.6)	27 (19.1)	0.001*
Prior congestive heart failure	203 (29.2)	49 (34.8)	0.192
Decompensated heart failure <12 mo	76 (10.9)	15 (10.6)	1.000
Stroke	97 (14.0)	17 (12.1)	0.593
Chronic kidney disease	177 (25.5)	37 (26.2)	0.833
Peripheral artery disease	65 (9.4)	35 (24.8)	0.001*
COPD	74 (10.6)	17 (12.1)	0.656
Comorbidities at index, n (%)			
Unstable angina	58 (8.3)	14 (9.9)	0.513
Acute myocardial infarction	340 (48.9)	65 (46.1)	0.580
ST-segment–elevation myocardial infarction	159 (22.9)	16 (11.3)	0.002*
Non–ST-segment–elevation myocardial infarction	181 (26.0)	49 (34.8)	0.039*
Acute decompensated heart failure	151 (21.7)	26 (18.4)	0.430
Cardiogenic shock	25 (3.6)	10 (7.1)	0.066
Atrial fibrillation/flutter	230 (33.1)	32 (22.7)	0.017*
Ventricular tachyarrhythmia	31 (4.5)	16 (11.3)	0.002*
Cardiopulmonary resuscitation	25 (3.6)	12 (8.5)	0.021*
Out-of-hospital	11 (1.6)	8 (5.7)	0.008*
In-hospital	14 (2.0)	4 (2.8)	0.525
Stroke	44 (6.3)	11 (7.8)	0.575
Heart rhythm on admission, n (%)			
Sinus rhythm	432 (62.2)	105 (74.5)	0.049*
Atrial fibrillation	236 (34.0)	33 (23.4)	
Atrial flutter	7 (1.0)	1 (0.7)	
Pacemaker rhythm	20 (2.9)	2 (1.4)	
Baseline laboratory values, median (IQR)			
Potassium, mmol/L	3.9 (3.6–4.2)	3.9 (3.6–4.2)	0.629
Creatinine, mg/dL	1.05 (0.88–1.34)	1.06 (0.86–1.35)	0.965
eGFR, mL/min/1.73 m^2	69 (49–88)	71 (50–89.00)	0.601
Hemoglobin, g/dL	12.7 (10.8–14.2)	12.9 (11.0–14.2)	0.509
Platelet count, ×10^9/L	230 (184–285)	241 (199–311)	0.018*
HbA_{1c}, %	5.8 (5.5–6.7)	6.2 (5.7–7.5)	0.021*

(*Continued*)

Table 1. Continued

	Non-CTO (n=695)	CTO (n=141)	*P* value
LDL-cholesterol, mg/dL	95 (72–127)	101 (77–129)	0.058
NT-pro BNP, pg/mL	2530 (958–5832)	2477 (1233–5504)	0.746
Cardiac troponin I, μg/L	0.10 (0.02–1.34)	0.24 (0.03–1.89)	0.053

Level of significance *P*<0.05. CABG indicates coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CTO, chronic total occlusion; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; IQR, interquartile range; LDL, low-density lipoprotein; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; and PCI, percutaneous coronary intervention.

*Indicates statistical significance.

Table 2. Heart Failure–Related Data and Procedural Data

	Non-CTO (n=695)	CTO (n=141)	*P* value
NYHA functional class, n (%)			
I/II	486 (69.9)	103 (73.1)	0.798
III	143 (20.6)	24 (17.0)	
IV	66 (9.5)	14 (9.9)	
Heart failure pathogenesis, n (%)			
Ischemic cardiomyopathy	663 (95.4)	137 (97.2)	0.294
Nonischemic cardiomyopathy	5 (0.7)	0 (0.0)	
Hypertensive cardiomyopathy	6 (0.9)	0 (0.0)	
Congenital heart disease	6 (0.9)	0 (0.0)	
Valvular heart disease	0 (0.0)	1 (0.7)	
Tachycardia associated	4 (0.6)	1 (0.7)	
Tachymyopathy	0 (0.0)	1 (0.7)	
Pacemaker-induced cardiomyopathy	2 (0.3)	0 (0.0)	
Unknown	9 (1.3)	2 (1.4)	
Echocardiographic data			
Tachycardic atrial fibrillation, n (%)	38 (5.5)	3 (2.1)	0.063
LVEF, %, median (IQR)	45 (45–47)	45 (44–47)	0.613
IVSd, median (IQR)	12 (11–13)	12 (10–13)	0.870
LVEDD, mm, median (IQR)	49 (44–53)	50 (45–54)	0.039†
TAPSE, mm, median (IQR)	21 (18–23)	20 (18–23)	0.153
Diastolic dysfunction, n (%)	507 (72.9)	111 (78.7)	0.172
Aortic stenosis,* n (%)	69 (9.9)	11 (7.8)	0.531
Aortic regurgitation,* n (%)	24 (3.5)	5 (3.5)	1.000
Mitral regurgitation,* n (%)	75 (10.8)	12 (8.5)	0.545
Tricuspid regurgitation,* n (%)	68 (9.8)	14 (9.9)	1.000

Level of significance *P*<0.05. CTO, chronic total occlusion; IQR, interquartile range; IVSd, interventricular septal end-diastole; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and TAPSE, tricuspid annular plane systolic excursion.

*Only moderate to severe valve disease has been considered.

†Indicates statistical significance.

Prognostic Impact of Coronary CTO Related to CAD Types and Coronary Revascularization

HFmrEF patients with CTO revealed the highest rates of long-term all-cause death at 30 months compared with patients with multivessel CAD HFmrEF and patients with single-vessel CAD HFmrEF (*P*=0.001; Figure 3C). Successful CTO-PCI was associated with improved long-term all-cause death at 30 months (21% versus 38%; HR, 0.49 [95% CI, 0.24–0.99]; *P*=0.046; Figure 3D).

DISCUSSION

The present study investigates the presence and prognostic impact of coronary CTO in patients hospitalized with HFmrEF. To the best of our knowledge, this analysis demonstrates for the first time that the presence of a coronary CTO significantly deteriorates the long-term prognosis in patients with HFmrEF. Coronary CTO were found in 17% of patients with HFmrEF and CAD. The CTO-related adverse prognostic impact in HFmrEF was observed for the primary end point of long-term all-cause death at 30 months (33% versus 19%), as well as for the secondary end point of long-term MACCE (60% versus 32%), even after multivariable adjustment. Patients with CTO HFmrEF revealed the worst prognosis compared with other forms of CAD. Notably, successful CTO-PCI was associated with significantly improved long-term survival.

Patients with HFmrEF represent one fourth of all patients with HF. Nonetheless, they are usually underrepresented in clinical research and are prone to fall overboard compared with the increasing scientific evidence for HFpEF and HFrEF. For instance, the latter types of HF syndrome are supported by stronger evidence for guideline-recommended pharmacotherapies and cardiac implantable electronic devices, which have not consistently been evaluated for HFmrEF, if at all, within underpowered clinical trials.[23] In contrast, a comprehensive and concise characterization of patients with HFmrEF is lacking in the literature, and therefore, clear guideline recommendations are limited. Our working group recently established the HARMER registry, specifically focusing

Table 3. Data Retrieved From Coronary Angiography Regarding CAD and CTO Characteristics

	Non-CTO (n=695)	CTO (n=141)	*P* value
CAD types, n (%)			
Single-vessel disease	187 (26.9)	12 (8.5)	0.001†
2-vessel disease	193 (27.8)	31 (22.0)	
3-vessel disease	315 (45.3)	98 (69.5)	
CABG	20 (2.9)	17 (12.1)	
Coronary revascularization			
PCI, n (%)	435 (62.6)	92 (65.2)	0.568
Number of stents, n, median (IQR)	2 (1–3)	3 (1–4)	0.033†
Total stent length, mm, median (IQR)	44.0 (24–78)	50.0 (24–96)	0.101
Send to CABG, n (%)	41 (5.9)	14 (1.0)	0.092
Affected vessel, n (%)			
RCA	495 (71.2)	130 (92.2)	0.001†
LMT	98 (14.1)	29 (20.6)	0.054
LAD	548 (78.8)	121 (85.8)	0.065
LCx	444 (63.9)	114 (80.9)	0.001†
Ramus intermedius	70 (10.1)	27 (19.1)	0.004†
CABG with relevant stenosis	20 (2.9)	17 (12.1)	0.001†
PCI target vessel, n (%)			
RCA	202 (29.1)	38 (27.0)	0.686
LMT	46 (6.6)	15 (10.6)	0.135
LAD	218 (31.4)	48 (34.0)	0.601
LCx	160 (23.0)	34 (24.1)	0.865
Ramus intermedius	16 (2.3)	6 (4.3)	0.302
CABG	8 (1.2)	6 (4.3)	0.024†
Affected CTO vessel, n (%)*			
RCA	…	70 (49.6)	…
LAD	…	20 (14.2)	…
LCx	…	15 (10.6)	…
Ramus intermedius	…	1 (0.7)	…
Multivessel CTO	…	35 (24.8)	…
CTO revascularization, n (%)			
CTO PCI	…	54 (38.3)	…
Successful CTO PCI	…	47 (87.0)	…
CTO lesion characteristics, n (%)			
CTO length ≥20 mm	…	81 (57.4)	…
Severe calcification	…	47 (33.3)	…
Bending >45°	…	48 (34.0)	…
J-CTO score ≥3	…	46 (32.6)	…
Poor distal vessel quality	…	62 (44.0)	…
Morphology of proximal stump, n (%)			
Tapered	…	59 (41.8)	…
Blunt	…	60 (42.6)	…
Ambigious	…	11 (7.8)	…
In-stent	…	7 (5.0)	…
Ostial	…	4 (2.8)	…
Type of collateralization, n (%)			
Bridging	…	18 (12.8)	…
Ipsilateral	…	70 (49.6)	…
Contralateral	…	119 (84.4)	…
Epicardial	…	77 (54.6)	…
Intramyocardial	…	130 (92.2)	…
Werner classification, n (%)			
CC0	…	11 (7.8)	…
CC1	…	61 (43.3)	…
CC2	…	69 (48.9)	…

Level of significance $P<0.05$. Werner Classification CC0, no continuous connection; CC1, threadlike connections; CC2, side-branch like connections. CABG indicates coronary artery bypass grafting; CTO, chronic total occlusion; IQR, interquartile range; J-CTO, Japan–Chronic Total Occlusion; LAD, left anterior descending artery; LCx, left circumflex artery; LMT, left main trunk; PCI, percutaneous coronary intervention; and RCA, right coronary artery.

*The CTO-specific characteristics are applicable only for the CTO subgroup.

†Indicates statistical significance.

on the exact prevalence, characterization of comorbidities and risk stratification of consecutive patients hospitalized with HFmrEF. Among others, it has been demonstrated that CAD is the predominant causative pathology in 69% of patients with HFmrEF, followed by nonischemic causes, including primary cardiomyopathies in 8% and other secondary forms of cardiomyopathy (23%).[25] However, the distinct rates and impact of different types of CAD, including coronary CTO, have rarely been investigated for HFmrEF.

A previous large-scale Swedish registry study found relevant CAD in half of overall HF patients.[26] However, the rates of CAD were higher in patients with HFmrEF and HFrEF (>50%) compared with patients with HFpEF (>40%).[26,27] With regard to coronary CTO, the exact rates of the different types of HF are underinvestigated. In general, coronary CTO are found in about 20% of all patients undergoing ICA.[11,28] As shown in COMMIT-HF (Clopidogrel and Metoprolol in Myocardial Infarction Trial), the highest rates of CTO were reported in patients with severely reduced LVEF (ie, <35%), estimated at 41%.[29] In contrast, coronary CTO are found less often in patients with preserved LVEF, where less complex types of CAD or single-vessel

Table 4. Follow-Up Data, Primary and Secondary End Points and Univariable Cox Regression Analyses

	Non-CTO (n=695)	CTO (n=141)	HR (95% CI)	*P* value
Primary end point, n (%)				
All-cause death, at 30 mo	131 (18.8)	46 (32.6)	1.936 (1.384–2.709)	0.001*
Secondary end points, n (%)				
All-cause death, at 12 mo	78 (11.2)	33 (23.4)	2.240 (1.491–3.365)	0.001*
Heart failure–related rehospitalization, at 30 mo	102 (14.9)	24 (17.4)	1.197 (0.767–1.867)	0.441
Cardiac rehospitalization, at 30 mo	189 (27.7)	64 (46.4)	1.969 (1.482–2.615)	0.001*
Coronary revascularization, at 30 mo	84 (12.3)	43 (31.2)	2.846 (1.970–4.112)	0.001*
Acute myocardial infarction, at 30 mo	31 (4.5)	16 (11.6)	2.671 (1.461–4.884)	0.004*
Stroke, at 30 mo	20 (2.9)	5 (3.6)	1.255 (0.471–3.343)	0.594
MACCE, at 30 mo	220 (31.7)	85 (60.3)	2.498 (1.943–3.211)	0.001*
Follow-up data, median (IQR)				
Hospitalization time, d	8 (5–14)	8 (5–14)	…	0.752
ICU time, d	1 (0–2)	1 (0–2)	…	0.640
Follow-up time, d	1182 (605–1896)	926 (315–1673)	…	0.007*

Level of significance $P<0.05$. CTO indicates chronic total occlusion; HR, hazard ratio; ICU, intensive care unit; and MACCE, major adverse cerebrovascular and cardiac event.

*Indicates statistical significance.

CTO are more commonly seen.[26,28] The present study revealed CTO rates at 17% in HFmrEF, accompanied by an increasing rate of coronary 3-vessel disease. In contrast, patients with non-CTO HFmrEF had higher rates of CABG or single- or double-vessel non-occlusive CAD. One might speculate that HFmrEF reflects a transitional stage toward HFrEF, where CAD has progressed in the background, often accompanied by multiple CTO and ultimately resulting in a decline in cardiac performance. The latter might be translated into an adverse long-term prognosis even for patients with HFmrEF CTO. Therefore, these patients reflect a high-risk subset of patients endangered by higher rates of MACCE and the highest risk of all-cause death at long-term follow-up. Recently, we were able to demonstrate the increasing risk of up-front and life-threatening recurrent ventricular tachyarrhythmias and cardiac arrest in patients with coronary CTO.[30,31]

Of note, only long-term HF-related rehospitalization was similar in patients with CTO compared with patients with non-CTO HFmrEF at present. However, overall HF-related rehospitalization is significantly higher in HFrEF compared with HFmrEF (14.6% versus 8.7%) at 1 year.[6] From a clinical perspective, a mild reduction in cardiac output can delay clinical deterioration in cardiac decompensation even longer. In contrast, however, the onset of acute HF also worsens the prognosis of patients with HFmrEF in the long term, as recently demonstrated by our study group.[32]

The presence of a CTO is an indicator of increasing multimorbidity.[33] The HF syndrome encompasses numerous cardiac pathologies and noncardiac comorbidities.[23] Accordingly, a substantial overlap between HFmrEF and HFrEF was seen for younger age, male sex, and the higher burden of CAD.[27,34] Diabetes was present in almost half of patients with CTO HFmrEF. A cardiorenal syndrome was observed in 26% of patients with CTO HFmrEF, highlighting the role of chronic kidney disease in HFmrEF. Peripheral artery disease was almost twice as common in the present CTO HFmrEF population (25%) compared with reported numbers of overall HF counts (14%),[26,27] emphasizing the increasing risk of multiside artery disease in HFmrEF. These findings suggest that the presence of a coronary CTO is again a surrogate indicator of multimorbidity and the highest cardiovascular risk in patients with HFmrEF, necessitating early targeted management, diagnostics, and therapies to prevent further deterioration and adverse outcomes.

Although no systematic ischemia testing or viability assessment was performed in the present registry, several pathophysiological mechanisms could explain the observed survival benefit after successful CTO-PCI. CTO lesions often result in large areas of hibernating but viable myocardium that show no absolute ischemia but still have insufficient collateralized blood supply.[35] Revascularization may lead to an improvement in regional and global ventricular function, a reduction in arrhythmia burden, and stabilization of HF progression. In addition, successful CTO-PCI may mitigate the effects of persistent myocardial strain, adverse ventricular remodeling, and progressive ischemic cardiomyopathy, thereby improving long-term survival. These considerations are consistent with the concept that CAD burden itself is one of the strongest predictors of death in patients with HF, even stronger than LVEF restriction, as recently demonstrated.[36]

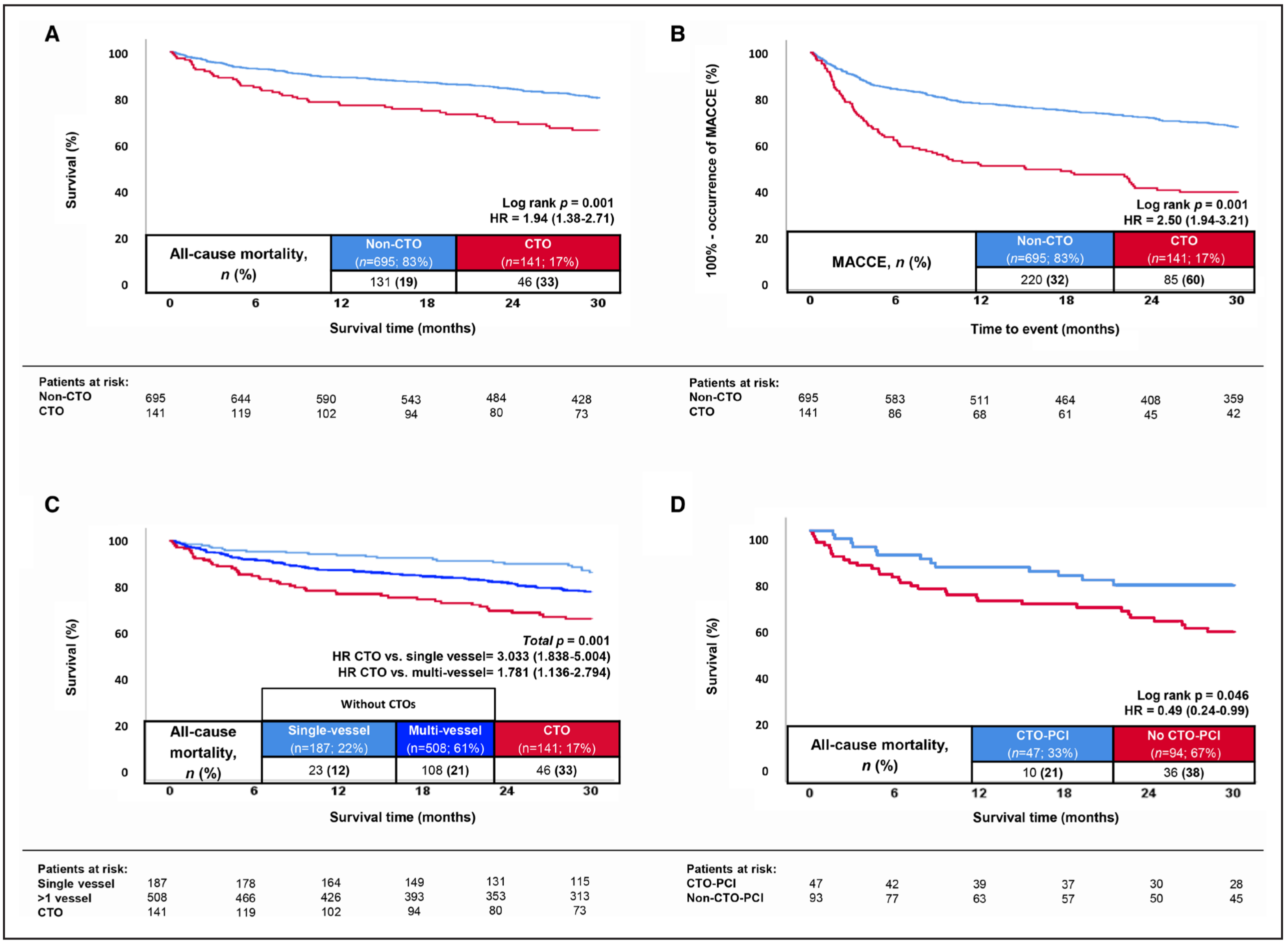

Figure 3. Kaplan–Meier survival analyses.

A, Primary end point: all-cause death for CTO vs non-CTO HFmrEF. **B**, MACCEs for CTO vs non-CTO HFmrEF. **C**, Long-term all-cause mortality rate for different types of CAD. **D**, Long-term all-cause mortality rate for CTO PCI vs non-CTO PCI (ie, both optimal medical treatment and non-CTO PCI included). CTO indicates chronic total occlusion; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; and PCI, percutaneous coronary intervention.

Prospective randomized controlled trials evaluating the benefit of CTO-PCI at the different stages of systolic HF are lacking. European guidelines recommend myocardial revascularization at a class I, level A recommendation only for patients with functionally significant CAD, specifically for those with left main stem stenosis or single- or multi-vessel CAD in the presence of LVEF >35% in addition to guideline-directed medical therapies to improve survival.[37] In contrast, patients with CAD with LVEF <35% are recommended to be treated either by CABG or PCI on the basis of careful evaluation by a heart team based on class I to II, level B to C only.[37] Notably, the referenced studies in the guidelines included low rates of CTO with corresponding unclear or negligible CTO revascularization rates. The Euro CTO trial recently demonstrated both improvement of symptoms and reduction of MACCE at long-term follow-up in patients undergoing successful CTO-PCI compared with patients with conservatively treated CTO in the presence of HFpEF.[15,38] Recent evidence suggests that CAD is a stronger predictor for all-cause death in patients with HF than LVEF.[36] Furthermore, a gradual increase in mortality rate was observed with increasing severity of CAD.[36] The recent consensus document of the Euro CTO club emphasizes that CTO are linked to increased death, especially in patients with HF, as untreated CTO may contribute to progressive myocardial dysfunction in the presence of viable myocardium.[35] Given the poor prognosis for patients with CTO HFmrEF, as seen in the present study, coronary revascularization may be considered for this subgroup since all-cause death was significantly lower following successful CTO-PCI. Transferring the moderate numbers of CTO-PCI from the present research toward daily practice might potentially be associated with more benefits for these high-risk patients in preventing further decline in cardiac function and improving long-term outcomes. However, in the case of future randomized controlled trials, the present findings still need to be confirmed.

Table 5. Multivariable Cox Regression Analyses Regarding All-Cause Death and MACCE at 30 Months

	All-cause death at 30 mo			MACCE at 30 mo		
	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
Model 1						
Age (per 1 year increase)	1.068	(1.047–1.089)	0.001[†]	1.020	(1.008–1.032)	0.001[†]
BMI (per 1 kg/m² increase)	0.976	(0.939–1.014)	0.212	0.995	(0.968–1.022)	0.708
Male sex	1.439	(0.974–2.125)	0.067	1.346	(0.998–1.817)	0.052
Congestive heart failure	1.465	(1.026–2.091)	0.036[†]	1.228	(0.935–1.614)	0.140
Chronic kidney disease	1.575	(1.084–2.289)	0.017[†]	1.328	(0.996–1.771)	0.053
CABG	1.301	(0.838–2.019)	0.241	1.436	(1.027–2.008)	0.034[†]
Diabetes	1.489	(1.058–2.096)	0.023[†]	1.242	(0.961–1.605)	0.098
Acute myocardial infarction	1.147	(0.814–1.617)	0.434	1.015	(0.785–1.312)	0.911
CTO	1.870	(1.255–2.787)	0.002[†]	2.147	(1.608–2.865)	0.001[†]
Model 2*						
CTO	1.929	(1.269–2.931)	0.002[†]	2.201	(1.636–2.960)	0.001[†]

Level of significance $P<0.05$. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CTO, chronic total occlusion; HR, hazard ratio; MACCE, major adverse cardiac or cerebrovascular event; MRA, mineralocorticoid receptor antagonist; and SGLT2, sodium–glucose cotransporter 2.

*Model 2 was additionally adjusted for concomitant treatment with β blockers, ACEi/ARB, MRA, and SGLT2 inhibitors.

†Indicates statistical significance.

Study Limitations

This single-center observational and retrospective registry-based analysis reflects a realistic picture of the consecutive health care supply of patients hospitalized with HFmrEF. However, the study has several limitations; the retrospective and single-center study design may influence results by measured and unmeasured confounding factors. First, the number of patients with CTO undergoing PCI procedures was small, and decisions were made clinically, which could introduce variability and bias in patient outcomes. Moreover, detailed reasons for deferred or failed CTO revascularization (eg, anatomic complexity, frailty, or lack of viable myocardium) could not be systematically captured, which limits further interpretation of revascularization outcomes. Second, cardiac magnetic resonance imaging was not performed systematically, as no specific clinical practice guidelines for the diagnostic workup of HFmrEF were available at the time of patient enrollment. Consequently, the presence of myocardial scarring or viability could not be routinely assessed. Third, due to the single center and retrospective registry-based analysis HF-related and cardiac rehospitalization were assessed at our institution only. Fourth, due to the retrospective design of the HARMER registry, the exact number of patients without CAD excluded invasively by ICA before the index event was not available and prior stress testing or ischemia documentation before ICA was not systematically recorded. In most cases, the decision for ICA was based on clinical presentation and the treating physician's discretion, particularly as a large proportion of patients presented with unstable angina or acute myocardial infarction at index hospitalization. In addition, this study design introduces a selection bias toward patients with a higher pretest probability of CAD, as the decision to perform ICA was based on clinical judgment, symptoms, and available noninvasive testing. As such, generalization to all patients with HFmrEF must be interpreted with caution. Fifth, inclusion criteria focus on patients with CAD and CTO and exclude patients without CAD and those without sufficient documentation, potentially missing insights into non-CAD aspects of HFmrEF. Finally, causes of death beyond index hospitalization were unavailable for the present study.

CONCLUSIONS

Coronary CTO are a common finding in patients presenting with HFmrEF. The presence of CTO deteriorates the long-term prognosis of patients with HFmrEF, while coronary revascularization of CTO by PCI showed a beneficial impact on the long-term mortality rate. Although the present study demonstrates higher rates of all-cause death and cardiac rehospitalization at 30 months for patients with CTO, current guidelines and appropriate use criteria for myocardial revascularization do not provide specific recommendations for managing this subpopulation.

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Supplemental Material

Table S1

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