Influence of documented history of coronary artery disease on outcomes in patients admitted for worsening heart failure with reduced ejection fraction in the EVEREST trial

Robert J. Mentz¹, Bradley D. Allen², Mary J. Kwasny², Marvin A. Konstam³, James E. Udelson³, Andrew P. Ambrosy⁴, Angela J. Fought², Muthiah Vaduganathan⁵, Christopher M. O'Connor¹, Faiez Zannad⁶, Aldo P. Maggioni⁷, Karl Swedberg⁸, Robert O. Bonow⁹, and Mihai Gheorghiade^{9*}

¹Duke University Medical Center, Durham, NC, USA; ²Northwestern University Feinberg School of Medicine, Chicago, IL, USA; ³The Cardiovascular Center, Tufts Medical Center, Boston, MA, USA; ⁴Stanford University School of Medicine, Stanford, CA, USA; ⁵Massachusetts General Hospital, Boston, MA, USA; ⁶Nancy University, Nancy, France; ⁷Associazione Nazionale Medici Cardiologi Ospedalieri Research Center, Florence, Italy; ⁸Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; and ⁹Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA

Received 22 May 2012; revised 6 July 2012; accepted 13 July 2012; online publish-ahead-of-print 11 September 2012

Aims	Data on the prognosis of heart failure (HF) patients with coronary artery disease (CAD) have been conflicting. We describe the clinical characteristics and mode-specific outcomes of HF patients with reduced ejection fraction (EF) and documented CAD in a large randomized trial.
Methods and results	EVEREST was a prospective, randomized trial of vasopressin-2 receptor blockade, in addition to standard therapy, in 4133 patients hospitalized with worsening HF and reduced EF. Patients were classified as having CAD based on patient-reported myocardial infarction (MI) or coronary revascularization. We analysed the characteristics and outcomes [all-cause mortality and cardiovascular (CV) mortality/HF hospitalization] of patients with and without documented CAD. All events were centrally adjudicated. Documented CAD was present in 2353 patients (57%). Patients with CAD were older and had more co-morbidities compared with those without CAD. Patients with CAD were more likely to receive a beta-blocker, but less likely to receive an angiotensin-converting enzyme (ACE) inhibitor or aldosterone antagonist ($P < 0.01$). After risk adjustment, patients with documented CAD had similar mortality [hazard ratio (HR) 1.12, 95% confidence interval (CI) 0.97–1.30], but were at an increased risk for CV mortality/HF hospitalization (HR 1.25, 95% CI 1.12–1.41) due to an increased risk for HF hospitalization (HR 1.26, 95% CI 1.10–1.44). Patients with CAD had increased HF- and MI-related events, but similar rates of sudden cardiac death.
Conclusion	Documented CAD in patients hospitalized for worsening HF with reduced EF was associated with a higher burden of co-morbidities, lower use of HF therapies (except beta-blockers), and increased HF hospitalization, while all-cause mortality was similar.
Keywords	Heart failure • Coronary artery disease • Outcomes • Hospitalization

Introduction

In the last several decades, the major underlying aetiology of heart failure (HF) has shifted from hypertension to coronary artery disease (CAD).^{1,2} Approximately 65% of patients admitted for

HF have CAD.³ Data suggest that the prognosis of HF patients with CAD is worse than those without CAD.^{4–8} An analysis from BEST (Beta-blocker Evaluation of Survival Trial) conducted in chronic systolic HF patients from 1995 to 1998 found that CAD was associated with increased mortality, but not an increased

* Corresponding author. Tel: +1 312 695 0051, Fax: +1 312-695-1434, Email: m-gheorghiade@northwestern.edu

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2012. For permissions please email: journals.permissions@oup.com.

risk for hospitalization.⁹ Similarly, a single-centre, cohort study found that the presence of CAD in patients admitted with HF, regardless of ejection fraction (EF), was associated with increased mortality.⁵ In the OPTIMIZE-HF registry (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure), CAD was associated with increased mortality at 60–90 days in patients admitted for HF with left ventricular systolic dysfunction [unadjusted hazard ratio (HR) 1.57, 95% confidence interval (CI) 1.11–2.22].¹⁰ However, following risk adjustment, this association was no longer significant (HR 1.33, 95% CI 0.89–1.99). Furthermore, prior coronary revascularization attenuated the association between CAD and mortality (unadjusted HR 1.32, 95% CI 0.89–1.96 vs. HR 1.79, 95% CI 1.22–2.62 in those with vs. without coronary revascularization, respectively). The association between CAD and mortality in those without prior revascularization also did not reach statistical significance following multivariable adjustment ($P = 0.061$). Thus, recent data have been conflicting regarding the independent role of CAD for prognosis in HF patients with reduced EF when assessed by multivariable analysis. We used data from the EVEREST (Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with Tolvaptan) trial of patients hospitalized for worsening HF with reduced EF to explore: (i) the baseline clinical characteristics of HF patients with and without documented CAD; and (ii) the association of documented CAD with post-discharge morbidity and mortality in a large cohort with adjudicated outcomes.

Methods

Study design and patient population

The design and results of the EVEREST programme have been reported previously.^{11,12} In brief, the trial was a global, event-driven, randomized, double-blind, placebo-controlled study of 4133 patients evaluating the efficacy of tolvaptan supplemented to standard HF therapy in patients hospitalized with worsening HF. Patients ≥ 18 years of age, hospitalized for worsening HF with an EF $\leq 40\%$, signs/symptoms of volume expansion, and New York Heart Association (NYHA) class III/IV symptoms were enrolled within 48 h of admission and followed for a median of 9.9 months. Significant exclusion criteria included cardiac surgery within 60 days of enrolment, cardiac mechanical support, biventricular pacemaker placement within the last 60 days, co-morbid conditions with an expected survival of < 6 months, acute myocardial infarction (MI), haemodynamically significant primary valvular disease, refractory end-stage HF, haemofiltration/dialysis, systolic blood pressure < 90 mmHg, creatinine > 3.5 mg/dL, potassium > 5.5 mEq/L, and haemoglobin < 9 g/dL. Background HF therapy was left to the discretion of the treating physician, with guideline-based recommendations in the protocol. The co-primary endpoints were all-cause mortality and cardiovascular (CV) mortality or HF hospitalization. The investigation conforms to the principles outlined in the Declaration of Helsinki. The EVEREST trial was approved by the appropriate regulatory authorities and Ethics Committees prior to patient enrolment, and written informed consent was obtained from each patient.

Adjudication and definition of endpoints

Coronary artery disease status was recorded on study enrolment by the clinician-investigator based on patient-reported history of previous MI or a history of coronary revascularization prior to the HF

hospitalization. Coronary revascularization included previous percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG).

The causes of death and hospitalization were adjudicated by a blinded clinical events committee. Mode of death was classified as CV, non-CV, or unknown, as previously described.¹³ In brief, CV death comprised sudden cardiac death, HF, acute MI, stroke, or other. Non-CV death was due to a specific non-CV event, whereas unknown death was defined as a death for which no information surrounding the event was available. Rehospitalization was defined as a non-elective hospital admission with a duration that extended over a change in calendar date and based on the primary reason for admission. Cardiovascular hospitalizations included HF, arrhythmia, acute MI, and stroke as previously defined.¹³ Non-CV hospitalizations were those without a CV classification.

Study endpoints and statistical analysis

Post-hoc analyses were performed on the entire randomized population, with patients grouped based on baseline CAD status. Baseline characteristics were compared using the Student's *t*-test or Wilcoxon rank sum test for continuous variables, and χ^2 tests for categorical variables as appropriate. A cause-specific analysis of the cause of rehospitalization and death, based on adjudicated endpoints, was pre-specified in the original trial design. For the present analysis, we determined event occurrences for CV rehospitalization and CV mortality in those with documented CAD compared with those without documented CAD. Univariate comparisons of the event rates between study groups were made using log-rank tests. The primary endpoints for the present analyses were mortality and CV mortality/HF hospitalization. The endpoints of CV mortality and HF hospitalization, which were pre-specified secondary endpoints, were also independently evaluated. Univariate time-to-event comparisons between those with and without a history of documented CAD were made using log-rank tests. Kaplan–Meier estimates of the event rates were calculated over the entire follow-up period. Hazard ratios and corresponding CIs were calculated relative to CAD status using a Cox proportional hazards model with and without adjustment for baseline covariates. Adjustment covariates included clinically relevant demographic (age, sex, region), clinical [admission systolic blood pressure, presence of atrial fibrillation/flutter on baseline electrocardiogram, EF, QRS duration, angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) use, beta-blocker use, aldosterone blocker use, digoxin use, intravenous inotrope use, diabetes, hypertension, and renal insufficiency], and laboratory values [brain natriuretic peptide/N-terminal pro brain natriuretic peptide (BNP/NT-proBNP), sodium, and blood urea nitrogen (BUN)] as in previous EVEREST analyses.¹⁴ Statistical significance was assessed using two-sided *P*-values. A *P*-value < 0.05 was considered statistically significant. All analyses were run in SAS v 9.2 (Cary, NC, USA).

Financial and material support for the EVEREST trial was provided by Otsuka, Inc., Rockville, Maryland. Database management was performed by the sponsor. Mary Kwasny conducted all final analyses for this report with funding from the Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Results

Documented history of CAD was present in 2353 patients (57%). Of these CAD patients, 2087 (88.7%) had a prior MI, 862 (33.6%) had a prior CABG, and 738 (31.4%) had a history of PCI. Table 1 presents baseline characteristics based on CAD status. Patients

Table 1 Baseline clinical and demographic characteristics of patients with and without documented coronary artery disease

	CAD (n = 2353, 57%)	No CAD (n = 1778, 43%)	P-value
Demographics			
Age, years	67.9 (10.3)	62.9 (13.1)	<0.001
Male	78.5	68.9	<0.001
Race			<0.001
Caucasian	89.9	79.6	
Black	5.1	10.8	
Hispanic	3.6	6.6	
Other	1.4	3.0	
Weight, kg	83.3 (17.8)	83.1 (20.2)	0.79
Height, cm	170.7 (9.1)	169.5 (9.8)	<0.001
Region			<0.001
Eastern Europe	36.7	38.5	
North America	36.4	22.2	
South America	10.3	25.7	
Western Europe	13.6	13.6	
Physical and laboratory findings			
Systolic BP, mmHg	120 (19)	121 (20)	0.39
Heart rate, b.p.m.	78 (15)	83 (16)	<0.001
Dyspnoea	91.1	90.9	0.82
JVD ≥ 10 cm	26.4	27.7	0.35
Rales	81.0	81.9	0.47
Peripheral oedema	89.4	89.7	0.77
Ejection fraction, %	27.7 (7.9)	27.2 (8.2)	0.03
BUN, mg/dL	27 (20, 37)	24 (18, 33)	<0.001
Creatinine, mg/dL	1.3 (1.1, 1.7)	1.2 (1.0, 1.5)	<0.001
Sodium, mg/dL	140 (137, 142)	140 (137, 143)	0.45
BNP, pg/mL	756 (314, 1554)	649 (271, 1427)	0.002
QRS duration, ms	124 (99, 152)	121 (95, 148)	<0.001
NYHA class IV	40.0	40.2	0.88
Atrial fibrillation/flutter on ECG	24.2	35.2	<0.001
Medical history			
Previous HF hospitalization	80.4	77.1	0.01
Hypertension	74.8	65.9	<0.001
Diabetes	44.7	30.7	<0.001
Hypercholesterolaemia	62.7	30.2	<0.001
Atrial arrhythmia	50.8	53.1	0.13
Ventricular arrhythmia	30.2	20.8	<0.001
COPD	11.2	8.6	0.01
Chronic kidney disease	32.5	19.3	<0.001
Peripheral vascular disease	25.9	14.5	<0.001
ICD	20.3	6.9	<0.001
Previous stroke	13.9	8.4	<0.001
Medications			
Diuretics	96.7	97.1	0.53
Beta-blockers	75.9	62.9	<0.001
Calcium channel blockers	10.6	10.7	0.95
ACE inhibitors/ARBs	82.5	86.5	0.001
Furosemide	86.7	89.4	0.01
Aldosterone blockers	50.5	59.1	<0.001
Digoxin	39.3	50.1	<0.001

Continued

Table 1 Continued

	CAD (n = 2353, 57%)	No CAD (n = 1778, 43%)	P-value
Nitrates	45.7	24.9	<0.001
Intravenous inotropes	4.1	3.4	0.24
Hydralazine	3.2	2.6	0.26
Aspirin	64.3	42.5	<0.001
Lipid-modifying agents	51.0	18.5	<0.001

Presented as mean (SD), %, or median (25th, 75th).

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; HF, heart failure; ICD, implantable converter defibrillator; JVD, jugular venous distention; NYHA, New York Heart Association.

with documented CAD tended to be older, male, Caucasian, and had a higher prevalence of hypertension, diabetes, vascular disease, and chronic kidney disease compared with those without documented CAD (all $P < 0.001$). CAD patients tended to have higher serum BUN, creatinine, and natriuretic peptide levels. They were less likely to receive an ACE inhibitor or aldosterone antagonist at baseline, but were more likely to receive aspirin, a lipid-modifying agent, and a beta-blocker compared with those without documented CAD (all $P < 0.01$).

The event rates for the primary outcomes are presented in Table 2. Patients with documented CAD had higher event rates for mortality and CV mortality/HF hospitalization (28.1% vs. 23.5%, $P = 0.004$ and 44.7% vs. 36.4%, $P < 0.001$, respectively). The CV mortality rate was higher in the group with documented CAD (21.6% vs. 18.1%, $P = 0.02$). There were between-group differences in the aetiology of CV deaths (Table 2). CAD patients tended to have slightly more HF deaths and a trend toward more MI deaths. The two groups had similar rates of sudden cardiac death ($P = 0.68$). Patients with documented CAD had increased event rates for both HF and MI hospitalizations compared with those without documented CAD ($P < 0.001$).

Figure 1 presents the Kaplan–Meier curves for the primary end-points in those with and without documented CAD. On univariate analysis, CAD was associated with increased mortality, CV mortality/HF hospitalization, CV mortality, and HF hospitalization (Table 3). After risk adjustment, the hazard associated with CAD for mortality was no longer significant (HR 1.12, 95% CI 0.97–1.30), but the risk for CV mortality/HF hospitalization remained increased (HR 1.25, 95% CI 1.12–1.41) (Table 3). CAD was not associated with risk-adjusted CV mortality (HR 1.15, 95% CI 0.97–1.35), but remained a significant predictor of HF hospitalization (HR 1.26, 95% CI 1.10–1.44).

Discussion

Multiple studies have suggested that CAD is associated with worse outcomes in HF patients.^{4,5,7,9} However, recent data have been conflicting regarding the independent role of CAD for prognosis in HF patients with reduced EF when assessed by multivariable analysis.¹⁰ The present analysis demonstrated that documented CAD was present in 57% of HF patients with reduced EF admitted for

Table 2 Event rates with and without documented coronary artery disease

Outcome	CAD (n = 2353)	No CAD (n = 1778)	Log rank P-value
All-cause mortality	662 (28.1)	418 (23.5)	0.004
CV mortality + HF hospitalization	1052 (44.7)	647 (36.4)	<0.001
CV mortality	507 (21.6)	322 (18.1)	0.02
Heart failure	278 (11.8)	165 (9.3)	0.01
Sudden cardiac death	163 (6.9)	118 (6.6)	0.68
Stroke	15 (0.6)	9 (0.5)	0.57
Acute MI	21 (0.9)	7 (0.4)	0.07
Other CV mortality	31 (1.3)	23 (1.3)	0.95
Non-CV mortality	154 (6.5)	96 (5.4)	0.14
CV hospitalization	840 (35.7)	554 (31.2)	<0.001
HF hospitalization	800 (34.0)	486 (27.3)	<0.001
MI hospitalization	58 (2.5)	9 (0.5)	<0.001
Stroke hospitalization	40 (1.7)	29 (1.6)	0.89
Arrhythmia hospitalization	115 (4.9)	77 (4.3)	0.40
Other CV hospitalization	223 (9.5)	119 (6.7)	0.001

Presented as number (%).

CAD, coronary artery disease, CV, cardiovascular, HF, heart failure, MI, myocardial infarction.

worsening HF. Compared with those without documented CAD, patients with CAD tended to have more co-morbidities and were less often treated with ACE inhibitors and aldosterone blockers. The presence of documented CAD identified a subgroup with a 25% increased risk for CV mortality or HF hospitalization that was driven by an increased risk for HF hospitalization. These conclusions are strengthened by data collection in the setting of a large trial with blindly adjudicated outcomes and an improved ability to adjust for apparent confounders to estimate the hazard associated with CAD more precisely.

The prevalence of CAD in this cohort was similar to that in previous studies,^{9,10} however, data have suggested a higher prevalence.^{3,5} The lower prevalence in the present study may

Figure 1 Kaplan–Meier analyses of (A) all-cause mortality and (B) cardiovascular (CV) death or hospitalization for heart failure (HF) in patients with vs. without documented coronary artery disease (CAD).

Table 3 Outcomes for heart failure patients with systolic dysfunction with and without documented coronary artery disease

Outcome	Unadjusted		Adjusted ^a	
	HR (95% CI)	Wald P-value	HR (95% CI)	Wald P-value
All-cause mortality	1.20 (1.06–1.35)	0.004	1.12 (0.97–1.30)	0.13
CV mortality + HF hospitalization	1.29 (1.17–1.43)	<0.001	1.25 (1.12–1.41)	<0.001
CV mortality	1.20 (1.04–1.38)	0.01	1.15 (0.97–1.35)	0.11
HF hospitalization	1.32 (1.18–1.47)	<0.001	1.26 (1.10–1.44)	<0.001

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

^aAdjusted for randomization group, age, sex, region, ejection fraction, baseline atrial fibrillation/atrial flutter, systolic blood pressure, serum sodium, blood urea nitrogen, natriuretic peptide level, QRS duration, use of an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta-blocker, aldosterone blocker, digoxin, intravenous inotrope, diabetes, hypertension, and renal insufficiency.

have been due to patient-reported CAD, which would tend to exclude those with subclinical CAD. However, this CAD definition represents the classification scheme commonly used in clinical practice and previous HF studies.¹⁰ This definition is strengthened by prospective collection in the controlled setting of a clinical trial. Significant enrolment from Eastern Europe and South America, where patients are less likely to undergo cardiac catheterization, may have led to underestimation of CAD. However, since the majority of patients that were classified as having CAD had a prior MI, regional revascularization rates were less likely to contribute to differences in patient classification.

Our findings identify characteristics of the HF population with documented CAD that may influence strategies to improve patient care. First, CAD patients tended to be a heterogeneous group with more co-morbidities than those without CAD. Secondly, with the exception of greater beta-blocker use, the CAD patients were undertreated with evidence-based HF therapies. The between-group differences in HF medication use may be even more marked in routine clinical practice. By improving the management of co-morbid conditions and increasing the use of HF and CAD therapies, outcomes may be improved. Specifically, we demonstrated significant room for improvement in the use of aspirin, statins, and implantable cardioverter defibrillator (ICD) therapy. Moreover, future HF trials investigating CAD should include the elderly and those with co-morbidities to improve the generalizability of the results.

In contrast to previous studies,^{5,9} documented CAD was not associated with increased risk-adjusted mortality. However, one previous investigation was conducted prior to contemporary therapies⁹ and the other analysis was a small, single-centre study of HF patients with and without reduced EF.⁵ In contrast, our findings are supported by OPTIMIZE-HF where CAD was not associated with increased 60–90 day post-discharge mortality following multivariable risk adjustment in patients admitted for HF with systolic dysfunction.¹⁰ The present study extends these findings due to the longer follow-up period and data collection in a clinical trial.

Our findings should be distinguished from those demonstrating worse outcomes in HF patients with ischaemic vs. non-ischaemic cardiomyopathy.^{4,6,15,16} Since the standardized definition of ischaemic cardiomyopathy includes angiographic criteria,⁶ the present analysis does not necessarily capture the underlying aetiology of cardiomyopathy. For instance, a patient with subclinical left main disease would be classified as 'no CAD', but would actually have ischaemic cardiomyopathy. Thus, CAD status by clinical history should be distinguished from the underlying aetiology of HF.

Our finding of the lack of association between documented CAD and mortality following risk adjustment has several possible explanations. First, the severity of HF in these patients (40% with NYHA class IV symptoms) may have resulted in ischaemic events having a lesser impact on outcomes. Secondly, contemporary therapies may reduce the impact of CAD on overall and CV-specific mortality.^{17–19} For instance, HF patients with revascularized CAD exhibit similar mortality to those without CAD.¹⁰ This hypothesis is further supported by recent trials investigating therapies for CAD in chronic HF patients, which have been neutral with respect to mortality.^{20–22} Conversely, the present analysis may have had limited power and duration of follow-up

to detect between-group differences. For instance, while the event rates were high, the lack of coronary angiography on all patients may have resulted in the misclassification of patients with subclinical CAD. The non-CAD group may have contained a cohort of patients with undiagnosed CAD, which would bias the results toward the null.

While we did not observe higher mortality associated with documented CAD, we found higher CV mortality/HF hospitalization driven by the HF hospitalization component. CAD may be associated with increased hospitalization risk due to subclinical ischaemia with worsening of underlying HF.^{23–27} The increased risk for hospitalization in HF patients with CAD may also be related to the reduction in CAD-related mortality with contemporary therapies. With the improved survival of HF patients with CAD, there is a larger population at risk for rehospitalization.

There is a potential disconnection between the increased risk for rehospitalization associated with CAD without an associated increased mortality risk. Multiple studies have suggested an association between HF hospitalization and increased mortality.^{28–30} However, the results of the present study suggest that the increased hospitalization risk associated with documented CAD did not correlate with increased mortality. These findings are supported by a recent study demonstrating that the association between HF hospitalizations and mortality differs by baseline risk.³¹ Specifically, HF hospitalizations in the previous year conferred increased mortality in patients with 'low-risk' features (e.g. younger age, higher blood pressure). However, patients with 'high-risk' features demonstrated no consistent relationship between prior HF hospitalizations and mortality. In sum, HF patients with documented CAD may have a complex disease burden that increases their risk for hospitalization, but subsequent hospitalizations may impact their clinical course differently from the general population.

The increased HF hospitalization risk associated with documented CAD has important clinical implications. Hospitalizations for HF have continued to increase over time, and costs related to hospitalization account for ~75% of the total cost of HF care.³² There is the potential for a reduction in the burden of HF care through the use of strategies to reduce the risk associated with CAD. Both the STICH (Surgical Treatment for Ischemic Heart Failure) and CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trials demonstrated significant reductions in CV hospitalization with CAD therapies in chronic HF.^{21,33} Furthermore, an observational study in HF patients with acute MI not undergoing PCI found that patients receiving CAD therapy with clopidogrel had reduced mortality compared with those not receiving clopidogrel (HR 0.86, 95% CI 0.78–0.95).³⁴ Similar findings have been observed in a small prospective study in patients with acute decompensated HF without MI.³⁵ CAD therapies including antiplatelet agents may represent one strategy to improve outcomes in acute HF patients. Additional randomized studies are required to investigate these findings.

Cause-specific analyses of rehospitalization and mortality demonstrated that patients with CAD had significantly increased hospitalization rates for HF and MI, but similar rates of sudden cardiac death compared with those without CAD. The increased HF and MI event rates might be anticipated in a population with

underlying CAD; however, the lack of an increased risk for sudden cardiac death was unexpected. Contemporary therapies including beta-blockers and ICD therapies may have reduced the risk for sudden death. Nonetheless, data support that CAD is an important contributor to the high HF mortality rates.^{10,36} Thus, there is a need to investigate cause-specific mortality further in the contemporary HF population.

Limitations

This was a retrospective analysis from a clinical trial. Outside the context of a prospective, randomized, controlled trial, definitive cause-and-effect relationships are difficult to determine. The study population had strict inclusion and exclusion criteria, such that these findings may not apply to those with different baseline characteristics. Also, CAD status was defined by patient report, which could misclassify those with subclinical CAD. Furthermore, since previous coronary revascularization has been shown to reduce the association between CAD and worse HF outcomes,¹⁰ our results in a population with a significant revascularization history may underestimate the impact of CAD. Despite covariate adjustment, other measured and unmeasured factors may have influenced these findings. Future prospective studies will need to externally validate these associations with longer follow-up given the modest follow-up duration of 9.9 months in EVEREST.

Conclusion

The prevalence of documented CAD is high in patients hospitalized for worsening HF with reduced EF and is associated with older age, an increased burden of co-morbidities, lower use of evidence-based HF medications, and increased HF rehospitalizations. Our characterization of the clinical profiles and outcomes of patients hospitalized for HF with documented CAD in a contemporary HF randomized trial provides the basis for future, prospective studies designed to test novel therapeutic strategies targeting CAD in this patient population.

Funding

Financial and material support for the EVEREST trial was provided by Otsuka, Inc., Rockville, Maryland. Mary Kwasny conducted all final analyses for this report with funding from the Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Conflict of interest: M.A.K. receives research grants from and is a consultant for Otsuka, JNJ, Amgen, and Trevena. C.M.O. is a consultant for Merck, Trevena, Novella, Pfizer, GE Healthcare, Roche, Amgen, Martek, Actelion, and JNJ. F.Z. has received honoraria from and served on advisory boards for Pfizer. A.P.M. receives honoraria from Otsuka. K.S. receives research grants from AstraZeneca, Servier, and Amgen; honoraria from AstraZeneca, Otsuka, Servier, and Amgen; and is a consultant for Cytokinetics, Servier, and Novartis. M.G. is a consultant for Abbott Labs, Astellas, AstraZeneca, Bayer Schering PharmaAG, CorThera Inc., Cytokinetics Inc., DebioPharm S.A., Errekappa Terapeutici (Milan, Italy), Glaxo Smith Kline, JNJ, Medtronic, Novartis Pharma AG, Otsuka, Sigma

Tau, Solvay Pharmaceuticals, and Pericor Therapeutics. The other authors declare no conflict of interest.

References

- Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. *Circulation* 1998;**97**:282–289.
- Fox KF, Cowie MR, Wood DA, Coats AJ, Gibbs JS, Underwood SR, Turner RM, Poole-Wilson PA, Davies SW, Sutton GC. Coronary artery disease as the cause of incident heart failure in the population. *Eur Heart J* 2001;**22**:228–236.
- Gheorghiade M, Sopko G, De Luca L, Velazquez EJ, Parker JD, Binkley PF, Sadowski Z, Golba KS, Prior DL, Rouleau JL, Bonow RO. Navigating the crossroads of coronary artery disease and heart failure. *Circulation* 2006;**114**:1202–1213.
- Bart BA, Shaw LK, McCants CB Jr, Fortin DF, Lee KL, Califf RM, O'Connor CM. Clinical determinants of mortality in patients with angiographically diagnosed ischemic or nonischemic cardiomyopathy. *J Am Coll Cardiol* 1997;**30**:1002–1008.
- Purek L, Laule-Kilian K, Christ A, Klima T, Pfisterer ME, Perruchoud AP, Mueller C. Coronary artery disease and outcome in acute congestive heart failure. *Heart* 2006;**92**:598–602.
- Felker GM, Shaw LK, O'Connor CM. A standardized definition of ischemic cardiomyopathy for use in clinical research. *J Am Coll Cardiol* 2002;**39**:210–218.
- Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000;**342**:1077–1084.
- Manzano L, Babalis D, Roughton M, Shibata M, Anker SD, Ghio S, van Veldhuisen DJ, Cohen-Solal A, Coats AJ, Poole-Wilson PP, Flather MD. Predictors of clinical outcomes in elderly patients with heart failure. *Eur J Heart Fail* 2011;**13**:528–536.
- Gheorghiade M, Flaherty JD, Fonarow GC, Desai RV, Lee R, McGiffin D, Love TE, Aban I, Eichhorn EJ, Bonow RO, Ahmed A. Coronary artery disease, coronary revascularization, and outcomes in chronic advanced systolic heart failure. *Int J Cardiol* 2011;**151**:69–75.
- Rossi JS, Flaherty JD, Fonarow GC, Nunez E, Gattis Stough W, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, Yancy CW, Young JB, Davidson CJ, Gheorghiade M. Influence of coronary artery disease and coronary revascularization status on outcomes in patients with acute heart failure syndromes: a report from OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure). *Eur J Heart Fail* 2008;**10**:1215–1223.
- Gheorghiade M, Orlandi C, Burnett JC, Demets D, Grinfeld L, Maggioni A, Swedberg K, Udelson JE, Zannad F, Zimmer C, Konstam MA. Rationale and design of the multicenter, randomized, double-blind, placebo-controlled study to evaluate the Efficacy of Vasopressin antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST). *J Card Fail* 2005;**11**:260–269.
- Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007;**297**:1319–1331.
- O'Connor CM, Miller AB, Blair JE, Konstam MA, Wedge P, Bahit MC, Carson P, Haass M, Hauptman PJ, Metra M, Oren RM, Patten R, Pina I, Roth S, Sackner-Bernstein JD, Traver B, Cook T, Gheorghiade M. Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction: results from Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) program. *Am Heart J* 2010;**159**:841–849.
- Mentz RJ, Schmidt PH, Kwasny MJ, Ambrosy AP, O'Connor CM, Konstam MA, Zannad F, Maggioni AP, Swedberg K, Gheorghiade M. The impact of chronic obstructive pulmonary disease in patients hospitalized for worsening heart failure with reduced ejection fraction: an Analysis of the EVEREST trial. *J Card Fail* 2012;**18**:515–523.
- Adams KF Jr, Dunlap SH, Sueta CA, Clarke SW, Patterson JH, Blauwet MB, Jensen LR, Tomasko L, Koch G. Relation between gender, etiology and survival in patients with symptomatic heart failure. *J Am Coll Cardiol* 1996;**28**:1781–1788.
- Likoff MJ, Chandler SL, Kay HR. Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. *Am J Cardiol* 1987;**59**:634–638.
- Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–2007.
- The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
- Masoudi FA, Wolfe P, Havranek EP, Rathore SS, Foody JM, Krumholz HM. Aspirin use in older patients with heart failure and coronary artery disease: national prescription patterns and relationship with outcomes. *J Am Coll Cardiol* 2005;**46**:955–962.

20. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**372**:1231–1239.
21. Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Janosi A, Kamensky G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007;**357**:2248–2261.
22. Cleland JG, Calvert M, Freemantle N, Arrow Y, Ball SG, Bonser RS, Chattopadhyay S, Norell MS, Pennell DJ, Senior R. The Heart Failure Revascularisation Trial (HEART). *Eur J Heart Fail* 2011;**13**:227–233.
23. Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, Angelici L, Barlera S, Parrinello G, Maggioni AP, Tognoni G, Cohn JN. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation* 2007;**116**:1242–1249.
24. Hudson MP, O'Connor CM, Gattis WA, Tasissa G, Hasselblad V, Holleman CM, Gauden LH, Sedor F, Ohman EM. Implications of elevated cardiac troponin T in ambulatory patients with heart failure: a prospective analysis. *Am Heart J* 2004;**147**:546–552.
25. Perna ER, Macin SM, Canella JP, Augier N, Stival JL, Cialzeta JR, Pitzus AE, Garcia EH, Obregon R, Brizuela M, Barbagelata A. Ongoing myocardial injury in stable severe heart failure: value of cardiac troponin T monitoring for high-risk patient identification. *Circulation* 2004;**110**:2376–2382.
26. Perna ER, Macin SM, Cimbaro Canella JP, Alvarenga PM, Rios NG, Pantich R, Augier N, Farias EF, Jantus E, Brizuela M, Medina F. Minor myocardial damage detected by troponin T is a powerful predictor of long-term prognosis in patients with acute decompensated heart failure. *Int J Cardiol* 2005;**99**:253–261.
27. Masson S, Anand I, Favero C, Barlera S, Vago T, Bertocchi F, Maggioni AP, Tavazzi L, Tognoni G, Cohn JN, Latini R. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from 2 large randomized clinical trials. *Circulation* 2012;**125**:280–288.
28. Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J* 2007;**154**:260–266.
29. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, Pfeffer MA. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation* 2007;**116**:1482–1487.
30. Ahmed A, Allman RM, Fonarow GC, Love TE, Zannad F, Dell'italia LJ, White M, Gheorghiade M. Incident heart failure hospitalization and subsequent mortality in chronic heart failure: a propensity-matched study. *J Card Fail* 2008;**14**:211–218.
31. Kommuri NV, Koelling TM, Hummel SL. The impact of prior heart failure hospitalizations on long-term mortality differs by baseline risk of death. *Am J Med* 2012;**125**:e9–e15.
32. Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the U.S., 1979 to 2004. *J Am Coll Cardiol* 2008;**52**:428–434.
33. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, Ali IS, Pohost G, Gradinac S, Abraham WT, Yui M, Prabhakaran D, Szwed H, Ferrazzi P, Petrie MC, O'Connor CM, Panchavinnin P, She L, Bonow RO, Rankin GR, Jones RH, Rouleau JL. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med* 2011;**364**:1607–1616.
34. Bonde L, Sorensen R, Fosbol EL, Abildstrom SZ, Hansen PR, Kober L, Schramm TK, Bretler DM, Weeke P, Olesen J, Torp-Pedersen C, Gislason GH. Increased mortality associated with low use of clopidogrel in patients with heart failure and acute myocardial infarction not undergoing percutaneous coronary intervention: a nationwide study. *J Am Coll Cardiol* 2010;**55**:1300–1307.
35. Kozdag G, Yilmaci M, Ertas G, Celikyurt U, Sahin T, Kilic T, Ural D. Aspirin, clopidogrel, and warfarin use and outcomes in a cohort of 580 patients discharged after hospitalization for decompensated heart failure. *Heart Vessels* 2011;in press.
36. Uretsky BF, Thygesen K, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Packer M, Poole-Wilson PA, Ryden L. Acute coronary findings at autopsy in heart failure patients with sudden death: results from the assessment of treatment with lisinopril and survival (ATLAS) trial. *Circulation* 2000;**102**:611–616.