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Int J Cardiol. Author manuscript; available in PMC 2011 April 1.

Published in final edited form as:
Int J Cardiol. 2010 April 1; 140(1): 55–59. doi:10.1016/j.ijcard.2008.10.049.

Incident Coronary Revascularization and Subsequent Mortality in Chronic Heart Failure: A Propensity-Matched Study

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Abstract

Introduction—Ischemic heart disease (IHD) is common in heart failure (HF), yet the association between incident coronary revascularization and mortality in these patients has not been examined in a propensity-matched study.

Methods—In the Digitalis Investigation Group trial, 2853 patients without coronary revascularization and 120 patients with coronary revascularization during the first three years were alive at the end of three years. We used propensity scores to match 119 and 357 patients with and without coronary revascularization. Matched Cox regression models were used to estimate hazard ratio (HR) and 95% confidence interval (CI) for mortality during the fourth year of follow-up, for all patients and by the mean left ventricular ejection fraction (LVEF) of 35%.

Results—Coronary revascularization was associated with higher mean LVEF (36 % versus 32 %; p<0.0001) and prevalence of angina pectoris (48% versus 32%; p<0.0001) but fewer prior myocardial infarction (80% versus 87%; p=0.023), all of which were balanced post-match. All-cause mortality occurred in 5.9% and 6.2% patients respectively with and without coronary revascularization (HR for coronary revascularization, 0.95; 95% CI, 0.39–2.32; p=0.910). HR for mortality associated with coronary revascularization for patients with LVEF ≤35% and >35% were respectively 1.34 (95% CI, 0.48–3.71; p=0.578) and 0.61 (95% CI, 0.13–2.87; p=0.532).

Conclusion—Chronic HF patients with IHD receiving coronary revascularization were more likely to have angina and higher LVEF. However, in a balanced propensity-matched cohort, there was no association between coronary revascularization and mortality. The LVEF-associated variation in mortality needs to be prospectively studied.

Keywords

heart failure; revascularization; mortality; outcomes

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Presentation: An abstract based on the current analysis was presented at the Heart Failure society of America 12th Annual Scientific meeting in Toronto, Ontario, Canada, in September 2008.

Conflict of Interest Disclosures: None

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1. Introduction

Ischemic heart disease (IHD) is the leading cause of heart failure (HF), and coronary revascularization is a major treatment option for HF patients with IHD [1]. Yet, the role of coronary revascularization in chronic HF patients with IHD remains controversial [2–5]. To the best of our knowledge the effect of incident coronary revascularization on subsequent mortality has not been examined in a propensity-matched population of ambulatory chronic HF patients with low and normal left ventricular ejection fraction (LVEF).

2. Materials and methods

The Digitalis Investigator Group (DIG) trial enrolled 7788 ambulatory patients with chronic HF in normal sinus rhythm from 302 clinical centers in the United States and Canada from 1991 to 1993 [6,7]. Overall, 120 patients who underwent coronary revascularization during the first three years of the study and 2853 patients with IHD who did not undergo coronary revascularization were alive at the end of three years (Figure 1). IHD and hospitalization due to coronary revascularization were ascertained by study investigators and were not centrally adjudicated. The primary endpoints were mortality due to all causes, cardiovascular causes, and worsening HF. Data on vital status were 99% complete [8].

Using propensity scores for coronary revascularization, we assembled a balanced cohort of 119 patients who underwent coronary revascularization and 357 patients who were treated medically (Figure 1) [9,10]. Propensity scores for incident coronary revascularization for each of the 2973 patients with IHD were estimated using a non-parsimonious, multivariate logistic regression model, adjusting for key baseline covariates presented in Table 1. The propensity scores were then used for matching, and the details of the matching protocol have been described elsewhere [11–14]. Absolute standardized differences were estimated to examine covariate balance and were presented as a Love plot, developed by Thomas E. Love [11–13, 15,16].

The baseline characteristics of patients who underwent coronary revascularization and those who were treated medically were compared using Pearson's chi-square and Wilcoxon's rank-sum tests. Kaplan-Meier analysis and matched Cox regression analyses were used to determine the association of incident coronary revascularization with subsequent mortality during the fourth year of follow-up. All statistical tests were done using SPSS-15 for Windows [17].

3. Results

Patients had a mean (±SD) age of 62 (±10) years, 22% were women, and 10% were nonwhites. Before matching, patients with (versus without) coronary revascularization had a higher mean baseline LVEF (36 {±12} % versus 32 {±11} %; $p<0.0001$), were less likely to have prior myocardial infarction (80% versus 87%; $p=0.023$), but more likely to have unstable angina pectoris (48% versus 32%; $p<0.0001$). However, there were no differences in NYHA class symptoms. Pre-match imbalances (>10% indicate substantial imbalance) and post-match balances in baseline covariates are displayed in Table 1 and Figure 2.

Overall, 29 patients (6%) died, including 24 (5%) due to cardiovascular causes and 13 (3%) due to progressive HF, during 392 patient-years of subsequent follow-up. Kaplan-Meier plots for all-cause and cardiovascular mortality are displayed in Figure 3. All-cause mortality occurred in 5.9% (rate, 154/10000 person-years) of patients who underwent coronary revascularization and in 6.2% (rate, 161/10000 person-years) of matched patients treated medically (hazard ratio {HR}, 0.95; 95% confidence interval {CI}, 0.39–2.32; $p=0.910$; Table 2). Coronary revascularization was not associated with mortality caused by cardiovascular causes or progressive HF (Table 2). HR for mortality by coronary revascularization for patients

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with LVEF ≤35% and >35% were respectively 1.34 (95% CI, 0.48–3.71; p= 0.578) and 0.61 (95% CI, 0.13–2.87; p= 0.532; Table 3).

4. Discussion

The findings of our study demonstrate that chronic HF patients who underwent coronary revascularization were less likely to have a history of prior myocardial infarction but were more likely to have symptoms of unstable angina pectoris, and were also more likely to have a higher LVEF. However, when these and other key measured baseline characteristics were balanced after matching, incident coronary revascularization was not associated with subsequent mortality in patients with chronic systolic and diastolic HF with IHD.

The substantial yet non-significant reduction in mortality in patients receiving coronary revascularization before matching may be explained by baseline covariate imbalances such as younger age, a better comorbidity profile and a higher mean LVEF among those receiving coronary revascularization. However, when these covariates were balanced after matching, there was no substantial difference in mortality between patients receiving and not receiving coronary revascularization. Interestingly, there was a substantial but non-significant reduction in mortality in matched patients with LVEF >35% who received coronary revascularization. This is consistent with the findings from the Coronary Artery Surgery Study and the Veteran Affairs Cooperative Study that suggested that coronary revascularization was associated with improved survival in patients with IHD and LVEF >35% [18,19]. HF patients with normal or near normal LVEF are more likely to have viable ischemic myocardium, which has been shown to determine both the degree of improvement in LV function and the long-term outcomes after revascularization [20–25]. The association between a higher mean LVEF and the presence of viable ischemic myocardium may also explain the higher prevalence of unstable angina pectoris in patients receiving coronary revascularization in our study. One of the reasons for excluding patients with LVEF <35% from the Coronary Artery Surgery Study and the Veteran Affairs Cooperative Study was that they were considered high-risk for coronary revascularization. This notion is congruent with the findings from our subgroup analysis that indicate that among HF patients with IHD and LVEF ≤35%, the direction of association was toward an increased mortality in those receiving coronary revascularization. However, this association was not statistically significant and needs to be interpreted with caution. The association between coronary revascularization and outcomes in HF patients with IHD and LVEF <35% will be clarified when the findings from the currently ongoing Surgical Treatment for Ischemic Heart Failure (STICH) trial will be published [26].

The lack of a statistically significant association between coronary revascularization and mortality in our study may also be explained by the small sample size and lack of adequate power. However, the direction and the magnitude of the associations in our subgroup analysis are mechanistically plausible and suggest that coronary revascularization may not be safe in chronic HF patients with IHD and low LVEF. We also noted that HF patients who received coronary revascularization had lower prevalence of a history of prior myocardial infarction but a higher prevalence of angina pectoris. Patients with a history of prior myocardial infarction are less likely to have viable myocardium and thus less likely to have angina pectoris [22]. Therefore, angina pectoris may serve as marker of viable myocardium in HF patients with a history of prior myocardial infarction who should undergo tests for myocardial viability to identify those who might benefit from coronary revascularization. HF patients with non-viable ischemic myocardium may not benefit from coronary revascularization [27,28].

The findings of the current study are consistent with findings from a previous study that also examined the association between coronary revascularization and mortality [29]. In that study, in HF patients with IHD and LVEF <45% (mean, 25%), 5-year all-cause mortality occurred

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in 43% of patients (n=10) in the revascularization group and in 60% of those (n=67) who did not undergo revascularization (p=0.257). To the best of our knowledge, this is the first report of an association between incident coronary revascularization and subsequent total and cause-specific mortality in a propensity-matched population of chronic systolic and diastolic HF patients with IHD.

Lack of data on the type or timing of coronary revascularization is a key limitation of our study [30]. DIG participants were mostly younger men in normal sinus rhythm from the pre-beta-blocker era of HF therapy, which may limit generalizability to contemporary HF patients. Our propensity matching was able to balance all key baseline covariates. However, imbalances in unmeasured covariates are possible and may potentially confound our findings.

In conclusion, in chronic systolic and diastolic HF patients with IHD, younger age, higher LVEF and the presence of angina pectoris had bivariate association with coronary revascularization. Despite a non-significant association between incident coronary revascularization and subsequent mortality, the directions of these associations in our subgroup analysis suggest that in HF patients with IHD and LVEF >35%, the symptom of angina pectoris may be used to identify patients for further evaluation for myocardial viability and to identify those who might benefit from coronary revascularization.

Acknowledgments

Funding/Support: Dr. Ahmed is supported by the National Institutes of Health through a grant from the National Heart, Lung, and Blood Institute (5-R01-HL085561-02) and a generous gift from Ms. Jean B. Morris of Birmingham, Alabama.

"The Digitalis Investigation Group (DIG) study was conducted and supported by the NHLBI in collaboration with the DIG Investigators. This manuscript was prepared using a limited access dataset obtained by the NHLBI and does not necessarily reflect the opinions or views of the DIG Study or the NHLBI."

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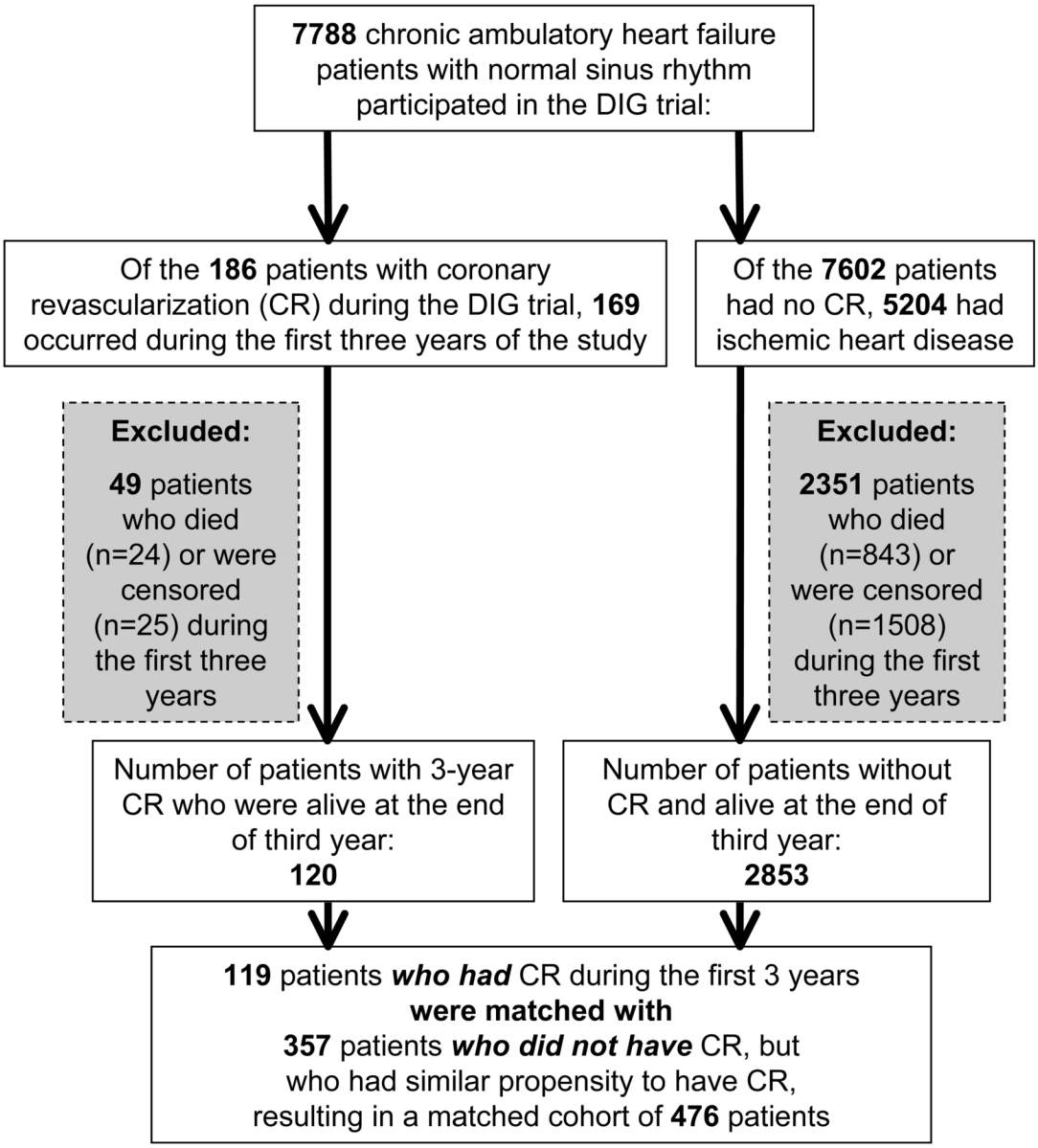

Figure 1.
Flow chart for the assembly of study cohort

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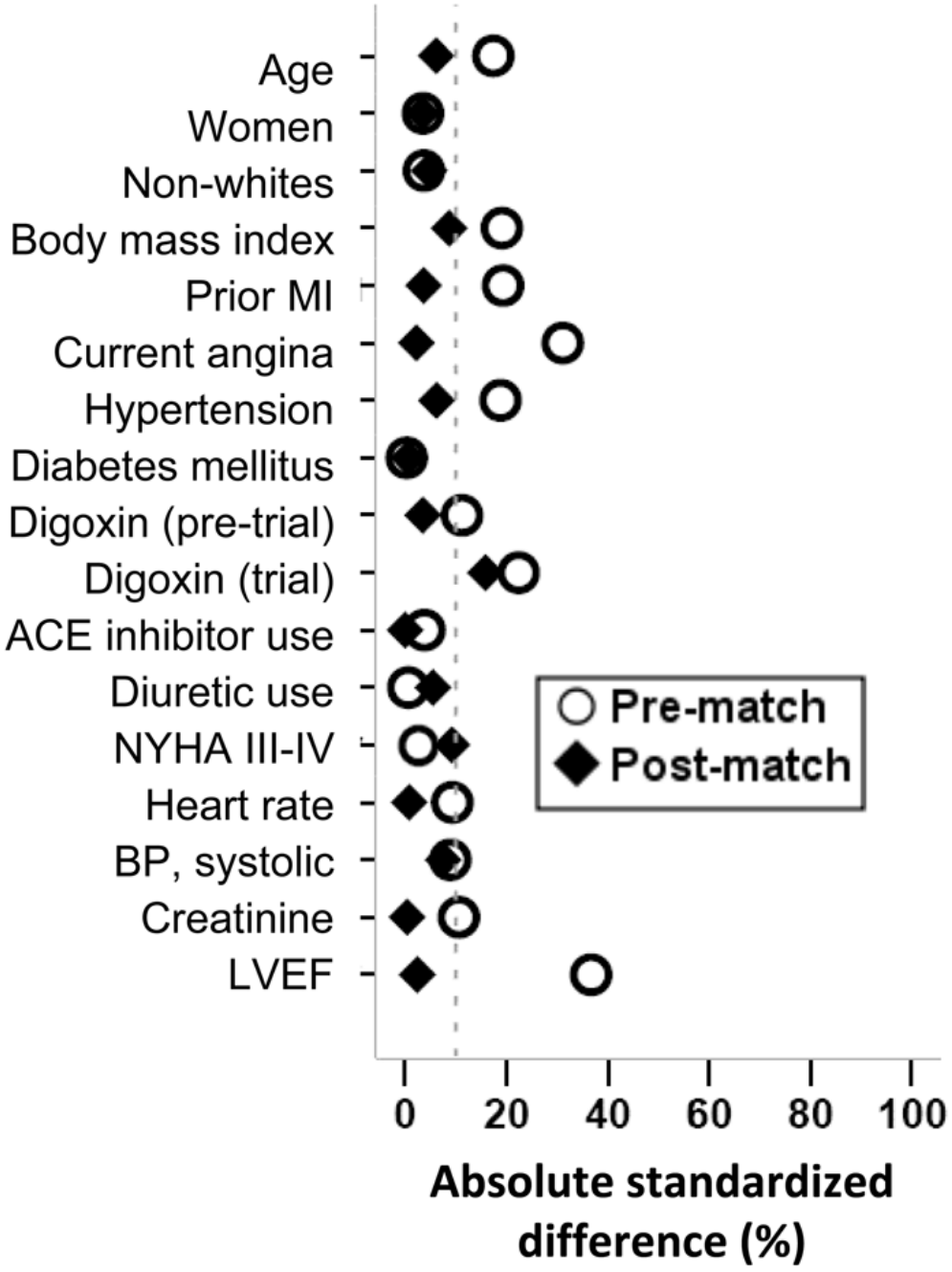

Figure 2.
Love plot for absolute standardized differences before and after propensity score matching comparing key covariate values for patients with and without coronary revascularization (MI= myocardial infarction; ACE=angiotensin-converting enzyme; NYHA=New York Heart Association; BP=blood pressure; LVEF=left ventricular ejection fraction)

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Figure 3a

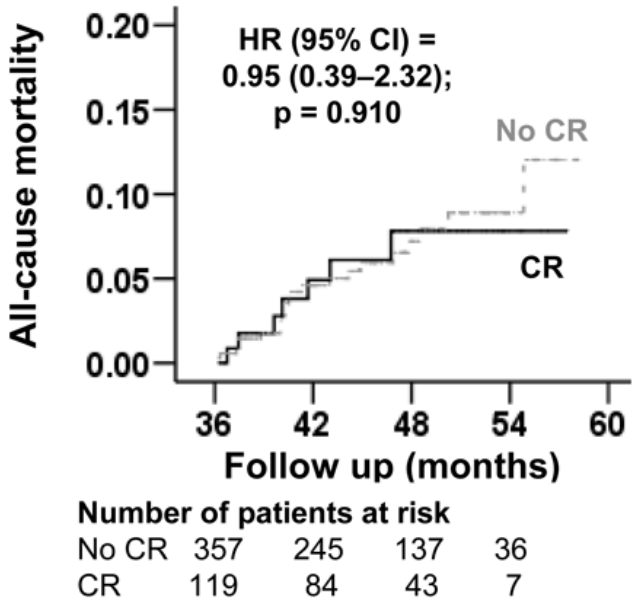

Figure 3b

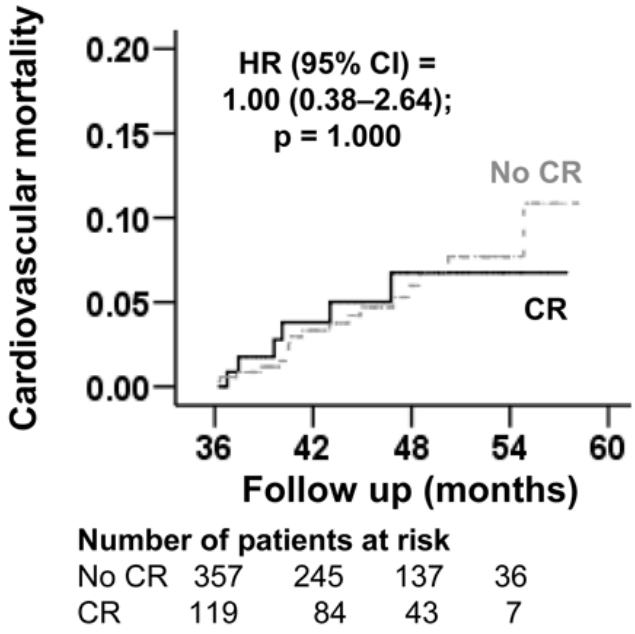

Figure 3.
Kaplan-Meier plots for mortality due to (a) all-causes and (b) cardiovascular causes (HR=hazard ratio; CI=confidence interval; CR=coronary revascularization)

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Table 1

Baseline patient characteristics by coronary revascularization during first three years, before and after propensity score matching

Variable	Before matching			After matching		
	No coronary revascularization (n=2853)	Coronary revascularization (n=120)	P value	No coronary revascularization (n=357)	Coronary revascularization (n=119)	P value
Age, years	64 (±10)	62 (±9)	0.074	62 (±10)	62 (±9)	0.571
Age ≥65 years	1465 (51%)	51 (43%)	0.057	156 (44%)	51 (43%)	0.873
Female	624 (22%)	28 (23%)	0.705	76 (21%)	27 (23%)	0.748
Non-white	232 (8%)	11 (9%)	0.685	38 (11%)	11 (9%)	0.663
Body mass index, kg/m^2	27 (±5)	28 (±4)	0.046	28 (±5)	28 (±4)	0.427
Ejection fraction, %	32 (±11)	36 (±12)	<0.0001	36 (±12)	36 (±11)	0.820
Ejection fraction > 45%	299 (11%)	19 (16%)	0.063	66 (19%)	18 (15%)	0.405
Comorbid conditions						
Prior myocardial infarction	2486 (87%)	96 (80%)	0.023	293 (82%)	96 (81%)	0.732
Current angina pectoris	904 (32%)	58 (48%)	<0.0001	167 (47%)	57 (48%)	0.832
Hypertension	1184 (42%)	61 (51%)	0.042	169 (47%)	60 (50%)	0.560
Diabetes mellitus	781 (27%)	33 (28%)	0.976	95 (27%)	32 (27%)	0.952
Chronic kidney disease	1276 (45%)	44 (37%)	0.082	135 (38%)	44 (37%)	0.870
Medications						
Digoxin (pre-trial use)	1177 (41%)	43 (36%)	0.237	135 (38%)	43 (36%)	0.743
Digoxin (trial use)	1396 (49%)	72 (60%)	0.018	185 (52%)	71 (60%)	0.137
ACE inhibitors	2667 (94%)	111 (93%)	0.671	330 (92%)	110 (92%)	1.000
Diuretics	2029 (71%)	85 (71%)	0.946	243 (68%)	84 (71%)	0.608
NYHA class III-IV	757 (27%)	31 (26%)	0.865	79 (22%)	31 (26%)	0.379
Heart rate, beats per minute	76 (±12)	75 (±13)	0.306	75 (±12)	75 (±13)	0.942
Systolic blood pressure, mm Hg	127 (±19)	128 (±19)	0.336	127 (±18)	128 (±19)	0.475
Serum creatinine, mg/dL	1.3 (±0.3)	1.2 (±0.3)	0.275	1.2 (±0.3)	1.2 (±0.3)	0.967

(ACE=angiotensin-converting enzyme; NYHA=New York Heart Association)

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Table 2

Mortality in chronic heart failure patients, before and after matching by propensity scores for coronary revascularization

	Rate, per 10,000 person-years (Events/total follow up years)		Absolute rate difference* (per 10,000 person-years)	Hazard ratio (95% confidence interval)	P value
	No coronary revascularization	Coronary revascularization			
Pre-match	N=2853	N=120			
All-cause	250 (273/10931)	153 (7/457)	−97	0.63 (0.30–1.33)	0.226
Cardiovascular	188 (206/10931)	131 (6/457)	−57	0.72 (0.32–1.62)	0.422
Worsening heart failure	95 (104/10931)	67 (3/457)	−28	0.71 (0.23–2.24)	0.557
Post-match	N=357	N=119			
All-cause	161 (22/1367)	154 (7/454)	−7	0.95 (0.39–2.32)	0.910
Cardiovascular	132 (18/1367)	132 (6/454)	0	1.00 (0.38–2.64)	1.000
Worsening heart failure	73 (10/1367)	66 (3/454)	−7	0.80 (0.21–3.06)	0.744

*Absolute differences in rates of events per 10,000 person-year of follow up were calculated by subtracting the event rates in the no coronary revascularization group from the event rates in the coronary revascularization group (before values were rounded)

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Table 3

All-cause mortality in matched chronic heart failure patients, by median left ventricular ejection fraction (LVEF) of 35%

	Rate, per 10,000 person-years (Events/total follow up years)		Absolute rate difference* (per 10,000 person-years)	Hazard ratio (95% confidence interval)	P value
	No coronary revascularization	Coronary revascularization			
LVEF ≤35% (range, 10% to 35%)	201 (14/697)	241 (5/207)	+ 40	1.34 (0.48–3.71)	0.578
LVEF >35% (range, 36% to 74%)	119 (8/670)	81 (2/247)	− 38	0.61 (0.13–2.87)	0.532

*Absolute differences in rates of events per 10,000 person-year of follow up were calculated by subtracting the event rates in the no coronary revascularization group from the event rates in the coronary revascularization group (before values were rounded)