

# Extent of Ejection Fraction Improvement After Revascularization Associated with Outcomes Among Patients with Ischemic Left Ventricular Dysfunction

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**Purpose:** Ejection fraction (EF) has been reported to be a major predictor of improved survival in patients with heart failure. However, it is largely unknown whether the extent of improvement in EF affects the subsequent risk of mortality. This study sought to investigate change in EF after revascularization and the implication of these changes on clinical outcomes among patients with ischemic left ventricular dysfunction.

**Patients and Methods:** We conducted a cohort study (No. ChiCTR2100044378) of patients with reduced EF ( $\leq 40\%$ ) who received revascularization and had EF reassessment by echocardiography 3 months after revascularization. Patients were categorized according to the absolute change in EF: 1) EF worsened group (absolute decrease in EF  $> 5\%$ ); 2) EF unchanged group (absolute change in EF  $-5\%$  to  $5\%$ ); 3) EF improved group (absolute increase in EF  $> 5\%$ ).

**Results:** Of 974 patients, 84 (8.6%) had EF worsened, 317 (32.5%) had EF unchanged and 573 (58.8%) had EF improved. The median follow-up time was 3.5 years, during which 143 patients died. For each 5-unit increments in EF, the risk of death decreased by 20% (hazard ratio, HR, per 5% increases, 0.80; 95% CI, 0.73–0.86;  $P < 0.001$ ). Compared with EF improvement group, patients with EF worsened (HR, 3.35; 95% CI, 2.07–5.42;  $P < 0.001$ ) and patients with EF unchanged (HR, 2.05; 95% CI, 1.40–3.01;  $P < 0.001$ ) had significantly higher risk of all-cause death.

**Conclusion:** Changes in EF were inversely associated with the risk of mortality. The extent of EF improvement after revascularization might be a potential factor which defines clinical outcomes.

**Keywords:** ejection fraction, left ventricular dysfunction, heart failure, revascularization

## Introduction

The cornerstone of treatment of patients with heart failure (HF) and reduced ejection fraction (EF) continues to be optimal medical therapy, which is associated with significant improvement in survival and quality of life.<sup>1,2</sup> Partial congestive HF patients with reduced EF have an opportunity for recovery of EF to a normal level after a period of appropriate therapy. Patients with recovered EF might have more favorable outcomes, including a lower risk of mortality,<sup>3–7</sup> HF hospitalization<sup>4,6,7</sup> and better quality of life<sup>8</sup> compared to patients with persistently reduced EF. EF has been reported to be a major predictor of improved survival in patients with HF and reduced EF.<sup>9–11</sup> For example, it has been demonstrated that after a period of appropriated therapy, patients with recovered EF (from EF  $< 35\%$  to EF  $> 40\%$ <sup>3</sup> or from EF  $< 45\%$  to EF  $\geq 45\%$ <sup>5</sup>) has a lower risk of long-term mortality compared to patients with unrecovered EF (EF remained  $\leq 40\%$  or  $< 45\%$ ). However, the association between EF improvement and survival benefit is not

consistent from literatures. One observational study indicated lack of improvement in EF after CABG was not associated with poorer outcome compared with that of patients with improved EF.<sup>12</sup> From the STICH (Surgical Treatment for Ischemic Heart Failure) trial, it was revealed that there was no relationship between changes in EF and subsequent death.<sup>13</sup> Whether the improvement in EF affects the subsequent risk of mortality needs to be further investigated.

Ischemic etiology is one of important risk factors for lack of EF improvement among patients with HF.<sup>3,6,14</sup> Revascularization including coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) may attenuate the ischemic state and reversing left ventricular (LV) remodeling,<sup>15–18</sup> thus improve the long-term outcomes of patients with LV dysfunction.<sup>19–22</sup> However, revascularization therapy among patients with LV dysfunction is not always effective. The extent and determinants of EF improvement after revascularization have not been well investigated.<sup>16,23–27</sup> The presence of myocardial viability might be one of correlates of EF improvement after coronary revascularization.<sup>23,28,29</sup> However, in different studies, about 12%<sup>29</sup> to 64%<sup>23</sup> patients remained EF unimproved after revascularization. We recently reported that diabetes mellitus (DM) associated with greater EF improvement after revascularization among patients with reduced EF.<sup>30</sup> The predictive factor associated with change in EF after revascularization needs to be further clarified.

Therefore, this study was performed to investigate 1) the extent of EF improvement following revascularization in patients with coronary artery disease (CAD) and preoperative EF  $\leq 40\%$ ; 2) the determinants of absolute change in EF after revascularization; 3) the association between absolute change in EF and clinical outcomes.

## Materials and Methods

### Patient Selection

This was a real-world cohort study that used data from Beijing Anzhen Hospital. The study was registered in Chinese Clinical Trial Registry (No. ChiCTR2100044378). The study protocol was approved by the hospital's ethics committee.

CAD patients with reduced EF ( $\leq 40\%$ ) who underwent CABG or PCI with a drug-eluting stent between January 2005 and December 2014, and with repeated EF measurements during follow-up were enrolled. Patients were excluded if they had concomitant noncoronary surgery, were diagnosed as ST-segment elevation myocardial infarction and had only one record of EF follow-up reassessment within 3 months after revascularization. The final study sample included patients who had EF reassessment by echocardiography 3 months after revascularization. Patients were then categorized according to the absolute change in EF: 1) EF worsened group (absolute decrease in EF  $> 5\%$ ); 2) EF unchanged group (absolute change in EF  $-5\%$  to  $5\%$ ); 3) EF improved group (absolute increase in EF  $> 5\%$ ).<sup>31</sup>

### Data Collection and Definitions

Baseline demographic, clinical, laboratory, angiographic parameters, and medical therapy for the study patients were ascertained from Beijing Anzhen Hospital medical records. Baseline EF was captured within 30 days before PCI or CABG. Follow-up EF values were defined as the first EF measurement 3 months<sup>32</sup> after revascularization assessed in Beijing Anzhen Hospital. Complete revascularization was defined as successful PCI (residual stenosis of  $< 30\%$ ) of all angiographically significant lesions ( $\geq 70\%$  diameter stenosis) in 3 coronary arteries and their major branches. A staged procedure within 90 days after discharge was acceptable. For CABG, grafting of every primary coronary artery with  $\geq 70\%$  diameter stenosis was accepted as complete revascularization.

Outcome data were obtained from medical records at Beijing Anzhen Hospital and through telephone follow-up. Death was regarded as cardiovascular in origin unless obvious non-cardiovascular causes could be identified. Any death during hospitalization for repeat coronary revascularization was regarded as cardiovascular death. The follow-up time for patients started at the time of the first available EF measurement.<sup>31,33,34</sup>

### Statistical Analysis

Categorical variables were summarized as frequencies with percentages and continuous variables were expressed as mean  $\pm$  SD. Baseline characteristics were compared among the EF worsened, EF unchanged and EF improved groups by using Chi-Square test for categorical variables and one-way ANOVA for continuous variables. Multinomial logistic

regression was used to identify independent correlates of patients in the three EF categories as defined above: worsened, unchanged or improved EF. Outcome with improved EF was set as the reference category to calculate the relative risk ratios (RRR) of variables to have worsened EF or unchanged EF. Variables of demographics and history, preoperative echocardiography values, angiography and medical therapies as well as clinical chemistry were included in the analysis. Cumulative incidences were estimated by the Kaplan–Meier method and compared by Log rank test. The risks of outcomes were analyzed with a Cox proportional hazards regression model. The proportional hazards assumption was tested for individual covariates and globally on the basis of Schoenfeld residuals. All statistical analyses were based on 2-tailed tests.  $P < 0.05$  was considered statistically significant. Statistical analyses were performed with Stata version 14.0 (StataCorp).

## Results

### Patients Characteristics

Among 1816 initially identified patients, 78 patients who died within 3 months after revascularization, 764 patients were further excluded because EF was not evaluated 3 months after revascularization. Finally, 974 patients who had an initial EF  $\leq 40\%$  and had echocardiography reassessment 3 months after revascularization were enrolled in this study. The differences of the characteristics at baseline between enrolled and excluded patients are indicated in [Supplemental Table 1](#).

The average age at baseline was  $64.7 \pm 10.9$  years ([Table 1](#)). Men comprised 83.5% of all subjects. Five hundred and fifty-six (57.1%) received PCI and 418 (42.9%) underwent CABG. After revascularization, 84 (8.6%) had EF worsened, 317 (32.5%) had EF unchanged and 573 (58.8%) had EF improved ([Figure 1A](#)). Age at baseline and sex distribution were similar among three groups ([Table 1](#)). The EF improved group had a significantly highest prevalence of DM ( $P = 0.008$ ) and lowest prevalence of myocardial infarction (MI) ( $P = 0.001$ ) compared with other two groups. The anatomic severity of coronary artery disease was similar among three groups. There was no significant difference in the proportions undergoing revascularization by PCI or CABG, and the groups had similar percentages of complete

**Table 1** Patient Characteristics at Baseline<sup>a</sup>

Characteristic	All Patients (N=974)	Worsened (n=84)	Unchanged (n=317)	Improved (n=573)	P value
<b>Demographics and History</b>					
Age, y	64.7 (10.9)	66.3 (9.9)	64.2 (10.8)	64.8 (11.0)	0.252
Men	813 (83.5)	73 (86.9)	265 (83.6)	475 (82.9)	0.651
Weight, kg	72.0 (11.1)	71.9 (12.2)	72.7 (10.7)	71.7 (11.1)	0.390
Current smoker	348 (35.7)	31 (36.9)	111 (35.0)	206 (36.0)	0.936
Hypertension	521 (53.5)	40 (47.6)	164 (51.7)	317 (55.3)	0.312
eGFR, mL/min/1.73m <sup>2</sup>	85.0 (24.3)	83.2 (24.9)	84.7 (24.9)	85.4 (23.8)	0.729
DM	333 (34.2)	19 (22.6)	98 (30.9)	216 (37.7)	0.008
Cerebral vascular disease	70 (7.2)	2 (2.4)	31 (9.8)	37 (6.5)	0.038
Atrial fibrillation	45 (4.6)	6 (7.1)	14 (4.4)	25 (4.4)	0.515
History of MI	452 (46.4)	48 (57.1)	166 (52.4)	238 (41.5)	0.001
History of PCI	176 (18.1)	18 (21.4)	60 (20.5)	93 (16.2)	0.200

(Continued)

Table 1 (Continued).

Characteristic	All Patients (N=974)	Worsened (n=84)	Unchanged (n=317)	Improved (n=573)	P value
<b>Angiography and therapy</b>					
Multi-vessel disease	769 (79.0)	69 (82.1)	244 (77.0)	456 (79.6)	0.497
Left main disease	58 (6.0)	6 (7.1)	17 (5.4)	35 (6.1)	0.805
PCI	556 (57.1)	50 (59.5)	176 (55.5)	330 (57.6)	0.748
CABG	418 (42.9)	34 (40.5)	141 (44.5)	243 (42.4)	0.748
Complete revascularization	527 (54.1)	47 (56.0)	179 (56.5)	301 (52.5)	0.497
ACEi/ARB/ARNI	495 (50.8)	46 (54.8)	155 (48.9)	294 (51.3)	0.593
β-Blocker	785 (80.6)	67 (79.8)	250 (78.9)	468 (81.7)	0.585
MRA	176 (18.1)	18 (21.4)	49 (15.5)	109 (19.2)	0.293
Aspirin	929 (95.4)	82 (97.6)	307 (96.9)	540 (94.2)	0.123
Clopidogrel/Ticagrelor	716 (73.5)	59 (70.2)	218 (68.8)	439 (76.6)	0.031
Loop diuretics	289 (29.7)	29 (34.5)	95 (30.0)	165 (28.8)	0.557
Digoxin	154 (15.8)	13 (15.5)	56 (17.7)	85 (14.8)	0.539

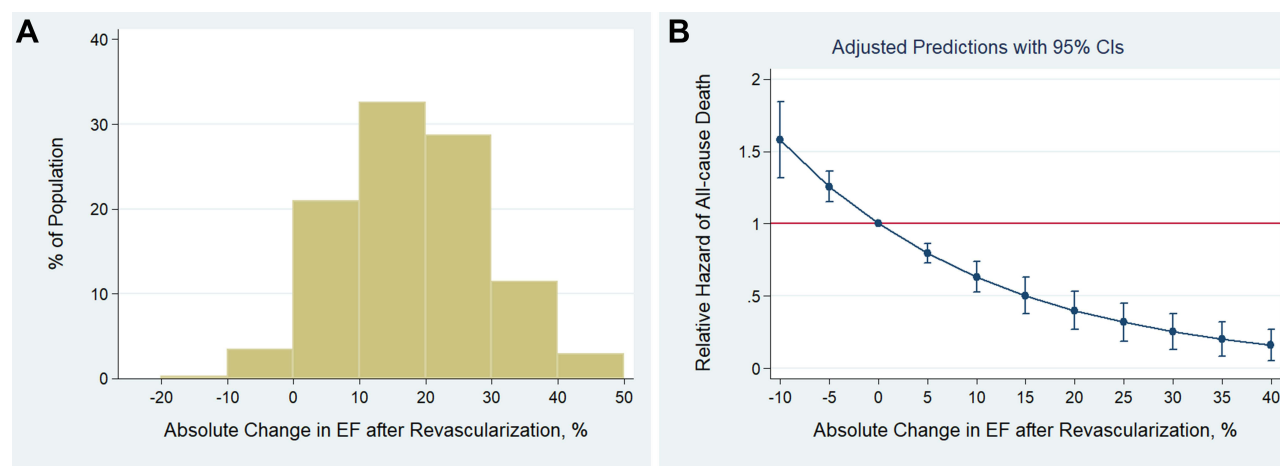
Note: <sup>a</sup>Values are mean (SD) or No. of patients (%).

**Abbreviations:** ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CABG, coronary artery bypass grafting; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; MRA, mineralocorticoid receptor antagonist.

revascularization. The EF improved group had a significantly highest proportion of use of clopidogrel or ticagrelor compared with other two groups ( $P=0.031$ ).

## Echocardiographic Characteristics

In the EF improved group, the preoperative EF was lowest compared with other two groups ( $P<0.001$ ) (Table 2). Mean (SD) EF improved significantly, from 35.8% (4.7%) to 52.0% (8.6%), in the EF improved group ( $P<0.001$ ). In



**Figure 1** Predictive role of EF improvement for survival. (A) Absolute change in EF after revascularization; (B) The predicted probabilities of all-cause death at different values of EF.

**Abbreviations:** EF, ejection fraction; CI, confidence interval.

**Table 2** Echocardiographic Characteristics <sup>a</sup>

Characteristic	All Patients (N=974)	Worsened (n=84)	Unchanged (n=317)	Improved (n=573)	P value
<b>Preoperative</b>					
EF, %	36.3 (4.3)	37.3 (2.8)	36.8 (3.7)	35.8 (4.7)	< 0.001
LVEDD, mm	58.5 (7.4)	61.7 (7.3)	59.8 (7.5)	57.3 (7.1)	< 0.001
LVESD, mm	46.0 (8.2)	49.3 (7.7)	47.5 (8.3)	44.6 (8.0)	< 0.001
MR (moderate or severe)	166 (17.0)	13 (15.5)	58 (18.3)	95 (16.6)	0.746
<b>Postoperative</b>					
EF, %	45.2 (11.2)	27.5 (4.1)	37.6 (4.7)	52.0 (8.6)	< 0.001
LVEDD, mm	57.5 (8.5)	66.1 (8.8)	60.7 (7.9)	54.5 (7.2)	< 0.001
LVESD, mm	43.2 (9.9)	54.9 (10.0)	47.5 (8.5)	39.2 (8.1)	< 0.001
MR (moderate or severe)	149 (15.3)	33 (39.3)	61 (19.2)	55 (9.6)	< 0.001
<b>Change of EF, %</b>	8.9 (11.0)	− 9.9 (3.8)	0.7 (3.0)	16.2 (7.5)	< 0.001
<b>Change of LVEDD, mm</b>	−0.9 (7.2)	4.4 (6.8)	0.8 (7.0)	−2.7 (6.7)	< 0.001
<b>Change of LVESD, mm</b>	−2.5 (8.6)	5.6 (7.5)	0.2 (7.7)	−5.3 (7.9)	< 0.001

**Note:** <sup>a</sup>Values are mean (SD) or No. of patients (%).

**Abbreviations:** EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation.

the EF unchanged group, the change in EF was small but statistically significant, from 36.8% (3.7%) to 37.6% (4.7%) ( $P<0.001$ ). In contrast, EF decreased significantly, from 37.3% (2.8%) to 27.5% (4.1%) in the EF worsened group ( $P<0.001$ ). Both preoperative and postoperative LV end-diastolic diameter (LVEDD) ( $P<0.001$ ) as well as end-systolic diameter (LVESD) ( $P<0.001$ ) were smallest in EF improved group compared with other two groups. With the most reduction of LV size, the severity of mitral regurgitation was lowest in EF improved group ( $P<0.001$ ). The mean duration between the preoperative and follow-up EF measurements in three groups was comparable (worsened group:  $5.0\pm3.6$  months; unchanged group:  $6.1\pm2.0$  months; improved group:  $5.9\pm2.6$  months,  $P=0.203$ ).

## Predictors of Change in EF

Compared to patients with EF improved, patients who had history of DM had less likely to have worsened EF (relative risk ratios [RRR], 0.48; 95% confidence interval [CI], 0.28–0.83;  $P = 0.008$ ) or unchanged EF (RRR, 0.74; 95% CI, 0.55–0.99;  $P = 0.043$ ) (Table 3). Compared to patients with EF improved, patients who had history of MI had higher likely to have worsened EF (RRR, 1.88; 95% CI, 1.18–2.98;  $P = 0.008$ ) or unchanged EF (RRR, 1.55; 95% CI, 1.17–2.04;  $P = 0.002$ ). Patients with higher preoperative EF had greater likely of being in the EF worsened group (RRR per 1% increase in EF, 1.10; 95% CI, 1.03–1.17;  $P = 0.005$ ) or EF unchanged group (RRR per 1% increase in EF, 1.06; 95% CI, 1.02–1.09;  $P = 0.002$ ). Severity of LV remodeling as indicated by LVESD and LVEDD also significantly associated with change in EF. Neither anatomic severity of coronary vessels (as indicated by multivessel disease and left main disease) nor extent of revascularization (complete vs incomplete) was an independent correlate of change in EF. Compared to patients with EF improved, patients who had clopidogrel or ticagrelor had less likely to have unchanged EF (RRR, 0.67; 95% CI, 0.49–0.91;  $P = 0.011$ ).

**Table 3** Baseline Factors Associated with Worsened EF or Unchanged EF in Comparison with Improved EF

Variables	Worsened		Unchanged	
	RRR (95% CI)	P value	RRR (95% CI)	P value
Age	1.01(0.99–1.04)	0.233	0.99(0.98–1.01)	0.381
Male sex	1.37(0.70–2.68)	0.358	1.05(0.73–1.52)	0.790
Weight	1.00(0.98–1.02)	0.826	1.01(1.00–1.02)	0.171
Current smoking	1.04(0.65–1.68)	0.865	0.96(0.72–1.28)	0.780
Hypertension	0.73(0.46–1.16)	0.187	0.87(0.66–1.14)	0.304
DM	0.48(0.28–0.83)	0.008	0.74(0.55–0.99)	0.043
eGFR	1.00(0.99–1.01)	0.452	1.00(0.99–1.00)	0.680
Cerebral vascular disease	0.35(0.08–1.49)	0.157	1.57(0.95–2.58)	0.076
History of MI	1.88(1.18–2.98)	0.008	1.55(1.17–2.04)	0.002
Atrial fibrillation	1.69(0.67–4.24)	0.267	1.01(0.52–1.98)	0.970
History of PCI	1.41(0.80–2.48)	0.237	1.33(0.94–1.89)	0.111
Preoperative EF	1.10(1.03–1.17)	0.005	1.06(1.02–1.09)	0.002
Preoperative LVEDD	1.09(1.05–1.12)	<0.001	1.05(1.03–1.07)	<0.001
Preoperative LVESD	1.08(1.04–1.11)	<0.001	1.04(1.03–1.06)	<0.001
Preoperative MR (moderate or severe)	0.92(0.49–1.73)	0.799	1.13(0.79–1.61)	0.516
Multivessel disease	1.18(0.65–2.14)	0.585	0.86(0.62–1.19)	0.363
Left main disease	1.18(0.48–2.90)	0.715	0.87(0.48–1.58)	0.650
PCI*	1.08(0.68–1.73)	0.738	0.92(0.70–1.21)	0.550
Complete revascularization	1.15(0.72–1.82)	0.558	1.17(0.89–1.54)	0.259
ACEi/ARB/ARNI	1.15(0.73–1.82)	0.554	0.91(0.69–1.19)	0.491
Beta-blocker	0.88(0.50–1.57)	0.554	0.84(0.59–1.18)	0.309
MRA	1.16(0.66–2.04)	0.602	0.78(0.54–1.13)	0.183
Aspirin	2.51(0.59–10.64)	0.213	1.88(0.91–3.86)	0.127
Clopidogrel/Ticagrelor	0.72(0.43–1.20)	0.204	0.67(0.49–0.91)	0.011
Loop diuretics	1.30(0.80–2.12)	0.283	1.06(0.78–1.43)	0.713
Digoxin	1.05(0.56–1.98)	0.877	1.23(0.85–1.78)	0.268

**Note:** \*CABG was set as reference to PCI.

**Abbreviations:** ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation. MRA, mineralocorticoid receptor antagonist; RRR, relative risk ratios.

## Outcomes

The median follow-up time was 3.5 years, during which 143 patients died and 117 patients were cardiac death. Greater extent of EF improvement after revascularization was significantly associated with lower risk of all-cause death. For each 5-unit increments in EF, the risk of death decreased by 20% (hazard ratio, HR, per 5% increases, 0.80; 95% CI, 0.73–

**Table 4** Risk of Outcomes

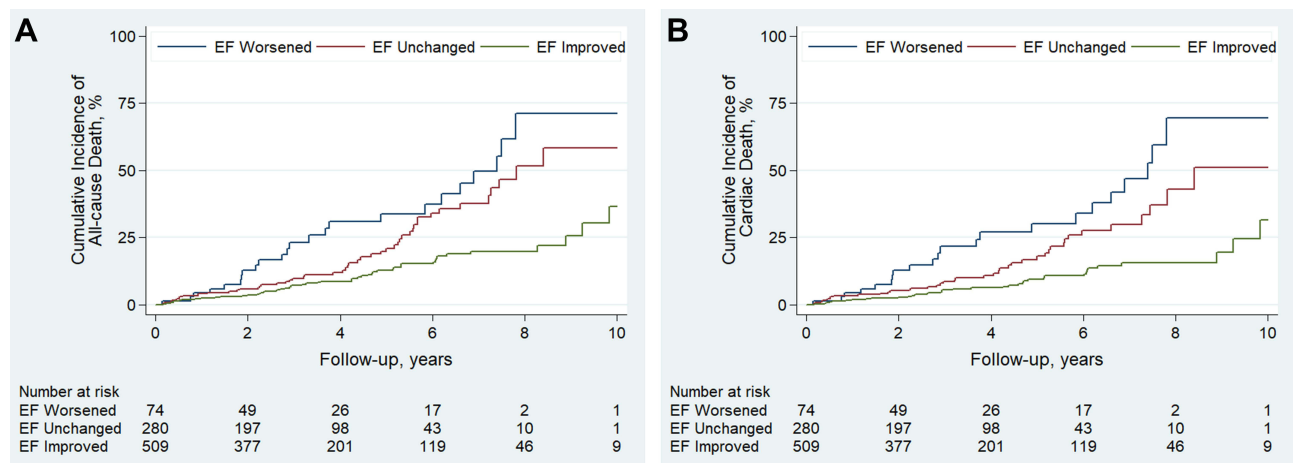
Outcomes	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
<b>All-cause Death</b>				
EF worsened	3.35 (2.07–5.42)	<0.001	3.07 (1.90–4.98)	<0.001
EF unchanged	2.05 (1.40–3.01)	<0.001	2.03 (1.38–2.98)	<0.001
EF improved	Reference		Reference	
<b>Cardiac Death</b>				
EF worsened	4.12 (2.45–6.93)	<0.001	3.79 (2.25–6.39)	<0.001
EF unchanged	2.23 (1.44–3.45)	<0.001	2.20 (1.43–3.41)	<0.001
EF improved	Reference		Reference	

**Note:** HR was adjusted by age and sex.

**Abbreviations:** EF, ejection fraction; HR, hazard ratio; CI, confidence interval.

0.86;  $P<0.001$ ) (Figure 1B). Compared with EF improvement group, patients with EF worsened had significantly higher risk of all-cause death (HR, 3.35; 95% CI, 2.07–5.42;  $P<0.001$ ) and cardiovascular death (HR, 4.12; 95% CI, 2.45–6.93;  $P<0.001$ ) (Table 4, Figure 2A and B). Similarly, compared with EF improvement group, patients with EF unchanged had significantly higher risk of all-cause death (HR, 2.05; 95% CI, 1.40–3.01;  $P<0.001$ ) and cardiovascular death (HR, 2.23; 95% CI, 1.44–3.45;  $P<0.001$ ). Furthermore, patients with EF worsened had significantly higher risk of all-cause death (HR, 1.63; 95% CI, 1.00–2.66;  $P=0.048$ ) and cardiovascular death (HR, 1.85; 95% CI, 1.10–3.11;  $P=0.020$ ) compared with EF unchanged group. Those findings persisted in adjusted model.

In addition, there were 123 (14.6%) patients had repeated revascularization by either PCI or CABG during follow-up. The EF improved group (17.1%) had a significantly highest proportion of repeated revascularization compared with EF unchanged group (12.2%) and EF worsened group (6.9%) ( $P=0.030$ ).



**Figure 2** The association between EF improvement and survival after revascularization. (A) Kaplan–Meier curves estimating incidence of all-cause death; (B) Kaplan–Meier curves estimating incidence of cardiac death.

**Abbreviations:** EF Worsened, absolute decrease in EF >5%; EF Unchanged, absolute change in EF –5% to 5%; EF Improved, absolute increase in EF >5%. EF, ejection fraction.



## Discussion

Available data suggest that HF might not always be a progressive disease. Several therapies including guideline-directed medical therapy,<sup>14</sup> cardiac resynchronization therapy<sup>31</sup> and revascularization<sup>17,18,23</sup> might improve EF for patients with LV dysfunction. Ischemic etiology is one of important risk factors for lack of EF improvement among patients with HF.<sup>3,6,14</sup> However, the extent of EF improvement after revascularization has not been well-established. A study enrolled 47 CAD patients with initial EF <50% who underwent coronary revascularization demonstrated that 42.6% had EF improved  $\geq 10\%$ .<sup>17</sup> In the current study, after revascularization in patients with reduced EF ( $\leq 40\%$ ), about 10% remained follow-up EF worsened (absolute decrease in EF  $> 5\%$ ), about 30% had follow-up EF unchanged (absolute change in EF  $-5\%$  to  $5\%$ ) and about 60% had EF improved (absolute increase in EF  $> 5\%$ ).

In the current study, DM, no prior MI, lower preoperative EF and less LV enlargement were identified as factors associated with greater EF improvement after revascularization. The mismatch between blood supply and cardiac metabolic requirements in ischemic heart was more severe in diabetic compared with non-diabetic myocardium. Thus, revascularization might have greater effect on LV remodeling in patients with DM.<sup>30</sup> Patients with history of MI might have less viable myocardium which resulted in less opportunity to have EF improvement following revascularization. It has been reported that preoperative EF less than 27% was one of three prognostic factors which associated with greater survival benefit from CABG.<sup>27</sup> Lower preoperative EF and less LV enlargement might represent a critical cardiac stage that might benefit more from revascularization. In the current study, no guideline-directed medical therapy for HF was found to be predictive of EF improvement. One potential reason was that the effect of medication was attenuated by revascularization. After revascularization, only 200 (20.5%) had a follow-up EF  $\leq 35\%$ . Furthermore, although complete revascularization did not associate with EF improvement, the EF improvement group had highest proportion of repeated revascularization during follow-up. Considering the course of the disease, a possibility can be that EF initially improves after successful revascularization but subsequently worsens, and this feature is suspicious of recurrence of significant coronary stenosis. The association between repeat revascularization and EF improvement needs to be further investigated. In this study that extent of EF improvement was firstly identified, to our knowledge, as a factor associated with clinical outcomes after revascularization among CAD patients with reduced EF. For each 5-U increments in EF, the risk of death decreased by 20%. Compared with EF improvement group, patients with EF worsened or unchanged had significantly higher risk of all-cause death and cardiovascular death. Whether extent of EF improvement has clinical implication for ICD implantation-decision making needs to be further investigation.

All patients in the current study underwent isolated CABG. Moderate to severe mitral regurgitation were not treated simultaneously. However, mitral regurgitation might have a great impact on cardiac function recovery and outcomes.<sup>35</sup> This needs to be further investigated.

Since the present study was designed as a single-center and observational study, there is a possibility of patients selection bias. Since institutions and specific methods for measuring EF vary, only EF measurements by echocardiography in Anzhen Hospital were adopted. This restriction improved the accuracy of the EF measurements but increased the number of excluded patients. Of 1948 person-time EF measurements, 948 (97.3%) EF measurements before revascularization and 898 (92.2%) EF measurements during follow-up were by Simpson. It would be better to have myocardial viability test before PCI/CABG, nevertheless, it was sometimes difficult to perform for HF patients. There was little data of myocardial viability in current study cohort. Minimal patients ( $n = 11$ ) had ICD therapy during the follow-up. This might overestimate the mortality especially for patients with EF worsened according to the current therapeutic strategy.

## Conclusion

After revascularization in patients with reduced EF ( $\leq 40\%$ ), about 10% remained follow-up EF worsened, about 30% had EF unchanged and about 60% had EF improved. Patients with EF improvement were more likely to have DM, have no prior MI, have lower preoperative EF and have less LV enlargement. Changes in EF were inversely associated with the risk of mortality. The extent of EF improvement after revascularization might be a potential factor which defines clinical outcomes.



## Data Sharing Statement

The datasets are available from the corresponding author (Jinghua Liu) upon reasonable request.

## Ethical Approval and Informed Consent

The Ethics Committee of the Beijing Anzhen Hospital approved the study. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki. Because this was a retrospective cohort study and waiver of informed consent will not adversely affect the rights and welfare of the subjects, written informed consent from the patients was waived.

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## Disclosure

All authors declare that they have no conflicts of interest in this work.

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