Accepted Manuscript

Implications of Coronary Artery Disease in Heart Failure with preserved Ejection Fraction

Seok-Jae Hwang, MD, PhD Vojtech Melenovsky, MD, PhD Barry A. Borlaug, MD

PII: S0735-1097(14)02000-2

DOI: 10.1016/j.jacc.2014.03.034

Reference: JAC 20055

To appear in: *Journal of the American College of Cardiology*

Received Date: 26 November 2013

Revised Date: 5 February 2014

Accepted Date: 4 March 2014

Please cite this article as: Hwang S-J, Melenovsky V, Borlaug BA, Implications of Coronary Artery Disease in Heart Failure with preserved Ejection Fraction, *Journal of the American College of Cardiology* (2014), doi: 10.1016/j.jacc.2014.03.034.

Implications of Coronary Artery Disease in Heart Failure with preserved Ejection Fraction

Seok-Jae Hwang, MD, PhD,[1,2] Vojtech Melenovsky MD, PhD,[1,3]
Barry A. Borlaug, MD[1]

[1]*Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic Rochester, Rochester, MN, USA* [2]*Division of Cardiology, Department of Internal Medicine, Gyeongsang National University Hospital, Jinju, Korea*
[3]*Department of Cardiology, Institute of Clinical and Experimental Medicine - IKEM, Prague, Czech Republic*

Short title: Coronary artery disease in HFpEF

Disclosures: None.

Acknowledgements: The authors thank Dr. Robert L. Frye for his very helpful critique.

Address for correspondence:
Barry A. Borlaug, MD
Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic Rochester
Mayo Clinic and Foundation, 200 First Street SW, Rochester, Minnesota 55905
E-mail: borlaug.barry@mayo.edu
Tel: +1 507 284 4442, Fax: +1 507 266 0228

Abstract

Objectives: Investigate the characteristics, evaluation, prognostic impact and treatment of coronary artery disease (CAD) in heart failure and preserved ejection fraction (HFpEF).

Background: CAD is common in patients with HFpEF, but it remains unclear how CAD should be categorized, evaluated for, and treated in HFpEF.

Methods: Clinical, hemodynamic, echocardiographic, treatment and outcome characteristics were examined in consecutive patients with previous HFpEF hospitalization undergoing coronary angiography. **Results:** Of 376 HFpEF patients examined, 255 (68%) had angiographically-proven CAD. Compared to HFpEF patients without CAD, patients with CAD were more likely to be male, display CAD risk factors and be treated with anti-ischemic medications. However, symptoms of angina and heart failure were similar in patients with and without CAD, as were measures of cardiovascular structure, function and hemodynamics. Compared to patients without CAD, HFpEF patients with CAD displayed greater deterioration in EF and increased mortality, independent of other predictors (HR 1.71, CI 1.03, 2.98, p=0.04). Complete revascularization was associated with less deterioration in EF and lower mortality compared to patients that were not completely revascularized, independent of other predictors (HR 0.56, CI 0.33, 0.93, p=0.03).

Conclusions: CAD is common in patients with HFpEF and is associated with increased mortality and greater deterioration in ventricular function. Revascularization may be associated with preservation of cardiac function and improved outcomes in patients with CAD. Given the paucity of effective treatments for HFpEF, prospective trials are urgently needed to determine the optimal evaluation and management of CAD in HFpEF.

Key words: Heart failure, Heart failure with preserved ejection fraction, Diastolic heart failure, Coronary artery disease, Revascularization

Introduction

Approximately half of patients with heart failure (HF) have a preserved ejection fraction (HFpEF).(1) In contrast to HF with reduced EF (HFrEF), there is no proven effective treatment for HFpEF.(2) Accordingly, current studies and guidelines endorse treatment of commonly-observed comorbidities.(3-5) It has also recently been proposed that HFpEF represents a heterogenous group of diseases, which may accordingly respond differently to treatments.(6) This heterogeneity might be minimized by sub-grouping HFpEF patients according to the presence or absence of key comorbidities. Coronary artery disease (CAD) qualifies as a viable candidate for sub-classification because it is common in HFpEF,(1) and because it plausibly explains the pathophysiology, as myocardial ischemia causes diastolic and systolic dysfunction,(7-11) which are both common in patients with HFpEF.(2,12)

However, because CAD and HFpEF are associated with common risk factors such as aging and hypertension, it is also possible that CAD and HFpEF simply coexist in many patients without any mechanistic relationship. As such, it remains unclear whether HFpEF patients with CAD should be diagnostically grouped separately from those without CAD, how and when to evaluate for CAD in patients presenting with HFpEF, and how to manage CAD once it is identified, at least in the absence of an acute coronary syndrome.

As a first step toward better understanding of the implications of CAD in patients with HFpEF, we investigated the clinical, structural, functional, hemodynamic and outcome characteristics in a rigorously-phenotyped group of patients with unequivocal, previously-hospitalized HFpEF and angiographically-verified CAD as compared to patients without significant CAD. To provide further insight into therapeutics, we then examined the associations of revascularization with survival and ventricular function in HFpEF patients with CAD.

Methods

Study population

All patients dismissed from St. Mary's Hospital at the Mayo Clinic with the primary diagnosis of heart failure (ICD-9 code 428) between January 1, 2004 and December 31, 2012 were identified. From this group, individuals who had undergone echocardiography were identified and crossed with the Mayo catheterization laboratory database to identify all patients with coronary angiography within 1 year of hospital dismissal and echocardiography within 6 months prior to angiography. Data from the first angiogram were used for patients with >1 study. HFpEF was defined by clinical diagnosis of decompensated HF according to the admitting physician and LVEF≥50% within 6 months of hospitalization. In addition to HF hospitalization, all HF patients had to fulfill the Framingham criteria and/or demonstrate elevated left heart filling pressures at catheterization (pulmonary capillary wedge pressure, PCWP or LV end diastolic pressure, LVEDP; >15mmHg at rest or ≥25mmHg with exercise) in studies performed specifically in the evaluation of dyspnea.(13) Patients with significant valvular disease (>moderate left-sided regurgitation or >mild stenosis), severe pulmonary disease, acute coronary syndrome (defined by ≥2 of the following: increasing cardiac enzymes, ischemic electrocardiographic changes, typical chest pain), primary renal, hepatic or pulmonary vascular disease, high output heart failure, chest radiation, severe anemia (≤9.0 gm/dl), constrictive pericarditis, and infiltrative, restrictive, or hypertrophic cardiomyopathies were excluded.

Study design

HFpEF patients were divided into those with and without significant anatomic coronary artery disease (CAD), defined by angiographic stenosis >50% in one or more epicardial coronary arteries with visual reference lumen diameter ≥2.5 mm, prior infarction, or any prior

revascularization. All angiograms were interpreted by a single experienced interventional cardiologist (SJH). Syntax score was calculated as previously described.(14,15) Clinical, hemodynamic, stress testing and echocardiographic data were abstracted from detailed chart review and compared in HFpEF patients with and without CAD. Ischemia on noninvasive stress testing was defined as ST segment depression >2mm, new regional wall motion abnormalities on echocardiography or reversible perfusion defects on myocardial nuclear imaging.

Complete revascularization was defined as treatment of all >50% coronary stenoses in epicardial vessels by percutaneous intervention and/or coronary bypass grafting. Incomplete revascularization was defined as intervention on ≥1 significant stenoses, but with residual lesion(s) of >50% stenosis. The impact of the presence or absence of CAD and the impact of revascularization in HFpEF patients with CAD was assessed from follow up echocardiography performed no sooner than 6 months after angiography, and by assessing vital status ascertained through chart review and use of the Social Security Death Index.

Assessment of Cardiovascular Structure, Function and Hemodynamics

Two-dimensional and Doppler echocardiography was performed to assess LV morphology, systolic and diastolic function according to ASE guidelines by experienced sonographers and echo-cardiologists.(16) Right and left heart catheterization was performed in the supine position via the jugular or femoral veins and femoral or radial arteries using fluid filled catheters.(13) Hemodynamic parameters including right and left heart filling pressures, pulmonary artery pressures, cardiac output, pulmonary and systemic arterial resistance, compliance and elastance were determined as described previously.(17)

Statistical analysis

Continuous variables were reported as mean ± standard deviation or median (IQR) and compared by ANOVA, paired t test or Mann-Whitney U test. Categorical variables were expressed as number (%) and were compared by Chi-square or Fisher's Exact test. Regression was used to adjust for potential confounding, where the dependent variable was the normally distributed continuous (linear least squares regression) or categorical (logistic regression) outcome variable of interest. The impact of the presence of CAD on survival, and impact of revascularization in patients with CAD was assessed by the Kaplan-Meier method with Cox regression analysis to adjust for other univariate predictors of death. Univariate predictors were selected based upon previously published studies showing association with increased mortality in HFpEF(18,19) and sufficient availability of data in the sample population. In the primary treatment analysis "revascularization" was considered as patients receiving complete revascularization, while patients receiving no revascularization and "incomplete revascularization" were included together in the comparator group.(20)

Results

Over the 8 year study period, there were 4331 unique patients that had been admitted with the primary diagnosis of heart failure who had undergone both echocardiography and angiography within the protocol-specified timelines relative to hospitalization (Figure 1). From this sample of HF patients, 52.6% had reduced EF and 47.4% had preserved EF. After exclusion of preserved EF patients with acute coronary syndrome, primary valvular heart disease, cardiomyopathies and other exclusion criteria, 376 patients with HFpEF were identified constituting the study population. Of this group, 255 (68%) had CAD and 121 (32%) did not have CAD (Table 1). Of HFpEF patients with CAD, 3-vessel disease was present in 36%, 2-

vessel in 36%, 1-vessel in 28%. Mean Syntax score in patients with CAD was 19±14. Indications for angiography are provided in Supplemental Table 1.

Clinical characteristics in HFpEF patients with and without CAD

Compared to HFpEF patients without CAD, patients with CAD were slightly older, more likely to be male, more likely to display typical CAD risk factors including hypertension, diabetes, dyslipidemia, and smoking history, and more likely to be treated with anti-ischemic medicines including beta blockers, nitrates, statins and aspirin (Table 1). However, none of these parameters effectively distinguished CAD from no CAD (all area under the receiver operating curve<0.7, Supplementary Table 2). There were no differences between HFpEF patients with or without CAD in body mass, atrial fibrillation, or use of other HF therapies including inhibitors of the renin-angiotensin-aldosterone axis and diuretics.

Patients with and without CAD reported severe HF symptoms (>50% NYHA class III or IV), with no group differences (Table 1). Intriguingly, the proportion of patients reporting any angina or severe angina (Canadian cardiovascular society class ≥ II) was not different in HFpEF patients with or without CAD (Table 1). Anginal symptoms were similarly prevalent in patients with or without diabetes (35 vs 37%, p=0.4). Troponin T levels were assessed during HF hospitalization in 81 patients (22%) and were slightly higher in patients with CAD (Table 1), though troponin levels did not identify the presence of CAD in logistic regression analysis (p=0.9, Supplementary Table 1). Compared to patients without CAD, HFpEF patients with CAD displayed more renal dysfunction and a trend for higher BNP levels, though the latter difference was not observed after accounting for differences in renal function (p=0.2).

Baseline Ventricular Structure and Function

LV chamber size, mass, stroke volume and cardiac output were similar in patients with or without CAD (Table 2). LV mass and relative wall thickness were slightly greater and EF slightly lower in HFpEF patients with CAD compared to patients without CAD, though these differences were attenuated after adjusting for age and sex. LV diastolic function, estimated pulmonary artery systolic pressure (PASP), and arterial properties were similar in HFpEF patients with and without CAD, with the exception of echo-estimated LV filling pressures (E/e' ratio) which were elevated in both groups but were significantly higher in HFpEF patients with CAD compared to patients without CAD.

Evaluation for Ischemia

Over one-half of HFpEF patients underwent stress testing prior to angiography (57% vs 53% of patients with and without CAD, p=0.5; Table 2). Treadmill ECG testing was performed in 16%, stress echocardiography in 39% and nuclear testing in 45%. Among patients undergoing stress testing, 70% with angiographically proven CAD were found to display ischemia at the time of stress testing, with a 30% false negative rate (Figure 2). Defining CAD using the more stringent criterion of stenosis ≥70% produced a similar 28% false negative rate. Conversely, nearly half (45%) of HFpEF patients with no significant anatomic CAD on angiography were found to display a positive test. Rates of false positive and false negative tests were similar in patients presenting with or without angina (Figure 2). Overall accuracy of stress testing to classify CAD was 66% with no significant difference between the modalities (p=0.18; Supplementary Table 3).

Invasive hemodynamics

Approximately one-third and one-half of HFpEF patients with and without CAD underwent invasive hemodynamic assessment (Table 3). On average, HFpEF patients displayed

systemic hypertension, elevated right and left heart filling pressures, mild pulmonary hypertension, preserved resting cardiac output, and mild to moderate pulmonary vascular disease, but there were no differences noted in any hemodynamic parameters between HFpEF patients with or without CAD. A subset of patients underwent invasive exercise evaluation, which showed elevation in cardiac filling pressures and exercise-induced pulmonary hypertension with stress, but again there were no differences between patients with or without CAD. A smaller subset of patients received nitroprusside infusion, which also showed no discernible differences in central hemodynamic responses in patients with or without CAD.

Impact of CAD on Ventricular Function and Mortality

Repeat echocardiography was performed in 218 patients (59% of patients CAD, 55% of patients without CAD, p=0.5) a median interval of 1314 days (IQR 655, 1947) after catheterization. Baseline characteristics were similar in patients who did or did not undergo repeat echocardiography (Supplementary Table 4). Systolic function (LVEF) deteriorated in patients with CAD but not in patients without CAD (Figure 3A,B). Compared to patients without CAD, HFpEF patients with CAD experienced a 4-fold greater decline in EF over time (-4.6±10.3 vs -1.0±8.7%, p=0.01; Figure 3C). Documented myocardial infarction occurred in 10 patients with CAD and 1 patient without CAD (p=0.11). After excluding patients with known intercurrent infarction, EF deterioration remained significantly greater in patients with CAD (-3.3±9.5 vs -0.5±9.4%, p=0.02).

Over a median follow up of 1457 days (IQR 692, 2366), there were 112 deaths. HFpEF patients with significant anatomic CAD displayed higher mortality compared to HFpEF patients without CAD (HR 1.61, CI 1.06-2.59, p=0.026; Figure 4). Age, echo-estimated PASP, chronic kidney disease, atrial fibrillation, E/e' ratio, hemoglobin, and sodium were also univariate

predictors of death (Table 4). In multivariate analysis incorporating univariate predictors, the presence of CAD remained a significant predictor of increased risk of death (HR 1.71; CI 1.03, 2.98; p=0.04).

Impact of Revascularization in HFpEF patients with CAD

Of 255 HFpEF patients found to demonstrate significant CAD, 205 (80%) underwent revascularization (63% percutaneous intervention, 37% surgical bypass). Complete revascularization was performed in 102 patients, partial revascularization in 103 patients, and no revascularization in 50 patients. The clinical, echocardiographic, and hemodynamic characteristics as well as CAD severity of patients undergoing complete revascularization were not different from those undergoing incomplete/no revascularization (Supplementary Tables 5-8). The presence and severity of angina and ischemia burden on stress testing were not different between patients receiving complete, incomplete or no revascularization. The most common documented reasons for not pursuing revascularization were uncertain relation to symptoms, indeterminate severity lesions and absence of angina (Supplementary Table 9).

Repeat echocardiography was performed in 151 of the 255 patients with CAD a median of 1219 days (IQR 651, 1898) after catheterization. LVEF decreased on average in HFpEF patients with CAD (Figure 3D,E), though patients that were not completely revascularized experienced >2-fold greater decline in EF compared to patients undergoing complete revascularization (-2.7±8.9 vs -6.1±11.1, p=0.04) (Figure 3F). Longitudinal changes in EF were not different comparing patients with single-vessel disease to HFpEF patients without CAD (Supplementary Figure 1). The change in EF was not associated with mortality (p=0.2).

Over a median follow up of 1478 days (IQR 708, 2371), there were 87 deaths among HFpEF patients with CAD. HFpEF patients who underwent complete revascularization

displayed significantly improved survival compared to patients not undergoing complete revascularization (Figure 5A), with survival rates being similar to what was observed in HFpEF patients without CAD (Figure 5B). Similar results were observed in a sensitivity analysis where revascularization was defined as treatment of stenoses of ≥70% severity (p=0.03, Supplementary Figure 2), when comparing complete revascularization to partial or no revascularization separately (Supplementary Figure 3) and comparing surgical vs percutaneous revascularization (Supplementary Figure 4). Patients with multivessel disease or higher Syntax scores displayed better outcomes with revascularization compared to patients with single vessel disease or low Syntax scores (Figure 6). Survival in patients with single vessel disease was not different from HFpEF patients without CAD (Supplementary Figure 5), and outcomes were similar in CAD patients with negative and positive stress tests (p=0.5). Overall, differences in survival associated with revascularization status persisted after adjusting for other univariate predictors of death including age, chronic kidney disease, atrial fibrillation, pulmonary artery pressure, previous myocardial infarction and Syntax score (HR 0.56, CI 0.33, 0.93, p=0.03, Table 5).

Discussion

This is the first study to thoroughly examine the clinical, structural, functional, hemodynamic and prognostic implications of coronary artery disease (CAD) and its treatment in patients with HFpEF. We studied patients with unequivocal, rigorously adjudicated heart failure characterized by prior hospitalization, where alternative etiologies including acute coronary syndrome, valvular heart disease, cardiomyopathy, and pericardial disease were excluded. The presence of significant CAD, ascertained anatomically using the gold standard of coronary angiography, was observed in two-thirds of patients. Compared to HFpEF patients without CAD, patients with CAD were more likely to be male, display typical atherosclerotic risk factors, and

be treated with anti-ischemic medications. However, dyspnea and angina symptoms were similar, as were invasively measured hemodynamics and most indices of cardiovascular structure and function. Noninvasive stress testing poorly classified the presence or absence of anatomic CAD among patients with and without angina. Over a median follow up of 4 years, HFpEF patients with CAD experienced greater deterioration in systolic function and significantly worse survival compared to patients without CAD. However, HFpEF patients with CAD who underwent complete revascularization experienced less reduction in LVEF and improved survival compared to patients receiving incomplete or no revascularization, particularly among patients with more severe CAD. We conclude that despite numerous clinical, structural and hemodynamic similarities, important differences in natural history and response to treatment justify the diagnostic separation of HFpEF patients according to the presence or absence of CAD. The failure of symptoms and noninvasive testing to adequately identify or exclude CAD in patients with HFpEF raises questions regarding its optimal assessment in this population. While prospective trials are needed, the current exploratory data support the hypothesis that revascularization of CAD in patients with HFpEF might be effective to improve both ventricular function and survival in this population.

Community-based studies have shown that CAD, diagnosed based upon history of myocardial infarction, revascularization or electrocardiographic changes is common in HFpEF, being present in 40-50% of subjects.(1,19,21-23) The prevalence of angiographically ascertained CAD was higher in the current study (68%). While this higher prevalence is certainly due in part to referral bias, it is also possible that prior studies relying on clinical criteria might have underappreciated the burden of CAD in HFpEF. We observed that the presence of CAD was associated with greater reduction in LVEF over time, confirming and extending upon a recent

study from Dunlay and colleagues.(24) In contrast, reduction in EF to <50% was distinctly uncommon in HFpEF patients without CAD (Figure 3A). The worsening ventricular function did not appear to be completely explainable by clinically apparent intercurrent myocardial infarction, suggesting that CAD may adversely impact ventricular function in HFpEF through a combination of acute and chronic ischemic effects.

Despite the common presence of CAD in HFpEF, data regarding its prognostic implications and optimal treatment are sparse and somewhat conflicting. A study from the CASS registry showed that the presence of HF in patients with CAD and EF>45% was associated with increased risk of death.(25) However, two more recent studies observed no excess risk in HFpEF patients with CAD,(22,23) though CAD was defined clinically rather than angiographically. Importantly, most prior studies of HFpEF have not rigorously sub-phenotyped patients in order to exclude alternative etiologies of the clinical syndrome of HF. The current data show in a carefully-defined, homogenous, well-described HFpEF cohort that the presence of CAD is associated with increased risk of death, even after adjusting for other independent markers of risk. Changes in LV function and outcome were similar HFpEF patients with no CAD and patients with single vessel disease, suggesting that the adverse impact of CAD in HFpEF may be more related to multivessel disease; similar to what has been reported in HFrEF.(26) The differences observed between HFpEF patients with and without CAD in the current study in ventricular function and in outcome provide justification for the sub-categorization of HFpEF patients according to the presence or absence of CAD in both clinical practice and research.

It is notable that HFpEF patients with and without CAD did not differ in clinically meaningful ways in terms of anginal symptoms, laboratories, cardiovascular structure, function and hemodynamics. Demographics and comorbidities were more clearly different in patients

with and without CAD, with greater male prevalence and more atherosclerotic risk factors in the CAD group as expected. However, in receiver operating curve analysis, none of these factors effectively distinguished patients with CAD from those without CAD (Supplementary Table 2). Importantly, 30% of patients with anatomically proven CAD had a negative stress test result, suggesting that a substantial number of HFpEF patients may not receive potentially effective therapies if stress imaging alone were relied upon to exclude CAD. The common misclassification of the presence or absence of anatomically-defined CAD by stress testing observed in the current study suggests that there may be previously unrecognized limitations of stress testing in this population, although the rates of misclassification noted might be inflated by higher pre-test probability for CAD on average among referring cardiologists. Further study is required to identify the optimal diagnostic assessments for CAD in patients presenting primarily with the clinical syndrome of HFpEF.

No treatment has been shown to improve survival in HFpEF,(2) leading many authorities to emphasize treatment of commonly observed comorbidities such as CAD.(3-5) However, currently available data regarding optimal management of CAD in HFpEF are scant. An early study from the CASS registry showed that survival was similar in patients with HF, CAD and EF>45% treated medically and with revascularization,(25) though both medical and revascularization options have changed dramatically since that era. In a retrospective, observational series of patients admitted for acute pulmonary edema, Kramer and colleagues found that revascularization of CAD was not associated with a reduction in recurrent episodes of edema, though the sample size was small and there were very few deaths.(27) In the current study with a much larger sample and longer duration of follow up, complete revascularization

was associated with lower mortality, with outcomes that were not different than the HFpEF group without CAD.

Limitations

This sample is subject to referral bias because of the requirement for angiography. The prevalence of CAD would be expected to be lower in a randomly selected population of patients and we cannot determine how many patients were admitted for HFpEF who did not have an angiogram. The operating characteristics reported for stress testing in this study are affected by the cath-lab referral population, where presumably the pretest probability of CAD was on average higher among ordering physicians. All patients were required to have been hospitalized for HF, and these results may not apply to the larger ambulatory population of HFpEF patients who never require hospitalization. The retrospective, observational nature of this study does not permit conclusions regarding the causal effects of CAD or revascularization on LV function or outcome, or on the potential impact of CAD on the pathophysiology of HFpEF. It is possible that complete revascularization identifies a healthier subset of patients or one that is better treated, though medication use, symptoms, ischemia burden, LV function, CAD severity and other characteristics did not differ in subjects that did or did not receive complete revascularization (Supplementary Tables 4-7). This study did not assess the impact of revascularization on symptoms, because there was marked variability in follow up duration and completeness of documentation of symptoms at subsequent visits. This study did not assess the impact of CAD or revascularization on recurrent HF hospitalizations. Follow up echocardiography was not performed at consistent time points and was obtained only at the discretion of ordering cardiologists, and survival bias may also impact the longitudinal changes in LV function, though one would expect this to only bias the results toward the null.

Conclusions

Coronary artery disease is common in patients with HFpEF and noninvasive diagnosis may be less accurate in this cohort than has been previously recognized. While symptoms, ventricular structure, function, and hemodynamics are similar in patients with and without CAD, important and significant differences in outcome and response to treatment are present that suggest HFpEF should be nosologically sub-categorized according to the presence or absence of CAD. The presence of CAD is associated with worse outcome in HFpEF independent of other predictors, and complete revascularization may be associated with improved survival and less deterioration in LV function over time. Prospective trials are needed to determine the optimal techniques to identify and treat CAD in patients with HFpEF, a disease for which no current proven treatment exists.

References:

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355:251-9.
2. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J. 2011;32:670-9.
3. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62:e147-239.
4. Shah SJ, Gheorghiade M. Heart failure with preserved ejection fraction: treat now by treating comorbidities. JAMA 2008;300:431-3.
5. Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol 2012;59:998-1005.
6. Shah SJ. Matchmaking for the Optimization of Heart Failure with Preserved Ejection Fraction Clinical Trials: No Laughing Matter. J Am Coll Cardiol. 2013;62:1339-42.
7. Muller O, Rorvik K. Haemodynamic consequences of coronary heart disease with observations during anginal pain and on the effect of nitroglycerine. Br Heart J 1958;20:302-310.
8. Mann T, Goldberg S, Mudge GH, Jr., Grossman W. Factors contributing to altered left ventricular diastolic properties during angina pectoris. Circulation. 1979;59:14-20.

9. Serizawa T, Vogel WM, Apstein CS, Grossman W. Comparison of acute alterations in left ventricular relaxation and diastolic chamber stiffness induced by hypoxia and ischemia. Role of myocardial oxygen supply-demand imbalance. J Clin Invest 1981;68:91-102.

10. Kass DA, Midei M, Brinker J, Maughan WL. Influence of coronary occlusion during PTCA on end-systolic and end-diastolic pressure-volume relations in humans. Circulation 1990;81:447-460.

11. Choudhury L, Gheorghiade M, Bonow RO. Coronary artery disease in patients with heart failure and preserved systolic function. Am J Cardiol 2002;89:719-22.

12. Borlaug BA, Olson TP, Lam CS, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2010;56:845-54.

13. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise Hemodynamics Enhance Diagnosis of Early Heart Failure with Preserved Ejection Fraction. Circ Heart Fail. 2010;3:588-95.

14. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005;1:219-27.

15. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.

16. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction

with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.

17. Schwartzenberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. J Am Coll Cardiol. 2012;59:442-51.
18. Komajda M, Carson PE, Hetzel S, et al. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). Circ Heart Fail. 2011;4:27-35.
19. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail. 2011;13:18-28.
20. Kereiakes DJ. Complete Revascularization: A Quality-Performance Metric? J Am Coll Cardiol. 2013;62:1432-5.
21. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260-9.
22. Lee DS, Gona P, Vasan RS, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. Circulation 2009;119:3070-7.
23. Tribouilloy C, Rusinaru D, Mahjoub H, et al. Prognosis of heart failure with preserved ejection fraction: a 5 year prospective population-based study. Eur Heart J 2008;29:339-47.

24. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Heart Fail. 2012;5:720-6.

25. Judge KW, Pawitan Y, Caldwell J, Gersh BJ, Kennedy JW. Congestive heart failure symptoms in patients with preserved left ventricular systolic function: analysis of the CASS registry. J Am Coll Cardiol 1991;18:377-82.

26. Felker GM, Shaw LK, O'Connor CM. A standardized definition of ischemic cardiomyopathy for use in clinical research. J Am Coll Cardiol 2002;39:210-8.

27. Kramer K, Kirkman P, Kitzman D, Little WC. Flash pulmonary edema: association with hypertension and reoccurrence despite coronary revascularization. Am Heart J 2000;140:451-5.

FIGURE LEGENDS

Figure 1: Flow diagram showing identification of patients.

Figure 2: **Operating Characteristics of Stress Testing in HFpEF.** Accuracy for classification of the presence or absence of anatomic CAD based upon stress testing in the entire sample [A] and in HFpEF patients complaining of angina [B].

Figure 3: **Impact of CAD and revascularization on change on changes in LV function.** [A-C] In HFpEF patients without significant CAD there was no longitudinal change in EF whereas in patients with CAD there was reduction in EF, with multiple patients developing reduced EF (<50%, dotted lines). [D-F] The reduction in EF was attenuated with complete revascularization as compared to incomplete or no revascularization.

Figure 4: **Impact of CAD on survival in patients with HFpEF.** Kaplan-Meier plot showing reduced survival in HFpEF patients with CAD (red) compared to patients without CAD (black).

Figure 5: **Impact of revascularization on survival in patients with HFpEF with CAD.** Kaplan-Meier plots showing [A] greater survival in patients with CAD who were revascularized (green) compared to patients with CAD who were not completely revascularized (blue) and [B] similar survival in patients with CAD who were revascularized (green) and patients without significant CAD (black).

Figure 6: Impact of revascularization according to CAD severity. Kaplan-Meier plots showing survival among patients with CAD that were revascularized (blue) compared to those who were not completely revascularized (red) according to Syntax score and number of coronary vessels diseased.

Table 1. Baseline characteristics

	HFpEF without CAD (n=121)	HFpEF with CAD (n=255)	P value
Age (years)	71±10	73±9	0.01
Male sex (n, %)	30 (25%)	145 (57%)	< 0.0001
Body mass index (kg/m^2)	33.0±7.7	33.5±7.0	0.5
Past medical history			
Hypertension (n, %)	89 (74%)	215 (84%)	0.02
Diabetes (n, %)	36 (30%)	120 (47%)	0.002
Dyslipidemia (n, %)	58 (48%)	176 (69%)	<0.0001
Smoking ever (n, %)	44 (39%)	118 (51%)	0.04
Atrial fibrillation (n, %)	29 (24%)	68 (27%)	0.6
Chronic kidney disease (n, %)	40 (33%)	99 (39%)	0.3
Previous MI (n, %)	0 (0%)	52 (20%)	
Previous PCI (n, %)	0 (0%)	70 (27%)	
Previous CABG (n, %)	0 (0%)	78 (31%)	
Symptoms and Exam			
Dyspnea	110 (92%)	230 (93%)	0.7
Angina	39 (37%)	86 (36%)	1.0
NYHA ≥ class III	64 (53%)	137 (56%)	0.7

CCS ≥ class II	31 (30%)	78 (34%)	0.6
Jugular venous distention	33 (27%)	67 (27%)	0.9
Medications			
ACE inhibitor or ARB	67 (55%)	164 (65%)	0.07
Beta blocker	74 (61%)	186 (74%)	0.02
Loop diuretics	53 (44%)	127 (50%)	0.3
Aldosterone antagonist	4 (3%)	17 (7%)	0.2
Thiazide diuretics	23 (19%)	61 (24%)	0.3
Calcium channel blocker	36 (30%)	73 (29%)	0.9
Nitrate	12 (10%)	61 (24%)	0.0008
Statin	57 (47%)	175 (70%)	< 0.0001
Aspirin	58 (48%)	178 (71%)	< 0.0001
Laboratories			
Hemoglobin (g/dl)	12.5±1.7	12.3±1.7	0.3
Blood urea nitrogen (g/dl)	22.3±11.3	26.7±15.2	0.005
Creatinine (g/dl)	1.1±0.4	1.3±0.5	< 0.0001
Na (mmol/l)	140±3	140±3	0.1
BNP (pg/ml) (n=38/105)	182 (104, 468)	363 (187, 675)	0.008
Troponin T (ng/ml) (n=13/68)	0.02 (0.01, 0.05)	0.04 (0.02, 0.078)	0.04
Angiography			

Extent of CAD		
1 vessel disease	_	68 (28%)
2 vessel disease	_	85 (36%)
3 vessel disease	_	87 (36%)
Average number of vessels	_	2.1±0.8
Syntax score	_	19±14
Syntax grade		
score < 22	_	152 (63%)
score 22 to 32	_	45 (19%)
score ≥ 33	_	43 (18%)
Disease territory		
Left main disease	_	39 (16%)
LAD disease	_	162 (68%)
Diagonal disease	_	76 (32%)
LCX disease	_	152 (63%)
RCA disease	_	156 (65%)

Table 2. Structure, function and ischemia evaluation

	HFpEF without CAD	HFpEF with CAD	Non adjusted P value	Adjusted P value*
LV morphology and systolic function				
LV end diastolic volume (ml/m^2)	59±12	59±14	0.8	0.8
LV end systolic volume (ml/m^2)	21±7	22±9	0.3	0.4
LV mass index (gm/m^2)	100±25	109±29	0.005	0.08
Relative wall thickness	0.43±0.08	0.46±0.09	0.03	0.04
LA volume index (ml/m^2)	43±15	46±15	0.2	0.8
LV ejection fraction (%)	62±6	61±7	0.015	0.04
Stroke volume	87±21	91±23	0.1	0.8
Cardiac index	3.0±0.6	2.9±0.6	0.5	0.3
LV diastolic function				
Mitral E wave (m/s)	0.9±0.3	1.0±0.3	0.05	0.01
Mitral A wave (m/s)	0.8±0.3	0.8±0.3	1.0	0.7
Mitral deceleration time (msec)	195±54	199±48	0.5	0.7
Mitral e' velocity (m/s)	0.06 (0.05, 0.07)	0.06 (0.05, 0.075)	0.16	0.02
E/e' ratio	16±7	18±9	0.003	< 0.001

Estimated PASP (mmHg)	45±15	46±14	0.6	0.8
Vascular function				
Arterial elastance, mmHg/ml	1.4±0.4	1.4±0.4	0.3	0.7
Vascular resistance, dyne.s^{-1}.cm^{-5}	1414±422	1368±380	0.3	0.9
Arterial compliance, ml/mmHg	1.6±0.5	1.6±0.6	1.0	0.3
Stress test (total number /positive ischemia/%)				
Total	64/29 (45%)	145/102 (70%)	0.0006	
Treadmill test (n=31)	17/1 (6%)	14/1 (7%)	1.0	
Echocardiography (n=77)	27/13 (48%)	50/34 (68%)	0.09	
Nuclear (n=101)	20/15 (75%)	81/67 (83%)	0.4	

PASP: pulmonary artery systolic pressure; *adjusted for age and sex

Table 3. Invasive hemodynamics

	HFpEF without CAD	HFpEF with CAD	P value
Baseline	(n=63)	(n=85)	
Heart rate (bpm)	71±11	71±14	0.8
Systolic aortic pressure (mmHg)	145±29	147±30	0.7
RA pressure (mmHg)	11±6	11±5	0.9
PA systolic pressure (mmHg)	48±16	49±18	0.7
PA mean pressure (mmHg)	31±11	31±11	0.9
PCWP (mmHg)	18±7	18±7	0.9
LV end diastolic pressure (mmHg)	20±8	20±6	0.6
Cardiac index (L/min*m^2)	2.4±0.7	2.6±0.9	0.2
Pulmonary vascular resistance (WU)	2.9±1.9	2.7±1.6	0.6
Exercise	(n=33)	(n=28)	
Heart rate (bpm)	100±25	98±14	0.7
Aortic pressure (mmHg)	174±28	179±27	0.5
PA systolic pressure (mmHg)	60±12	63±14	0.4
Mean PA pressure (mmHg)	43±8	45±9	0.4
PCWP (mmHg)	29±6	27±6	0.1
LV end diastolic pressure (mmHg)	26±9	28±9	0.7
Cardiac index (L/min*m^2)	4.8±3.1	3.9±1.0	0.3
Pulmonary vascular resistance (WU)	2.1±1.1	2.6±2.0	0.4

Nitroprusside	(n=14)	(n=16)	
Heart rate (bpm)	71±13	72±14	0.9
Aortic pressure (mmHg)	110±58	119±21	0.6
PA systolic pressure (mmHg)	49±13	49±20	1.0
Mean PA pressure (mmHg)	32±11	32±11	0.8
PCWP (mmHg)	18±8	16±8	0.5
LV end diastolic pressure (mmHg)	14±8	14±4	0.9
Cardiac index (L/min*m^2)	4.2±2.3	3.1±0.6	0.2
Pulmonary vascular resistance (WU)	2.2±1.5	2.9±1.8	0.4

Table 4. Multivariable analysis for independent predictors of Survival in HFpEF patients (Cox proportional hazard model)

	Univariate model			Multivariate model (total χ^2:44.8)		
	χ^2	OR(95% CI)	P value	χ^2	OR(95% CI)	P value
Age (per 1 year increase)	17.16	1.05(1.03, 1.08)	< 0.001			
PASP (per 1mmHg increase)	15.35	1.03(1.02, 1.04)	< 0.001	4.67	1.02(1.00, 1.03)	0.03
Chronic kidney disease	13.73	2.02(1.40, 2.94)	< 0.001	8.11	2.10(1.26, 3.53)	0.004
Atrial fibrillation	8.26	1.80(1.21, 2.63)	0.004	5.66	1.83(1.11, 2.97)	0.02
E/e' ratio (per 1 increase)	7.89	1.03(1.01, 1.05)	0.005			
Hemoglobin (per 1g/dl decrease)	7.14	1.18(1.04, 1.30)	0.008			
Sodium (per 1mEq/l decrease)	5.27	1.08(1.01, 1.14)	0.022			
SBP (per 1 mmHg increase)	5.15	0.99(0.98,0.99)	0.023	7.59	0.99(0.98, 0.99)	0.006

Coronary artery disease	4.99	1.63(1.06, 2.59)	0.026	4.60	1.75(1.05, 3.03)	0.03
Men	3.79	1.45(0.99, 2.10)	0.052			
BMI (per 1kg/m^2 increase)	1.90	0.98(0.95, 1.01)	0.17			
Diabetes	1.11	1.22(0.84, 1.77)	0.29			

Chronic kidney disease: eGFR by Cockcroft-Gault formula < 60ml/min/1.73m^2, PASP: pulmonary artery systolic pressure, SBP: systolic blood pressure, BMI: body mass index

Table 5. Multivariable analysis for independent predictors of Survival in HFpEF patients with CAD (Cox proportional hazard model)

	Univariate model			Multivariate model(total χ^2:43.7)		
	χ^2	OR (95% CI)	P value	χ^2	OR(95% CI)	P value
Chronic kidney disease	14.02	2.25 (1.47, 3.45)	< 0.001	6.98	2.11 (1.21, 3.69)	0.008
Age(per 1 year increase)	13.96	1.05 (1.02, 1.08)	< 0.001			
Hemoglobin(per 1g/dl decrease)	10.19	1.23 (1.08, 1.39)	0.001	4.46	1.17 (1.01, 1.36)	0.035
Atrial fibrillation	8.14	1.93 (1.24, 2.97)	0.004	11.93	2.51 (1.50, 4.13)	< 0.001
PASP(per 1mmHg increase)	6.24	1.02 (1.00, 1.03)	0.01			
Revascularization	4.93	0.61 (0.38, 0.94)	0.03	7.98	0.50 (0.30, 0.81)	0.005
E/e' ratio(per 1 increase)	5.11	1.03 (1.00, 1.05)	0.024			
Systolic blood pressure(per 1mmHg increase)	3.22	0.99 (0.98, 1.00)	0.07			
Plasma sodium(per	3.04	1.06 (0.99,	0.08			

1mEq/l decrease)		1.13)	
BMI(per 1kg/m^2 increase)	1.73	0.98 (0.95, 1.01)	0.19
Syntax score(per 1 increase)	1.24	1.01 (0.99, 1.02)	0.27
Previous myocardial infarction	0.53	1.20 (0.72, 1.93)	0.47
Diabetes	0.32	1.13 (0.74, 1.73)	0.57

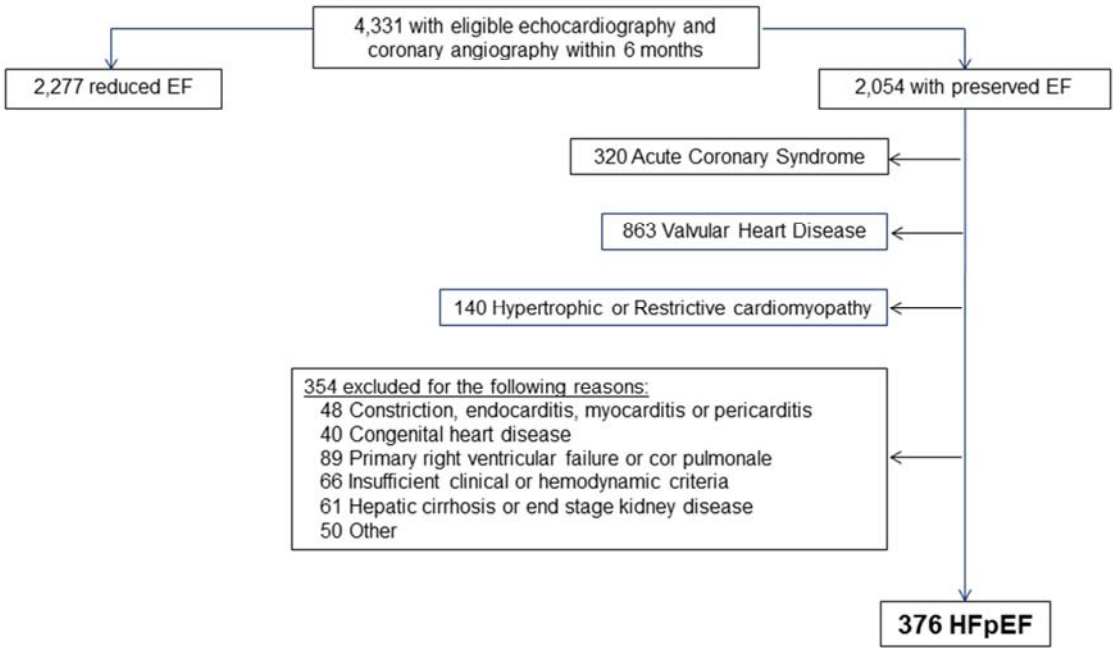


Figure 1

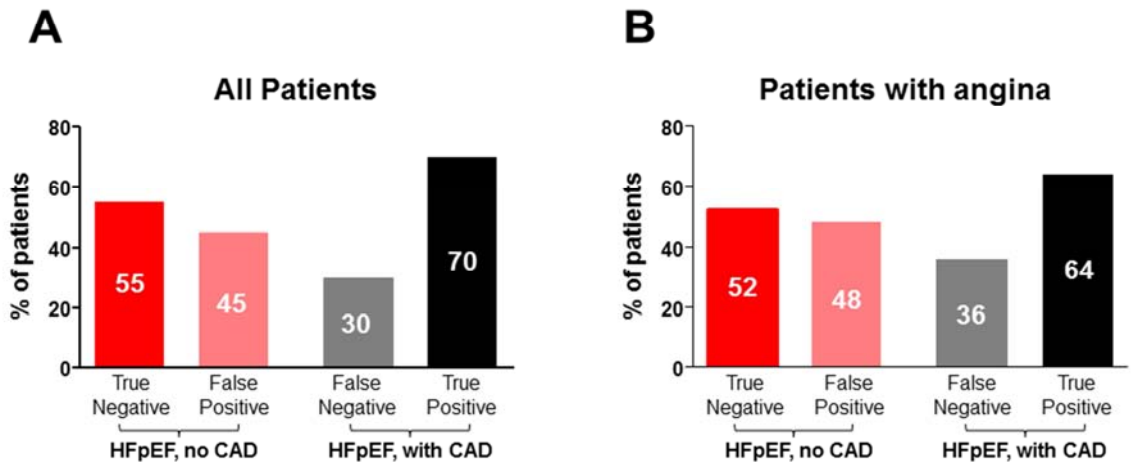


Figure 2

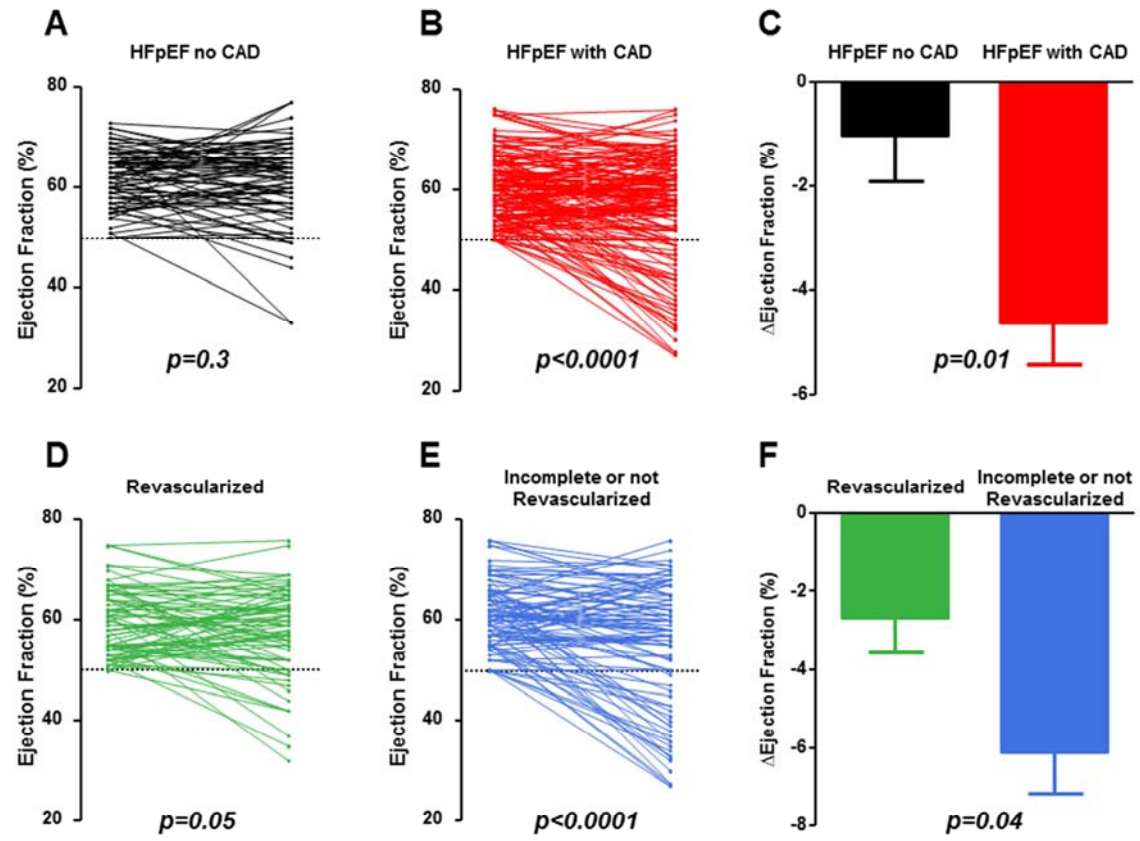
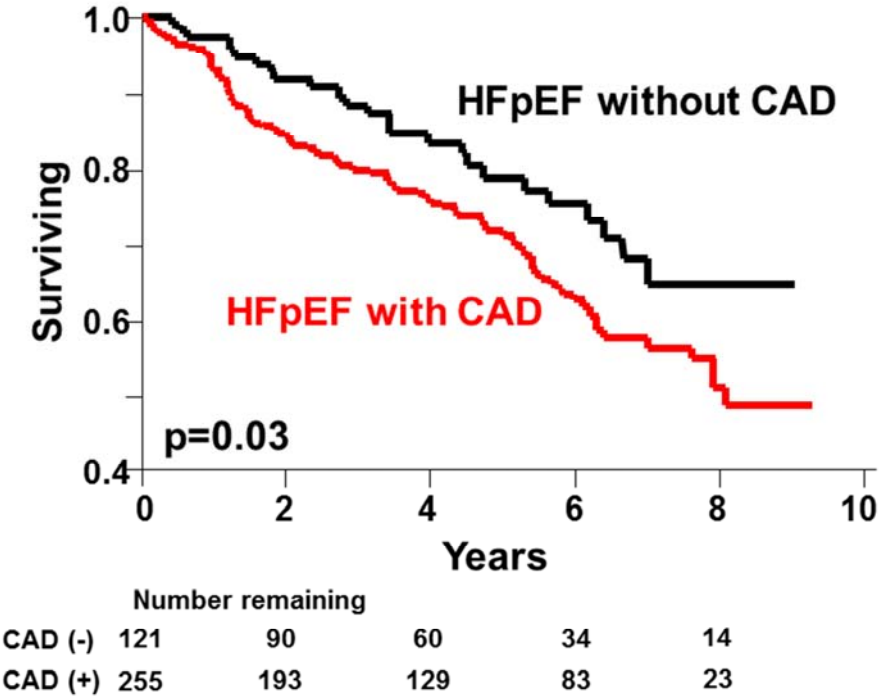


Figure 3



Number remaining					
CAD (-)	121	90	60	34	14
CAD (+)	255	193	129	83	23

Figure 4

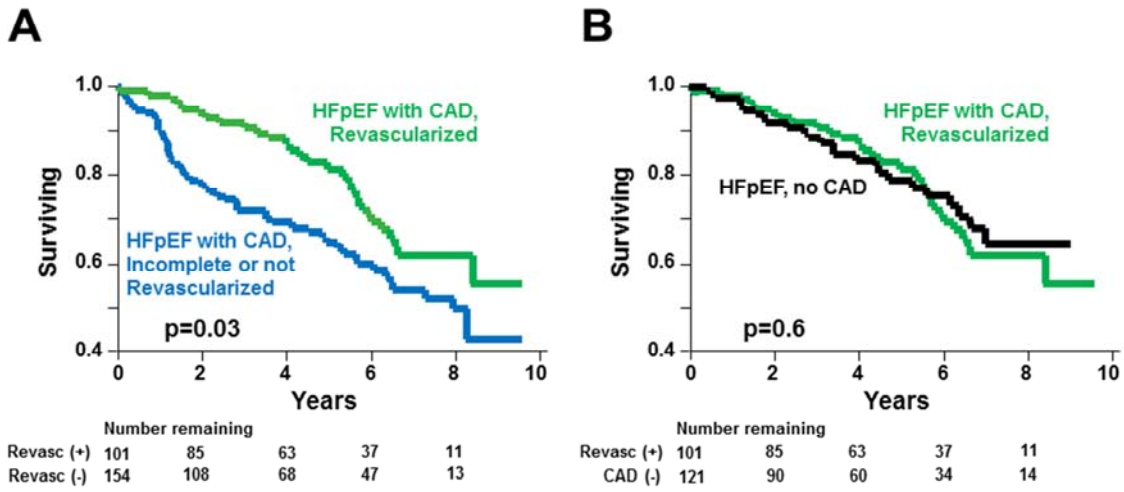


Figure 5

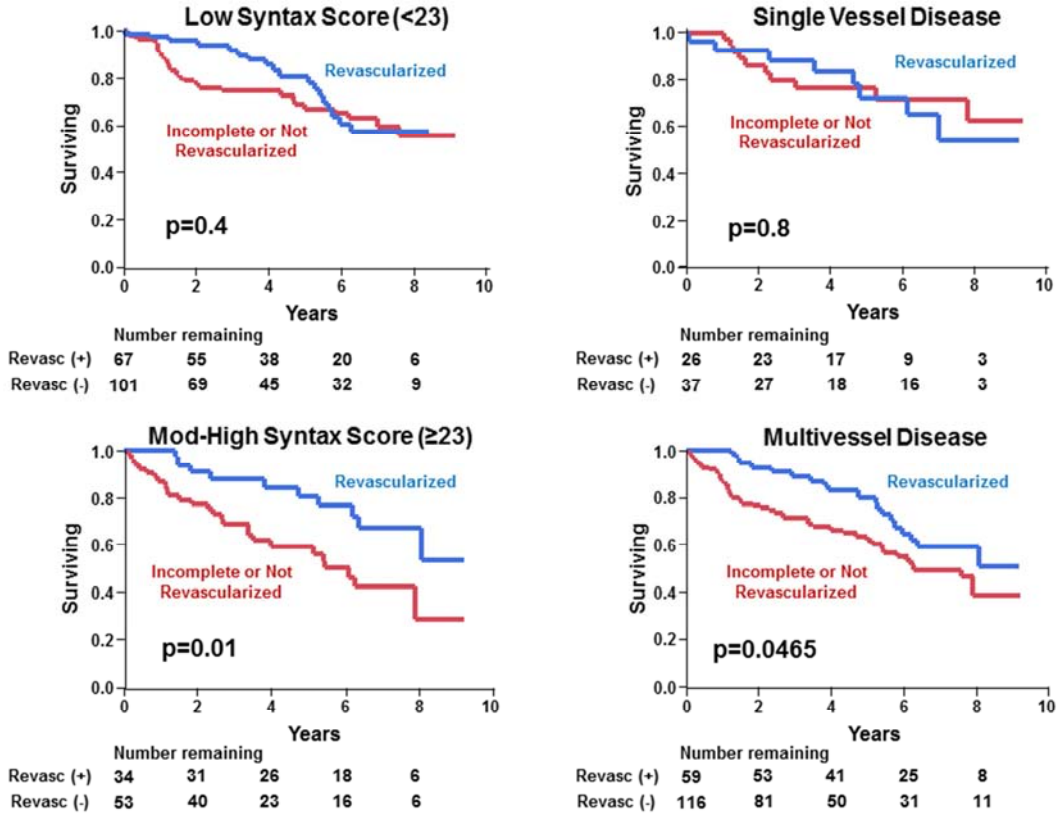


Figure 6

Supplementary Table 1: Indications for Coronary Angiography

Indication for Angiogram*	Number
Angina	138
Coronary artery disease	95
Dyspnea	71
Positive stress test	77
Pulmonary hypertension	43
Heart failure or cardiomyopathy	52

*>1 indication could be given ad lib by referring provider

Supplementary Table 2: Predictive Capability of Clinical parameters to identify CAD in HFpEF

Parameter	c-statistic in ROC curve analysis	P value
Male sex	0.66	<0.0001
Creatinine	0.64	<0.0001
Hyperlipidemia	0.61	<0.0001
Diabetes mellitus	0.59	0.001
E/e' ratio	0.59	0.004
Age	0.57	0.02
Smoking history	0.56	0.03
Hypertension	0.55	0.02
Troponin T	0.68	0.9

ROC: Receiver Operating Characteristic

Supplementary Table 3. Rates of True and False Positive/Negative Tests Across Modalities

	HFpEF without CAD (n=64)		HFpEF with CAD (n=145)		Overall	
	True negative	False positive	True positive	False negative	Accuracy	P value*
Stress ECG (n=31)	16/17 (94%)	1/17 (6%)	1/14 (7%)	13/14 (93%)	17/31 (55%)	
Stress echo (n=77)	14/27 (52%)	13/27 (48%)	34/50 (68%)	16/50 (32%)	48/77 (62%)	0.18
Nuclear (n=101)	5/20 (25%)	15/20 (75%)	67/81 (83%)	14/81 (17%)	72/101 (71%)	
Total (n=209)	35/64 (55%)	29/64 (45%)	102/145 (70%)	43/145 (30%)	137/209 (66%)	

*Omnibus chi square p value from 3x2 table comparing accuracy of all 3 testing modalities

Supplementary Table 4. Baseline characteristics of patients that did or did not have repeat echocardiography

	No repeat echo (n=158)	Repeat echo (n=218)	P value
Age (years)	71±10	73±8	0.1
Male sex (n, %)	84 (53%)	91 (42%)	0.02
Body mass index (kg/m^2)	33.4±7.4	33.3±7.1	0.9
Past medical history			
Hypertension (n, %)	119 (75%)	185 (85%)	0.02
Diabetes (n, %)	66 (42%)	90 (41%)	1.0
Dyslipidemia (n, %)	95 (60%)	139 (64%)	0.5
Smoking ever (n, %)	73 (49%)	89 (45%)	0.5
Atrial fibrillation (n, %)	41 (26%)	56 (26%)	1.0
Chronic kidney disease (n, %)	54 (34%)	85 (39%)	0.4
Previous MI (n, %)	18 (17%)	34 (23%)	0.3
Previous PCI (n, %)	47 (30%)	55 (25%)	0.4
Previous CABG (n, %)	29 (18%)	48 (22%)	0.4
Symptoms and Exam			
Dyspnea	144 (94%)	196 (92%)	0.7
Angina	45 (32%)	80 (40%)	0.1
NYHA ≥ class III	92 (60%)	109 (51%)	0.1
CCS ≥ class II	39 (28%)	70 (36%)	0.2
Jugular venous distention	41 (26%)	59 (27%)	0.9
Medications			
ACE inhibitor or ARB	93 (59%)	138 (64%)	0.3
Beta blocker	100 (64%)	160 (74%)	0.03
Loop diuretics	75 (48%)	105 (49%)	0.8
Aldosterone antagonist	10 (6%)	11 (5%)	0.7
Thiazide diuretics	32 (20%)	52 (24%)	0.4
Calcium channel blocker	41 (26%)	68 (32%)	0.3
Nitrate	26 (17%)	47 (22%)	0.2
Statin	98 (62%)	134 (62%)	1.0
Aspirin	100 (64%)	136 (63%)	1.0
Laboratories			
Hemoglobin (g/dl)	12±2	12±2	0.7
Blood urea nitrogen (g/dl)	26±15	25±14	0.7
Creatinine (g/dl)	1.2±0.5	1.2±0.4	0.7
Na (mmol/l)	140±3	140±3	0.2
BNP (pg/ml) (n=54/89)	441±428	472±496	0.7

Supplementary Table 5. Baseline characteristics according to Revascularization Status

	Incomplete or No revascularization (n=153)	Complete revascularization (n=102)	P value
Age (years)	73±9	73±8	0.8
Male sex (n, %)	91 (60%)	54 (53%)	0.3
Body mass index (kg/m^2)	33.3±7.5	33.9±6.1	0.5
Past medical history			
Hypertension (n, %)	125 (82%)	90 (88%)	0.2
Diabetes (n, %)	72 (47%)	48 (47%)	1.0
Dyslipidemia (n, %)	103 (67%)	73 (72%)	0.5
Smoking ever (n, %)	73 (53%)	45 (49%)	0.7
Atrial fibrillation (n, %)	41 (27%)	27 (27%)	1.0
Chronic kidney disease (n, %)	64 (42%)	35 (34%)	0.2
Previous MI (n, %)	31 (20%)	21 (21%)	1.0
Previous PCI (n, %)	62 (41%)	40 (39%)	0.9
Previous CABG (n, %)	45 (29%)	32 (31%)	0.8
Symptoms and Exam			
Dyspnea	137 (93%)	93 (94%)	0.8
Angina	53 (37%)	33 (35%)	0.8
NYHA ≥ class III	78 (53%)	59 (60%)	0.4
CCS ≥ class II	47 (34%)	31 (33%)	1.0
Jugular venous distention	40 (27%)	27 (27%)	1.0
Medications			
ACE inhibitor or ARB	99 (65%)	65 (66%)	1.0
Beta blocker	108 (71%)	78 (79%)	0.2
Loop diuretics	79 (52%)	48 (49%)	0.7
Aldosterone antagonist	12 (8%)	5 (5%)	0.5
Thiazide diuretics	31 (20%)	30 (30%)	0.07
Calcium channel blocker	45 (30%)	28 (28%)	0.9
Nitrate	44 (29%)	17 (17%)	0.04
Statin	104 (68%)	71 (71%)	0.7
Aspirin	107 (70%)	71 (71%)	0.9
Laboratories			
Hemoglobin (g/dl)	12±2	12±2	0.9
Blood urea nitrogen (g/dl)	28±16	25±15	0.2
Creatinine (g/dl)	1.3±0.5	1.2±0.4	0.3
Na (mmol/l)	140±4	140±3	0.1
BNP (pg/ml) (n=66/39)	563±515	406±404	0.1

Supplementary Table 6. Structure, function and ischemia evaluation according to revascularization status

	Incomplete revascularization (n=153)	Complete revascularization (n=102)	P value
LV morphology and systolic function			
LV end diastolic volume index (ml/m^2)	61±15	57±13	0.02
LV end systolic volume (ml/m^2)	22±8	22±10	0.9
LV mass index (gm/m^2)	111±30	105±27	0.1
Relative wall thickness	0.46±0.09	0.46±0.09	0.7
LA volume index (ml/m^2)	45±17	46±12	0.8
LV ejection fraction (%)	61±6	60±7	0.4
Stroke volume	92±24	91±22	0.9
Cardiac index	2.9±0.7	2.9±0.6	0.7
LV diastolic function			
Mitral E wave (m/s)	1.0±0.3	1.0±0.3	0.6
Mitral A wave (m/s)	0.8±0.3	0.8±0.3	0.8
Mitral deceleration time (msec)	202±48	194±49	0.2
Mitral e' velocity (m/s)	0.06±0.05	0.06±0.02	0.9
E/e' ratio	18±9	18±8	0.5
Estimated PASP (mmHg)	46±15	45±14	0.6
Vascular function			
Arterial elastance, mmHg/ml	1.4±0.4	1.4±0.4	0.7
Vascular resistance, dyne.s^{-1}.cm^{-5}	1360±368	1378±397	0.7
Arterial compliance, ml/mmHg	1.5±0.6	1.6±0.7	0.7
Stress test (total numbers /ischemia %)			
Treadmill test	10/1(10%)	4/0 (0%)	1.0
Echo stress test	29/20 (69%)	21/14 (67%)	1.0
Nuclear stress test	49/39 (80%)	32/28 (88%)	0.6

*PASP: pulmonary artery systolic pressure

Supplementary Table 7. Invasive hemodynamics according to revascularization status

	Incomplete revascularization	Complete revascularization	P value
Baseline	(n=54)	(n=32)	
Heart rate (bpm)	72±15	68±13	0.2
Systolic aortic pressure (mmHg)	143±30	154±29	0.1
RA pressure (mmHg)	11±6	11±4	0.6
PA systolic pressure (mmHg)	47±18	52±18	0.3
PA mean pressure (mmHg)	30±11	32±11	0.5
PCWP (mmHg)	17±7	20±6	0.1
LV end diastolic pressure (mmHg)	19±6	21±6	0.2
Cardiac index (L/min*m^2)	2.5±0.9	2.7±0.9	0.3
Pulmonary vascular resistance (WU)	2.8±1.6	2.6±1.7	0.6
Exercise	(n=20)	(n=8)	
Heart rate (bpm)	100±13	93±15	0.3
Aortic pressure (mmHg)	180±26	178±32	0.9
PA systolic pressure (mmHg)	62±15	67±12	0.4
Mean PA pressure (mmHg)	44±9	47±8	0.5
PCWP (mmHg)	26±6	28±6	0.5
LV end diastolic pressure (mmHg)	27±10	30±6	0.5
Cardiac index (L/min*m^2)	3.7±1.1	4.2±0.8	0.3
Pulmonary vascular resistance (WU)	3.0±2.4	1.9±1.0	0.2
Nitroprusside	(n=10)	(n=6)	
Heart rate (bpm)	69±13	76±16	0.4
Aortic pressure (mmHg)	110±20	128±18	0.1
PA systolic pressure (mmHg)	48±23	50±16	0.8
Mean PA pressure (mmHg)	32±13	32±9	1.0
PCWP (mmHg)	17±8	15±8	0.6
LV end diastolic pressure (mmHg)	14±5	15±4	0.6
Cardiac index (L/min*m^2)	3.0±0.7	3.3±0.4	0.3
Pulmonary vascular resistance (WU)	2.7±1.0	3.3±2.8	0.6

*PA: pulmonary artery

Supplementary Table 8. Comparison of CAD severity according to revascularization status

	Incomplete revascularization (n=153)	Complete revascularization (n=102)	P value
CAD characteristics			
Extent of CAD			0.8
1 vessel disease	41 (27%)	27 (31%)	
2 vessel disease	57 (37%)	28 (32%)	
3 vessel disease	55 (36%)	32(37%)	
multivessel disease	112 (73%)	60 (69%)	0.6
average number of vessel disease	2.1±0.8	2.1±0.8	0.8
Syntax score	18±13	21±15	0.2
Syntax grade			0.24
Score < 22	100 (65%)	52 (60%)	
Score 22-32	31 (20%)	14 (16%)	
Score > 32	22 (14%)	21 (24%)	
Disease territory			
LM disease	20 (13%)	19 (22%)	0.1
LAD disease	100 (65%)	62 (71%)	0.4
Diagonal disease	46 (30%)	30 (35%)	0.8
LCX disease	100 (65%)	52 (60%)	0.4
RCA disease	104 (68%)	52 (60%)	0.2
Revascularization characteristics	(n=103)	(n=102)	
Method of revascularization			0.9
PCI	66 (64%)	64 (63%)	
CABG	37 (36%)	38 (37%)	
Numbers of vessel revascularized			0.42
1 vessel revascularized	46 (47%)	44 (43%)	
2 vessel revascularized	29 (29%)	28 (27%)	
3 vessel revascularized	17 (17%)	23 (22%)	
4 vessel revascularized	7 (7%)	7 (7%)	
multivessel revascularized	53 (54%)	58 (57%)	0.7
average number of vessel revascularized	1.8±1.0	1.9±1.0	0.5
Revascularized vessel			
LM	2 (2%)	4 (4%)	0.7
LAD	57 (58%)	62 (61%)	0.7
Diagonal branch	20 (20)	22 (22%)	0.9
LCX	53 (54%)	56 (55%)	0.9
RCA	51 (52%)	53 (52%)	1.0

Supplementary Table 9: Reasons Cited for Not Revascularizing Patients with CAD

Reason for no revascularization	Number (%)
Indeterminate lesion or unclear relation to symptoms	28 (56%)
No reason provided	11 (22%)
No angina	7 (14%)
Adequate collateral flow	3 (6%)
Small distal territory	1 (2%)

Supplementary Table 10. Multivariate analysis for independent predictors of Survival in HFpEF with CAD after defining revascularization as treatment of stenoses >70% rather than >50% (Cox proportional hazard model)

	Univariate model			Multivariate model(total χ^2:43.7)		
	χ^2	OR (95% CI)	P value	χ^2	OR(95% CI)	P value
Chronic kidney disease	14.02	2.25 (1.47, 3.45)	< 0.001	6.98	2.11 (1.21, 3.69)	0.008
Age(per 1 year increase)	13.96	1.05 (1.02, 1.08)	< 0.001			
Hemoglobin(per 1g/dl decrease)	10.19	1.23 (1.08, 1.39)	0.001	4.46	1.17 (1.01, 1.36)	0.035
Atrial fibrillation	8.14	1.93 (1.24, 2.97)	0.004	11.93	2.51 (1.50, 4.13)	< 0.001
PASP(per 1mmHg increase)	6.24	1.02 (1.00, 1.03)	0.01			
Revascularization	4.93	0.61 (0.38, 0.94)	0.03	7.98	0.50 (0.30, 0.81)	0.005
E/e' ratio(per 1 increase)	5.11	1.03 (1.00, 1.05)	0.024			
Systolic blood pressure(per 1mmHg increase)	3.22	0.99 (0.98, 1.00)	0.07			
Plasma sodium(per 1mEq/l decrease)	3.04	1.06 (0.99, 1.13)	0.08			
BMI(per 1kg/m^2 increase)	1.73	0.98 (0.95, 1.01)	0.19			
Syntax score(per 1 increase)	1.24	1.01 (0.99, 1.02)	0.27			
Previous myocardial infarction	0.53	1.20 (0.72, 1.93)	0.47			
Diabetes	0.32	1.13 (0.74, 1.73)	0.57			

*Chronic kidney disease: eGFR by Cockcroft-Gault formula < 60ml/min/1.73m^2 , PASP: pulmonary artery systolic pressure, RVR: revascularization

Supplementary Figure Legends

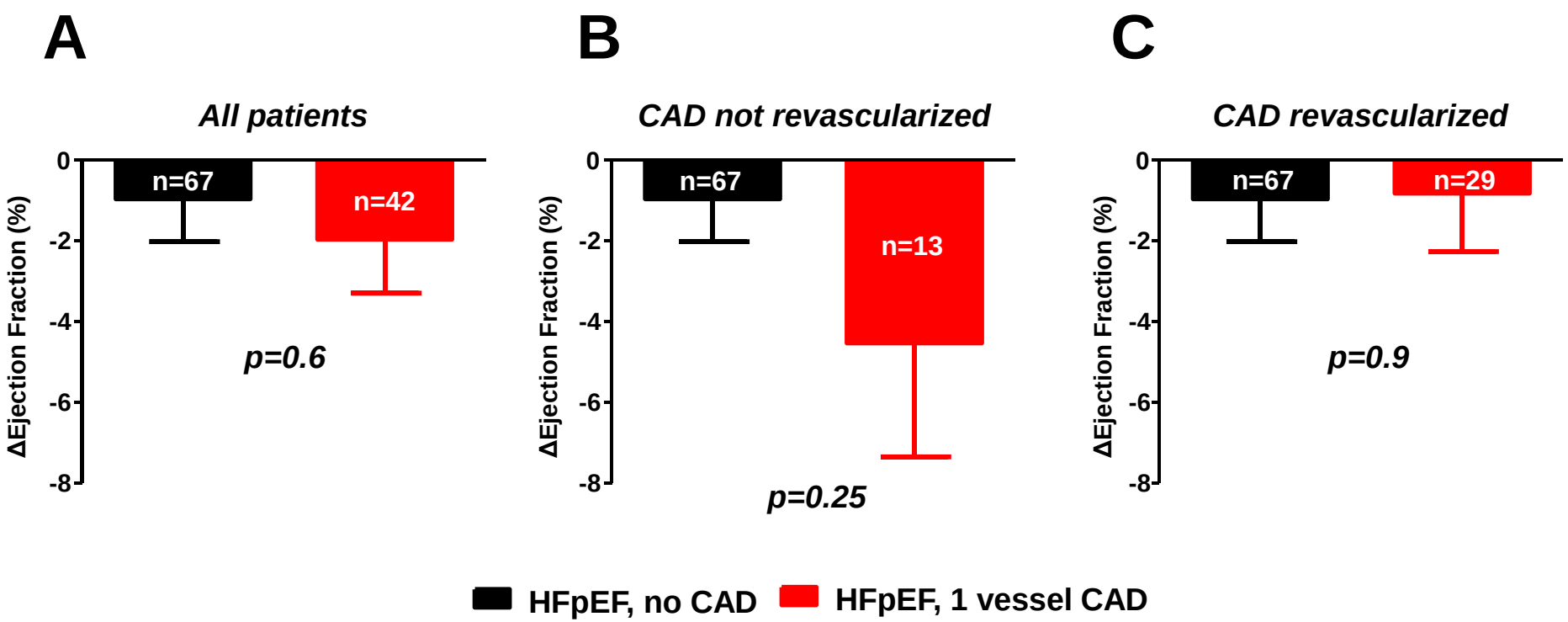
Figure 1: Longitudinal changes in EF in HFpEF patients with single vessel disease. Bar graphs show longitudinal changes in EF in HFpEF patients with no CAD (black) and patients with single vessel CAD (red) in the total sample [A], comparing no CAD to single vessel disease that were not revascularized [B], and comparing to single vessel disease with revascularization [C].

Figure 2: Impact of revascularization on survival in patients with CAD defined by stenosis ≥70%. Kaplan-Meier curve showing survival according to complete revascularization (revasc) versus partial or no revascularization among patients with HFpEF and CAD, defining revascularization as treatment of coronary lesions of >70% stenosis.

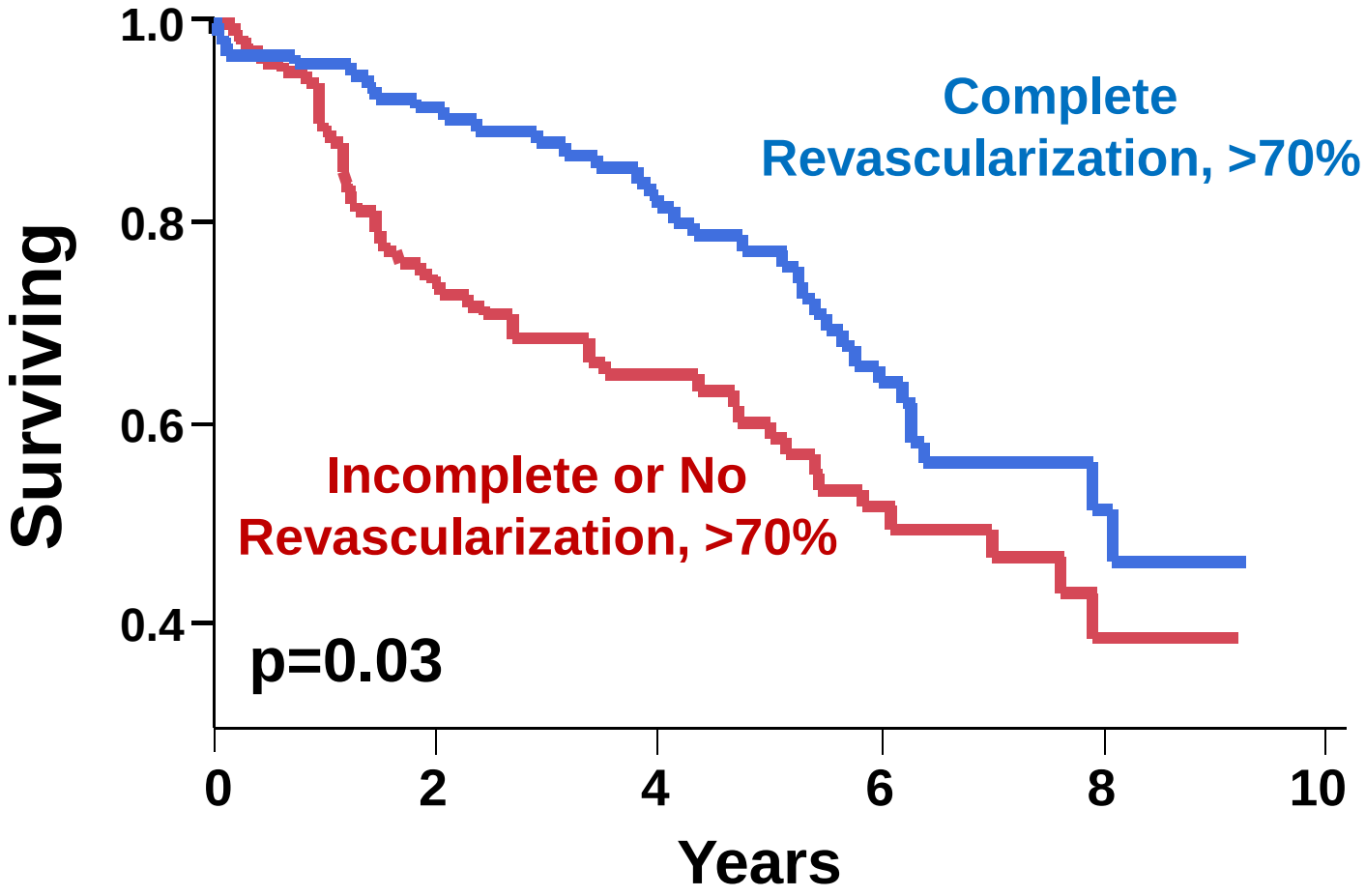
Figure 3: Impact of revascularization comparing complete, incomplete and no revascularization on survival. Kaplan-Meier curve showing survival according to complete revascularization (revasc) versus partial and no revascularization among patients with HFpEF and CAD.

Figure 4: Impact of mode of revascularization on survival. [A] Kaplan-Meier curve showing survival among HFpEF patients with CAD receiving complete revascularization (CR) with percutaneous intervention (PCI) and coronary artery bypass grafting (CABG) and [B] among all patients receiving any revascularization with PCI and CABG.

Figure 5: Survival in patients with CAD and single vessel disease compared to patients with no CAD. [A] Kaplan-Meier curve showing survival among HFpEF patients with no CAD (red) and patients with single vessel disease (blue) overall [A], and among patients with single vessel disease who were not revascularized [B] and who were revascularized [C].

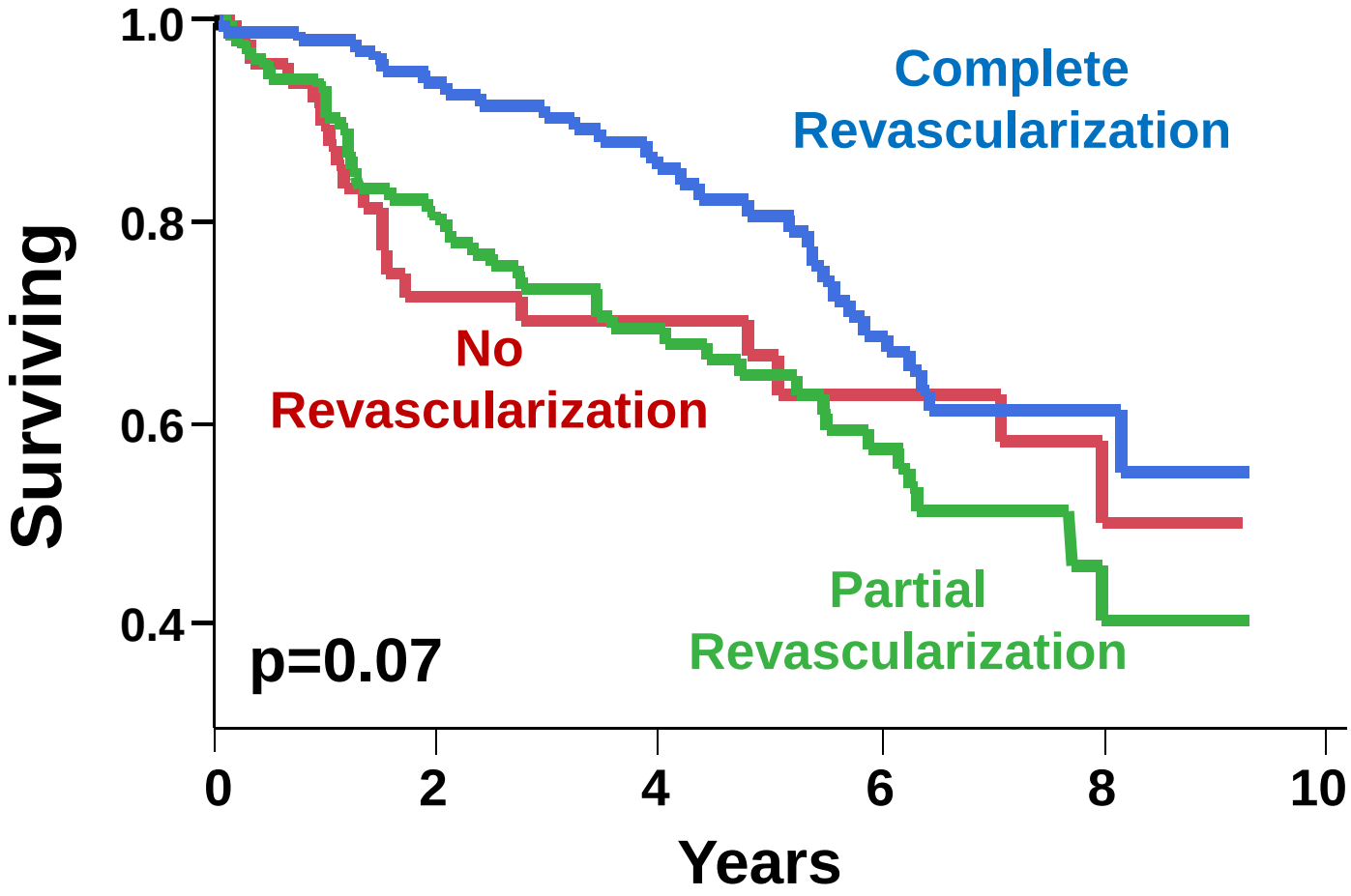


Supplementary Figure 1



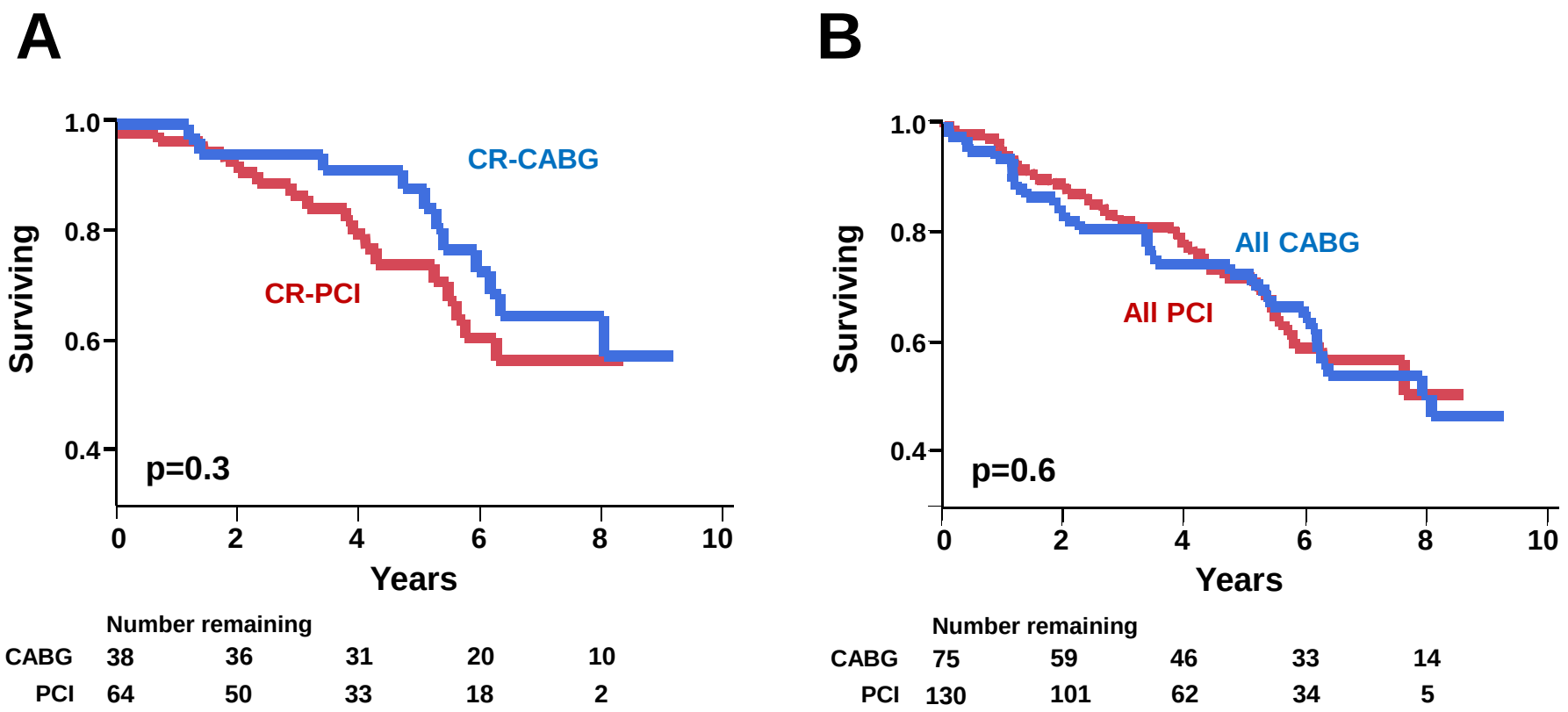
Number remaining					
Complete revasc	99	85	63	39	11
Partial/No revasc	104	75	48	30	9

Supplementary Figure 2

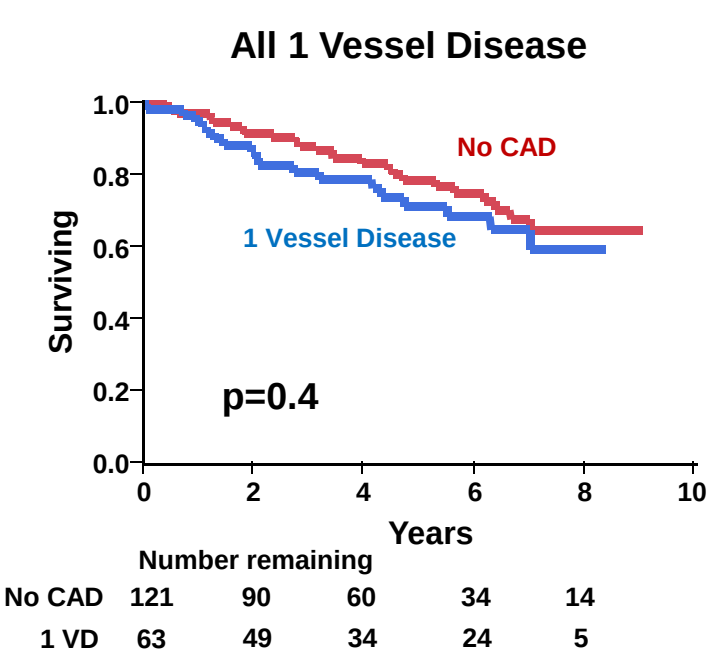


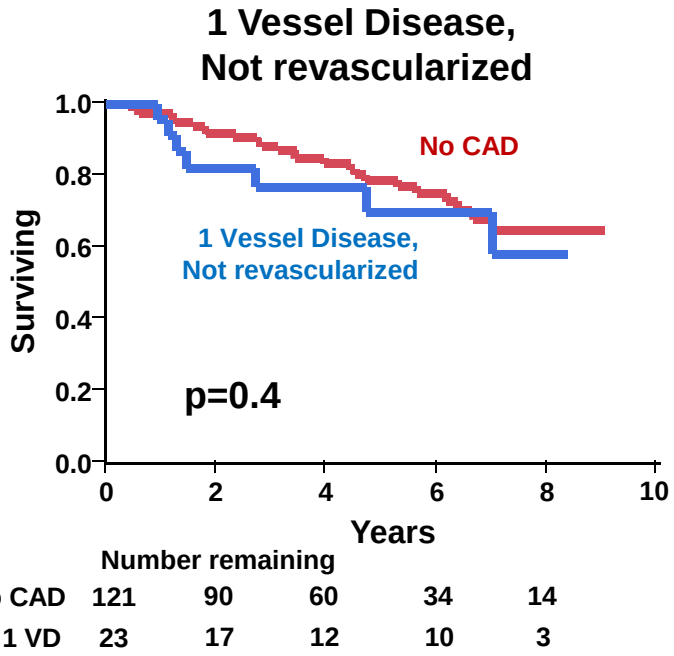
Number remaining					
Complete revasc	102	85	63	37	11
Partial revasc	103	75	46	30	8
No revasc	50	34	24	18	6

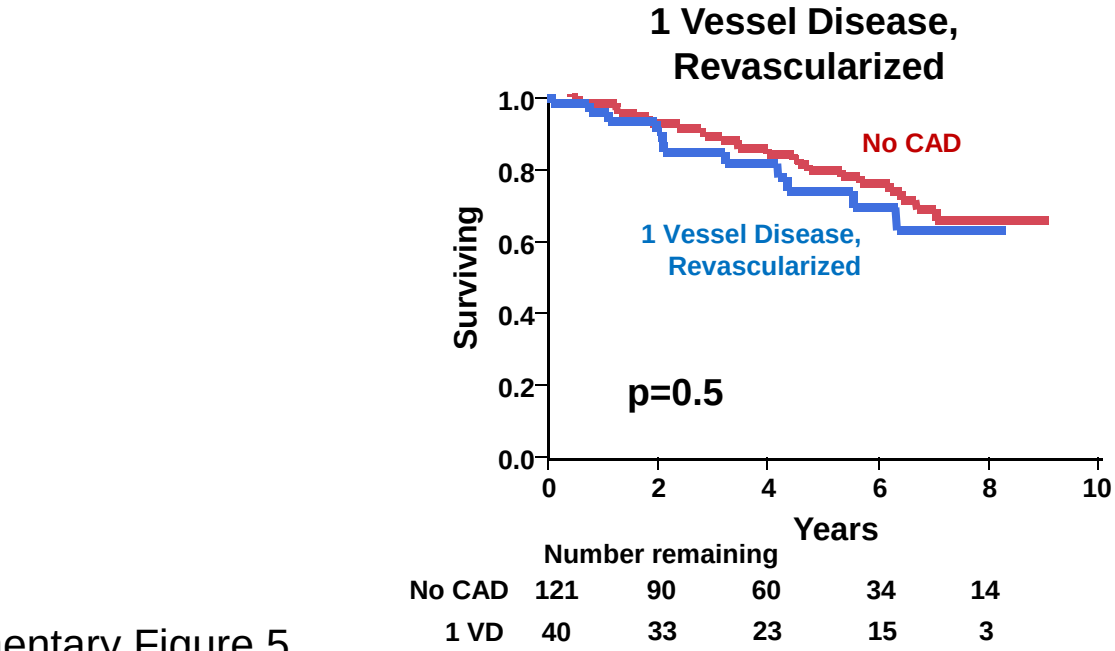
Supplementary Figure 3



Supplementary Figure 4







Supplementary Figure 5