Revascularization in Ischemic Heart Failure with Preserved Ejection Fraction: A Nationwide Cohort Study

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INTRODUCTION

Coronary atherosclerosis is one of the commonest comorbidities in heart failure regardless of ejection fraction. In Heart Failure with preserved Ejection Fraction (HFpEF) the presence of obstructive coronary artery disease may contribute to a distinct HFpEF phenotype.[1,2] Endothelial dysfunction, microvascular rarefaction and atherosclerosis have all been implicated in the pathogenesis of HFpEF, where myocardial ischemia may contribute to diastolic dysfunction and myocardial injury.[3–6] Although treatment for HFpEF remains limited, revascularization of obstructive coronary artery disease (CAD) is a potential treatment target given its high prevalence varying from >30-70% depending on the population studied[7,8].

Despite the common occurrence of CAD and HFpEF, there is only limited evidence to guide revascularization. A retrospective study observed a lesser decline in left ventricular ejection fraction over time and improved survival in the group that underwent revascularization.[9] Conversely, in a post hoc analysis of the ISCHEMIA trial, a benefit to revascularization could not be demonstrated even in the presence of moderate ischemia among the small (<200) HFpEF cohort.[10] Similar to older series[11], these data contrast to those of patients with a reduced ejection fraction where patients derive long term benefit from revascularization for severe CAD.[12] There is also increasing recognition that some patients with heart failure may exist across the continuum of EF.[13]

In contrast to non-ischemic HF where patients have similar risks of mortality between HFpEF and HFrEF (U shaped relationship between left ventricular ejection fraction and outcomes) and HF hospitalization regardless of EF,[14] we hypothesized that ischemic HF with significant CAD requiring CABG exists on a continuous spectrum with the highest risk of outcomes associated with low EF and progressively lower risk with preserved EF. To address this question, we evaluated a

large national cohort of patients undergoing isolated elective CABG from the Veteran Affairs (VA) Medical Centers in the United States, stratified by baseline HF status and EF.

METHODS

Data source

The VA Health Department has the largest integrated health system in the United States, with more than 170 hospitals and 1025 outpatient facilities. In the VA, electronic health records are stored in a central repository managed by the VA Informatics and Computing Center (VINCI), where patients are identified using Social Security information alone. The VA Surgical Quality Improvement Program (VASQIP) database is a quality assurance activity-derived database containing information on all patients who have undergone surgery within the VA system. We linked the VASQIP database to VINCI and identified all patients who underwent cardiac surgery in the VA for initial screening.

Study population

The study population included patients who underwent CABG for isolated stable CAD between January 1, 2005 and September 30, 2019 within the National VA Health System in the US. Patients undergoing CABG for acute coronary syndrome (ST elevation myocardial infarction, Non-ST elevation myocardial infarction and unstable angina), concomitant surgery for valvular replacement/repair, surgery for constrictive pericarditis, emergent CABG and those with cardiogenic shock were excluded from the study. **(Figure 1)**

Identification of different heart failure phenotypes

The presence of clinical HF was defined by ICD code for HF in addition to concurrent diuretic use for at least 30 days prior to CABG. Based on recent data suggesting that patients with low normal EF (<50-55%) respond to neurohormonal blockade,[13–17] we defined HFpEF using strict criteria of an EF>55%, HFrEF by an EF<40%, and HFmrEF by an EF of 40-55% **(Supplementary Table 1).** The HFpEF identification criteria has previously been validated in VA-VINCI with a sensitivity of 88%, specificity of 96% and a positive predictive value of 96%.[18]

Selection of controls/reference group

Patients undergoing CABG with no preoperative HF diagnosis were included as controls (i.e, no HF group). Patients with concurrent use of loop diuretic on admission were excluded from the control group. Population based studies have demonstrated that significant proportion of patients on loop diuretics with no clinical diagnosis of heart failure have unrecognised HFpEF. [19,20] In long term follow up, patients on loop diuretics with no diagnosis of HF had increased rates of HF hospitalisation similar to those with HFpEF signifying that these are plausibly unrecognised HFpEF. Therefore, these patients were excluded to increase the rigor and specificity of selecting true controls as presence of unrecognized HFpEF (patients on loop diuretics) in the control group might push results close to the null. We additionally excluded patients with asymptomatic LV systolic dysfunction and >2+ mitral regurgitation. This was done to increase the rigor and specificity of selecting true controls without occult HF.

Outcomes of interest

The primary outcome of interest was a composite of first heart failure hospitalization and all-cause mortality. Other outcomes of interest included median time to first heart failure hospitalization, recurrent heart failure hospitalization, and myocardial infarction (MI). Patients

were considered to have observed the event if they underwent readmission with the corresponding primary diagnosis.

Statistical analyses

Categorical data were presented as counts (percentage) while continuous data were presented as mean ± standard deviations (SD) when normally distributed; or medians with the interquartile (IQR) range if non-normally distributed. Pre-operative baseline characteristics and outcomes were compared between the 4 groups: No HF, HFpEF, HFmrEF and HFrEF. The χ^2 test was used for categorical data; depending upon distribution, continuous data were compared with the analysis of variance or the Kruskal-Wallis test.

Group-wise survival was estimated with the non-parametric Kaplan Meier method and tested with the log-rank test. The risk of observing our primary endpoint, adjusted for clinically important covariates, was obtained by fitting a semi-parametric Cox proportional hazards model (CPH). In the Kaplan Meier curve **(Figures 2A and 2B)** we observed a time-varying relationship between our heart failure group variable and the composite endpoint. The Therneau & Grambsch test confirmed that this variable failed the proportional hazards test. Thus, a segmented Cox model was fit splitting the follow-up period into three segments - 0-1 years, 1-5 years and beyond 5 years. Other variables included in the model were: age at surgery, sex, race, prior history of myocardial infarction, prior percutaneous intervention, prior stroke, chronic kidney disease, prior heart surgery, prior atrial fibrillation, peripheral vascular disease, and preoperative dialysis dependence. Hazard ratios (with 95% confidence intervals) were calculated for each HF group (HFpEF, HFmrEF and HFrEF) using the no HF group as control. This segmented Cox approach allowed us to reliably model the flexible time-varying hazard observed in the non-parametric Kaplan Meier curve.

Myocardial infarction was modeled with all-cause mortality as the competing risk event. The non-parametric cumulative incidence function was implemented to obtain event rates of myocardial infarction for each heart failure group during the study period. The median time to first heart failure hospitalization in each heart failure group was obtained and compared with the no HF group with the Wilcoxon rank sum test. In order to understand the heart failure burden in each phenotype, heart failure hospitalizations were also modeled as recurrent events. All heart failure hospitalizations for every patient during the study period were identified. To ensure that in-hospital transfers were not spuriously labelled as new admissions, any readmission beyond 7 days was defined as a new event, while those within that time frame were disregarded. A non-parametric mean cumulative count method was adopted to obtain the number of heart failure hospitalizations per 100 patient-years of follow-up in each HF group. The marginal means model, introduced by Wei, Lin and Weissfield, was used to model the heart failure burden. A multivariable model, including the same variables listed earlier, was fit to obtain the adjusted hazard ratio (with 95% confidence intervals) for heart failure hospitalizations in HFpEF, HFmEF and HFrEF patients compared to the reference group (no HF).

Missing data were minimal; chronic kidney disease (1.2%) and peripheral arterial disease (3%) were the only variables with more than 1% missing information. Simple imputation was performed to avoid losing data; according to variable type, missing fields were filled with either the mean or mode value for that particular variable. Statistical analysis was conducted in R 3.6.3 (The R Foundation for Statistical Computing, Austria).

RESULTS

Cohort characteristics

After applying the study inclusion and exclusion criteria, a total of 10396 patients were identified that underwent isolated CABG for stable CAD. Overall, 4740(46%) patients had no known HF; whereas 667(6%) had HFpEF, 2370(23%) had HFmrEF, and 2619(25%) had HFrEF **(Table 1)**. The median age of patients in the study cohort was 65 years (interquartile range 60 – 71) and was similar in all 4 cohorts. Patients with HFpEF were more likely to be Caucasian, obese, and have atrial fibrillation compared to other groups **(Table 1).** Patients with HFrEF who had CABG were more likely to have history of prior MI, advanced CKD (>stage 3), anemia, lower serum albumin and higher New York Heart Association (NYHA) score at baseline.

Overall survival following CABG stratified by heart failure phenotypes

The median follow-up for the entire cohort was 6.63 years (IQR 3.69 – 10.05). The estimated 5-year all-cause mortality following CABG progressively worsened as baseline LVEF declined being 14±0.5%, 16±1.3%, 24±0.9% and 29±0.9% in the no HF, HFpEF, HFmEF and HFrEF groups respectively **(Figure 2A**). A similar trend was observed at 10 years, although, mortality for HFpEF was similar to that of patients with no HF (35±0.8% vs 34±2.3%). Compared to these groups, a substantially higher 10-year mortality was observed with HFmrEF (50±1.2%) and HFrEF (58±1.1%). **(Figure 2A).** The 30-day unadjusted mortality rates were 1.9 %, 1.6%, 0.6% and 0.7 % in the HFrEF, HFmrEF, HFpEF, and the no HF group respectively.

Composite end point of mortality and HF hospitalization across HF phenotypes

At 5 years, the composite endpoint of all-cause mortality and first HF hospitalization also demonstrated a graded increase from no HF patients to HF patients with lower EF (18±0.5%, 21±1.6%, 35±1% and 43±1% in the no HF, HFpEF, HFmEF and HfrEF groups respectively)

(Figure 2B). Similar trends were seen at 10 years, with the no HF and HFpEF patients demonstrating largely similar risk in longer follow up (39±0.8%, 41±2.4%, 51±1.2% and 67±1% in the no HF, HFpEF, HFmEF and HFrEF groups respectively).

The change in the adjusted hazard ratios for each HF phenotype is obtained from the segmented hazard ratios with 95% CI for first one year of follow up, 1-5 years and the entire follow up period provide information on varying risk depending on follow up period (**Figure 2)**. Consistent with the above analyses, survival of patients with HFrEF following revascularization was the lowest, followed by HFmrEF and HFpEF **(Table 2).** Among HFpEF patients surviving beyond 1 year, the cumulative event rate gradually decreased to approach that of controls. Despite upfront risk with an increased hazard in the first year following revascularization, the long-term survival of HFpEF post CABG was comparable to CABG patients with no history of HF (HR 0.85, 95% CI 0.68-1.06) **(Table 2 and Figure 3 A-C).**

When the primary outcome was analyzed stratified by the degree of baseline systolic function, patients with HF and EF > 55% and those with EF of 45-54% had outcomes which were comparable to the reference group. There was a graded increased in adjusted HR for primary outcome with declining EF **(Figure 4).** The rates of post-operative mechanical support (including extracorporeal membrane oxygenation-ECMO, ventricular assisted device, IABP) were 2.6%, 12.6%,4.7%, and 3.4% in the no HF, HFrEF, HFmrEF and HFpEF groups respectively. Additionally, there was no statistically significant difference in the hazard for the primary outcome between the groups when use of mechanical support was included in the model

Heart failure hospitalizations following CABG stratified by heart failure phenotype

Overall, there were 3344 heart failure hospitalizations in the whole cohort. Consistent with baseline definitions, there was a low risk of future HF in the group with no HF at baseline, and risk progressively increased with lower EF at baseline from HFpEF to HFmrEF to HFrEF. At 5 years, the incidence of recurrent heart failure hospitalizations was 6.1 ± 0.5 (no HF), 21.9 ± 3.4 (HFpEF), 36.6 ± 2.4 (HFmrEF) and 49.9 ± 2.6 (HFrEF) per 100 patient years of follow up. At 10 years, the analogous risks were 14.3 ± 1.1, 43.9 ± 6.9, 65.9 ± 3.8 and 93.4 ± 4.8 heart failure hospitalizations per 100 patient years respectively **(Figure 5 A)**. The median time to first heart failure hospitalization post CABG was progressively shorter with a lower baseline EF **(Figure 5 B).** On adjusted analysis, HFpEF [HF 2.32(1.93 – 2.79); $p < 0.001$], HFmEF [HF 3.49(3.09 – 3.93); $p < 0.001$] and HFrEF [HR 5.01 (4.46 – 5.63); $p < 0.001$] had higher risk for heart failure hospitalizations compared to the control group.

Myocardial infarction following CABG stratified by HF phenotype and its impact on overall survival

Figure 6 describes the cumulative estimate for MI following revascularization for the entire cohort stratified by HF phenotype. In contrast with mortality and HF hospitalization rates, HFpEF patients post CABG had the highest rates of incident MI (9.8%), followed by no HF group (7.9%) with lower rates as baseline EF declined [HFmEF (6.2%), and HFrEF (5.3%)]. Compared to the no HF group, the crude risk of myocardial infarction was higher in the HFpEF [HR 1.52(1.11 – 2.08); $p = 0.007$] and HFmrEF [HR 1.31(1.07 – 1.56); $p = 0.008$].

Subgroup analyses

Additional analysis was performed to investigate the impact of diabetes mellitus on the primary outcome **(Supplementary Figure S1)** within individual heart failure phenotypes. Patients with diabetes mellitus had a higher risk for primary outcome across the spectrum of HFpEF, HFmrEF and HFrEF following revascularization. Sensitivity analyses performed after excluding patients with recent AMI revealed similar results.

DISCUSSION

In this nationwide analysis of predominantly men with severe CAD undergoing isolated CABG in the VA health system, we carefully stratified patients by baseline HF phenotype (HFpEF, HFmrEF, HFrEF) and compared their future risk of death, HF hospitalization and MI to a control group of patients without HF who underwent CABG **(graphical abstract)**. The major findings are as follows *i)* The long-term risk of death and heart failure hospitalization of patients with HFpEF undergoing CABG was comparable to that of patients without heart failure, despite having increased risk in the first year following CABG. ii) HFpEF patients post CABG continue to remain at higher risk for HF hospitalizations compared to controls despite similar overall survival. iii) Notably, the risk of death mortality and future HF hospitalization increased in a graded fashion as baseline EF declined to the HFmrEF and HFrEF ranges and were consistently higher than patients with HFpEF undergoing CABG iv) Although HFpEF patients had lower mortality and HF hospitalization post CABG compared to patients with a lower EF, the risk of future MI was highest in patients with HFpEF suggesting important residual risk from future coronary events in HFpEF. These data provide important estimates of long-term outcomes following CABG in HF across the spectrum of LVEF, as well as long term risk of recurrent HF hospitalizations, myocardial infarction and death, which appears to be strongly related to LVEF.

Data on Surgical Revascularization for stable CAD across the spectrum of HF

Randomized data for surgical revascularization for HF with severe CAD is limited to patients with HFrEF and significant systolic dysfunction (EF<35%) in the STICH trial. With 10 years of follow up, there was a reduction in death compared to medical therapy alone.[12] In the recent ISCHEMIA trial there appeared to be a benefit in a post hoc analysis of a small number of patients with mid-range EF [10], but no benefit was seen in HFpEF. There is no additional randomized evidence on CABG in patients with HFpEF to guide management decisions. Similar to the ISCHEMIA trial, the larger CASS registry could not demonstrate a survival advantage to CABG.[21] In a retrospective analysis, Borlaug et al demonstrated that patients undergoing revascularization compared to those who did not, had better survival and less decline in ejection fraction over time. However, the observational nature and unmeasured confounding inherent to the physician choosing not to revascularize the control group limits causal inference.[9]There are currently no randomized trials ongoing to evaluate CABG for CAD in HFpEF, and guidelines recommend managing CAD independent of HFpEF status.

In the absence of randomized data, real world data such as this are important to accurately inform providers and patients of the risks of intervention and expected long term outcomes. We demonstrate that despite an upfront risk for CABG in HFpEF, long term survival is similar to controls without HF, although higher risk of future HF hospitalization persists. A lower baseline EF seems to be a strong predictor of poorer long term outcomes following CABG. Following revascularization, HFpEF patients continue to have a risk of HF hospitalization but this may be lower than patients with more baseline systolic dysfunction. Whether CABG truly improves risk of HF hospitalization, mortality and functional status in HFpEF patients with severe CAD requires a prospective randomized trial.

Our results differ from those of a nationwide Swedish cohort and from the CREDO-Kyoto CABG Registry where HFpEF patients post CABG had increased adjusted hazard for mortality compared to those with no HF.[22,23] This could be related to differences in the diagnostic criteria for HFpEF, variations in CABG referral patterns, our longer follow up time, regional differences in HFpEF patient populations (our HFpEF cohort was more obese than prior studies and consistent with HFpEF cohorts from the US,[24] which may introduce a statistical obesity paradox), and the primary inclusion of a Veteran US population which was mostly male (since women may have poorer survival post CABG in HFpEF).[25] Future research is needed to understand the reasons for different CABG outcomes in HFpEF across countries.

CAD-HFpEF- A distinct phenotype on the spectrum of ischemic cardiomyopathy?

Concomitant CAD and myocardial infarction have prognostic implications in patients with HFpEF and are associated with a higher risk of cardiovascular death and heart failure hospitalization compared to HFpEF patients with no CAD or prior infarct.[26] Although it is clear that HFpEF can occur without CAD through comorbidity driven inflammation and associated changes in myocardial active and passive stiffness,[3,27] this does not preclude the addition of a superimposed myocardial insult from obstructive CAD. Myocardial ischemia can contribute to ischemia related active diastolic dysfunction and impaired exercise hemodynamic reserve, which is a hallmark of HFpEF,[28,29] and prior studies have suggested that exercise hemodynamics improve following revascularization.[30,31] This enhanced myocardial reserve may account for the lower risk of HF hospitalization in revascularized HFpEF patients,[32] compared to those with baseline systolic dysfunction which may not consistently normalize following revascularization. [33]Furthermore, baseline and subsequent myocardial infarcts can contribute to regional heterogeneity in myocardial systolic and diastolic performance,[34] adverse myocardial remodeling and future risk of decline in

systolic performance and EF,[35] and future risk of adverse outcomes.[26] Therefore, patients with HFpEF and severe CAD, may have an important contribution to their disease process from obstructive CAD, revascularization of which may acutely improve hemodynamic reserve and decrease short and long term risk for CV events.

Clinical and Research Implications

This conceptual framework coupled with the graded increment in events as baseline LVEF declines, suggests there may be a subset of HFpEF patients with severe CAD that represents a milder phenotype of ischemic cardiomyopathy with subtle myocardial impairment, that may not be identifiable by standard EF measures. Future research into novel methods to identify this subset of HFpEF patients with mild ischemic cardiomyopathy phenotype such as global left ventricular longitudinal strain are urgently needed,[36] as this subset of HFpEF-CAD patients may stand to benefit from traditional neurohormonal antagonists, [13–17] despite a preserved LVEF. Our data provides some evidence that HF patients with severe CAD may exist across as a continuum across the range of EF which provides an index of severity of their ischemic cardiomyopathy. This is in contrast to the survival patterns in the overall HF patient population (ischemic and non-ischemic), where patients with HFmrEF appeared to be have better survival than both HFpEF and HFrEF signifying a U-shaped relationship between EF and outcomes.[14,37] These hypotheses require future investigation and confirmation.

Strengths and limitations

Previous studies have shown a poor discriminative performance of clinical and non-invasive stress testing strategies for identification of CAD among patients with HFpEF. [11,25] Since our cohort included patients undergoing CABG, it is likely that these patients had angiographically

proven CAD with significant ischemic burden and this data cannot be extrapolated to revascularization for milder degrees of ischemia or less severe coronary disease. Unlike previous studies, we had included a rigorous definition of HFpEF which was well validated and excluded all potential alternative causes of cardiomyopathy (e.g., valvular cardiomyopathy, acute coronary syndromes, constrictive and restrictive cardiomyopathy), although our analysis is limited by the primary male population. However, this does exclude the confounding influence of sex which can complicate interpretation across EF spectrum which may vary by sex as observed in the PARAGON trial.[38] The baseline characteristics of HFpEF and HFrEF patients in our cohort were in line with the previous studies, with significantly higher prevalence of Caucasians, obesity and atrial fibrillation among patients with HFpEF and a higher prevalence of prior MI in patients with HFpEF. [21,26,27]The 10-year event rates in the HFrEF population following CABG in this study was similar to the revascularization arm of the STICH trial, signifying reasonable validity to the results of the analysis. [9]

While our study has several strengths there are some important limitations. The co-morbidity burden among the Veterans may be different from those in the population. The external applicability of the study to the general population needs further evaluation. The classification of HFpEF in this study required a higher ejection fraction than defined in the European Society of Cardiology guidelines (55% instead of 50%). This is because EF was only available as a nominal variable in the VASQIP database. EF was categorized into six groups <20%, 20-30%, 30-35%, 35-40%, 41-45%, 46-55% and > 55%. As this study included CABG eligible HFpEF population, the elderly frail co-morbid HFpEF with severe CAD were likely to have been under-represented as they could have undergone percutaneous revascularization. We were not able to reliably differentiate type 1 from type 2 MI in this large national cohort. However, we have included only

those with myocardial infarction as the primary diagnosis of hospitalization (and discharge) during follow up in the event rate calculation, making it less likely to be type 2 MI. Certain important information such as the cause of death, continuation or initiation of heart failure medications after discharge, data on myocardial viability and follow up echocardiogram were not available in this database. Furthermore, data on incomplete revascularization was not available in this database.

In Conclusion, this nationwide study suggests that HFpEF patients with CAD undergoing CABG have comparable long-term survival to controls, and this is better than survival in HF patients with reduced EF undergoing CABG. Despite revascularization, risk of HF hospitalization persists in HFpEF, although this occurs at a lower rate than patients with a reduced EF. Following surgical revascularization, HFpEF patients suffer the highest rates of future myocardial infarction emphasizing the importance of secondary CV prevention in HFpEF. Overall, the data supports the safety of CABG in HFpEF patients and suggests a possible continuum of risk for ischemic HF when stratified by baseline EF. It is possible that early intervention with revascularization in HFpEF can be performed with a long term survival rate approaching that of controls. Further randomized trials of the clinical benefit of CABG in HFpEF with severe CAD are needed, given the paucity of current treatment options available.

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Figure Legends:

Figure 1: Number of patients in the base cohort and study cohort

VASQIP: Veteran Affairs Surgical Quality Improvement Program; STEMI: ST elevation myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction; HF: Heart Failure;

HFpEF: Heart Failure with preserved ejection fraction; HFmrEF: Heart Failure with mid-range ejection fraction; HFrEF: Heart Failure with reduced ejection fraction; CAD: Coronary artery disease

Figure 2: Outcomes following CABG stratified by HF phenotypes 2A) All cause mortality 2B) Composite of all-cause mortality and heart failure hospitalization

HFpEF: Heart Failure with preserved ejection fraction; HFmrEF: Heart Failure with mid-range ejection fraction; HFrEF: Heart Failure with reduced ejection fraction

** Model was adjusted for surgery, sex, race, prior history of myocardial infarction, prior percutaneous intervention, prior stroke, chronic kidney disease, prior heart surgery, prior atrial fibrillation, peripheral vascular disease, and preoperative dialysis dependence*

Figure 3: Multisegmented Cox model for primary outcome stratified by different time periods 3A) 0-1-year 3B) 1-5 years 3C) 5-10 years

HR: adjusted hazard ratio; HF: Heart Failure; HFH: Heart Failure Hospitalization; HFpEF: Heart Failure with preserved ejection fraction; x axis: follow up time in years

** Group with no heart failure was used as the reference*

** Model was adjusted for surgery, sex, race, prior history of myocardial infarction, prior percutaneous intervention, prior stroke, chronic kidney disease, prior heart surgery, prior atrial fibrillation, peripheral vascular disease, and preoperative dialysis dependence*

Figure 4: Primary outcome stratified by different grades of systolic function

EF: left ventricular ejection fraction; HR: adjusted hazard ratio; HF: Heart Failure; HFH: Heart Failure Hospitalization; HFpEF: Heart Failure with preserved ejection fraction

** Group with no heart failure was used as the reference*

** Model was adjusted for surgery, sex, race, prior history of myocardial infarction, prior percutaneous intervention, prior stroke, chronic kidney disease, prior heart surgery, prior atrial fibrillation, peripheral vascular disease, and preoperative dialysis dependence*

Figure 5: Heart Failure burden following CABG stratified by HF phenotypes; 5A) Outcome: Heart Failure hospitalizations as a recurring event; 5B) Outcome: Median Time to First Heart Failure Hospitalization

HF: Heart Failure; HFpEF: Heart Failure with preserved ejection fraction; HFmrEF: Heart Failure with mid-range ejection fraction; HFrEF: Heart Failure with reduced ejection fraction; HFH: Heart Failure Hospitalization

** Model was adjusted for surgery, sex, race, prior history of myocardial infarction, prior percutaneous intervention, prior stroke, chronic kidney disease, prior heart surgery, prior atrial fibrillation, peripheral vascular disease, and preoperative dialysis dependence*

Figure 6: Cumulative incidence of myocardial infarction following CABG stratified by heart failure phenotypes

HFpEF: Heart Failure with preserved ejection fraction; HFmrEF: Heart Failure with mid-range ejection fraction; HFrEF: Heart Failure with reduced ejection fraction

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V.S was involved in the study design, data analysis, manuscript writing. S.V.D participated in data analysis. Y.NV.R, R.Z, M.K, P.S,Y.E, A.K, J.R, S.E.A, M.N.O, R.A.J, S.K.M.M, B.C, D.I.S, S.R, J.G.C, J.S were involved in manuscript preparation and participated in critical revision of all drafts of the manuscript.

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Figure 1: Numbers of Patients in the Base Cohort and Study Cohort.

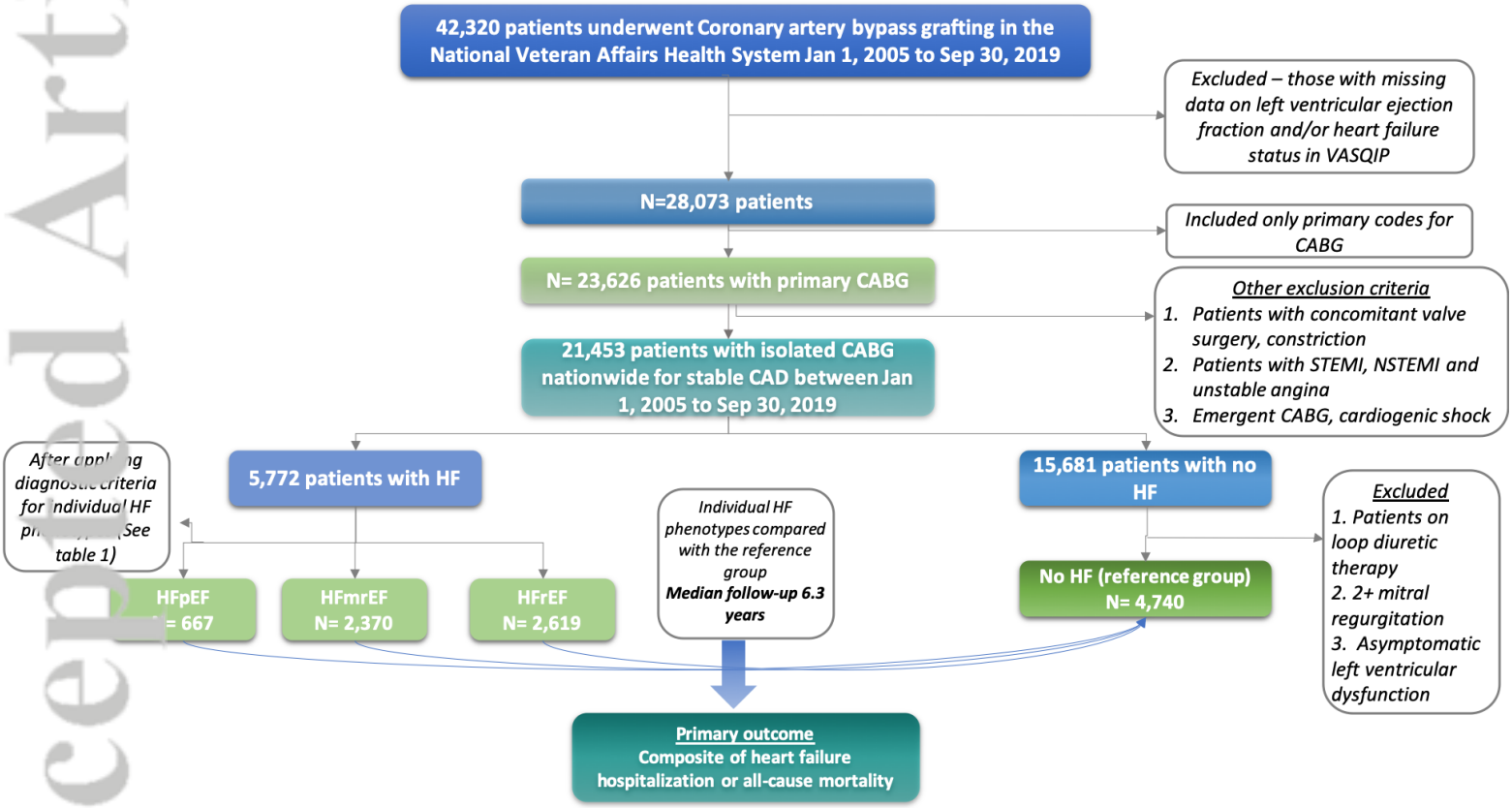


Figure 1.tiff

Figure 2: Outcomes following CABG stratified by HF phenotypes

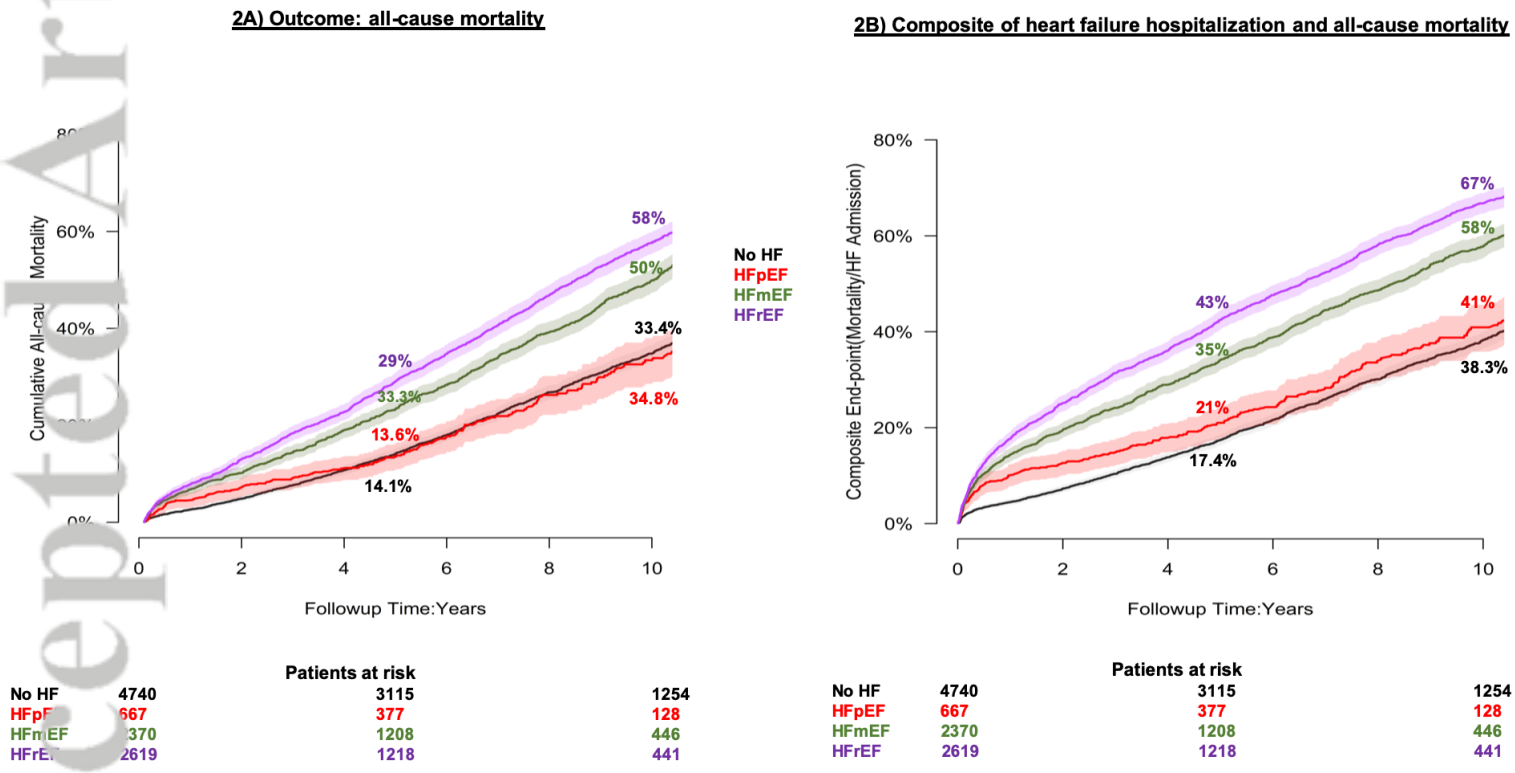


Figure 2.tiff

Figures 3A-C: Multisegmented Cox model for primary outcome stratified by different time periods (no HF as the reference group)

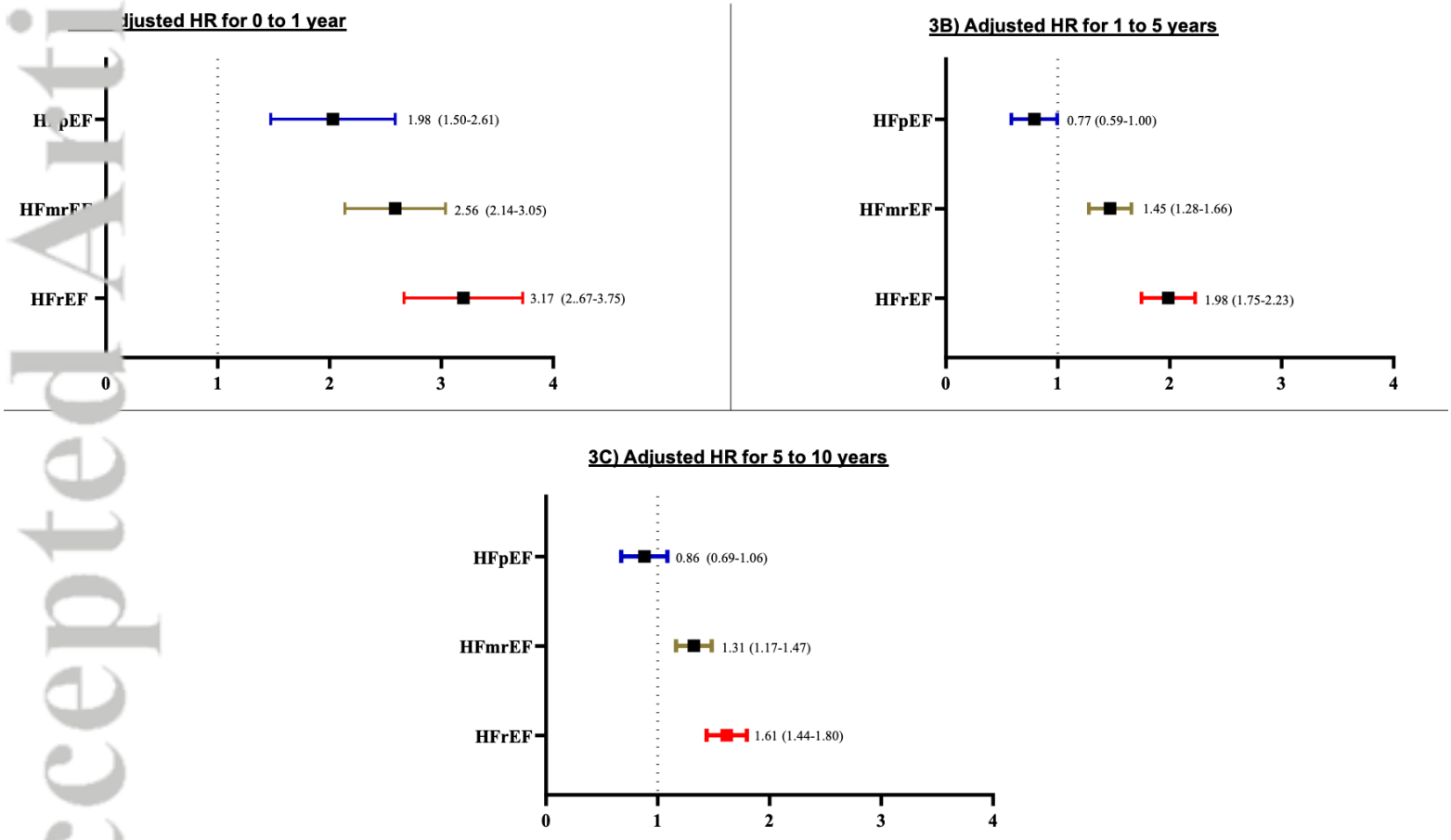


Figure 3.tiff

Figure 4: Primary outcome stratified by different grades of systolic function

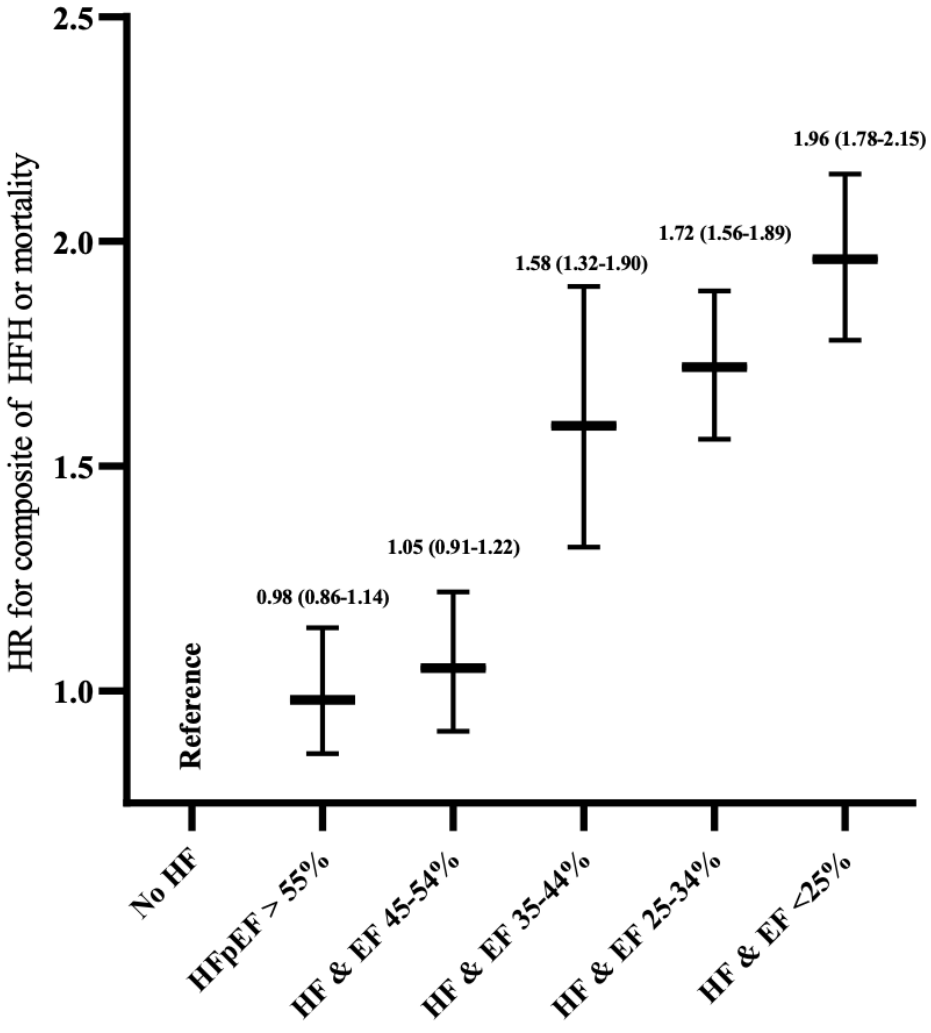


Figure 4.tiff

Figure 5: Heart Failure burden following CABG stratified by HF phenotypes

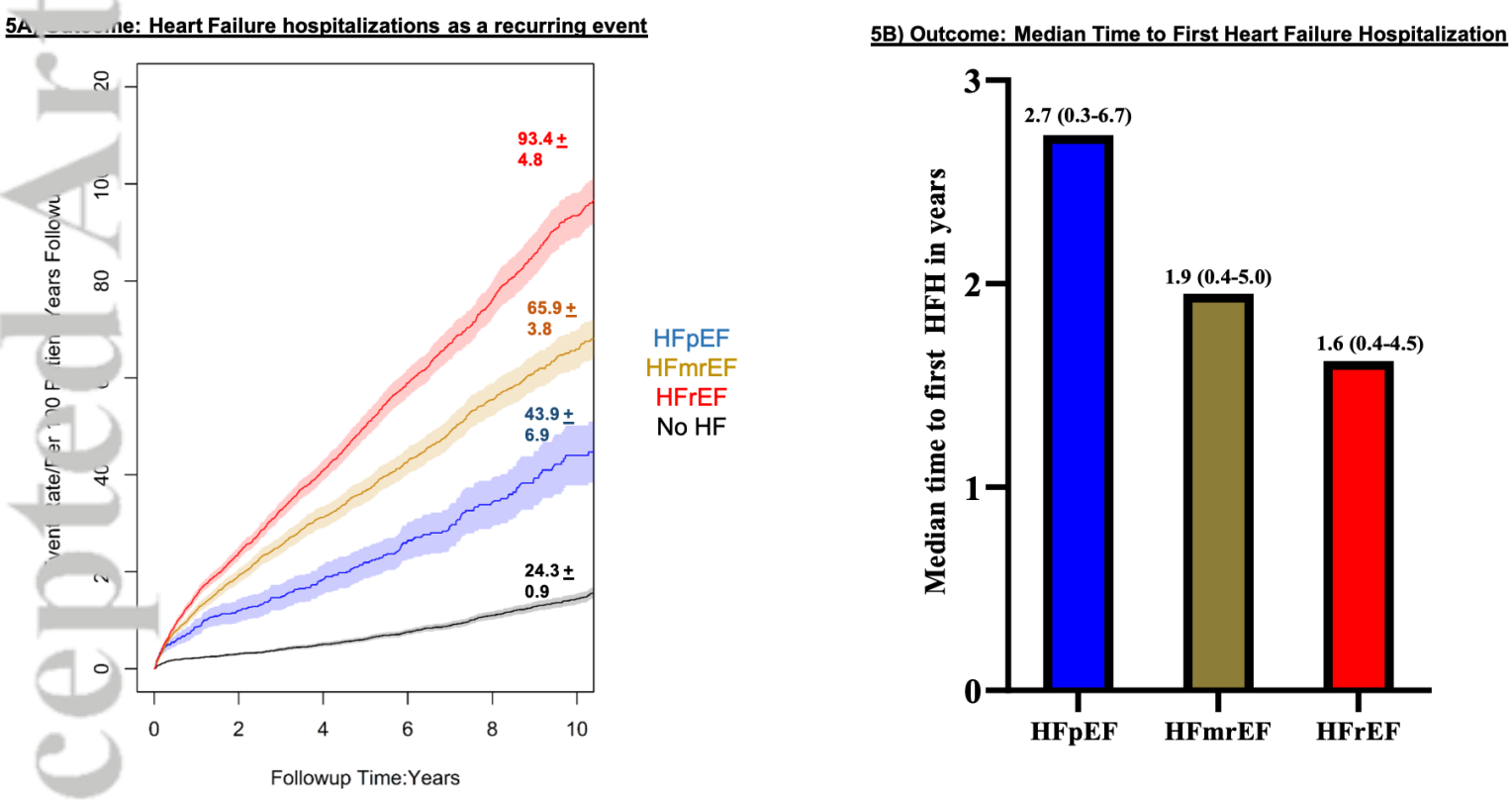


Figure 5.tiff

Figure 6: Cumulative incidence of myocardial infarction following CABG stratified by heart failure phenotypes

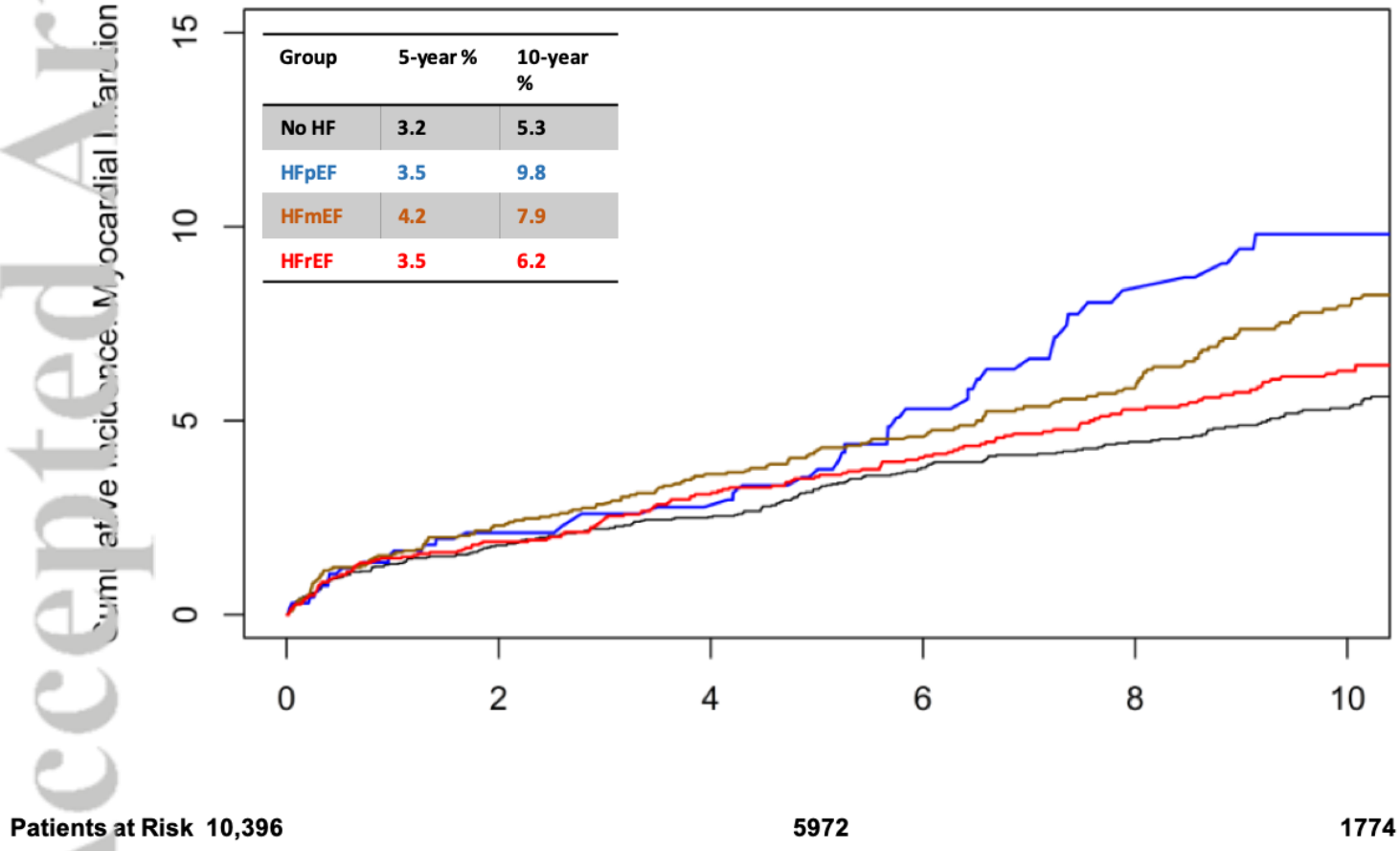
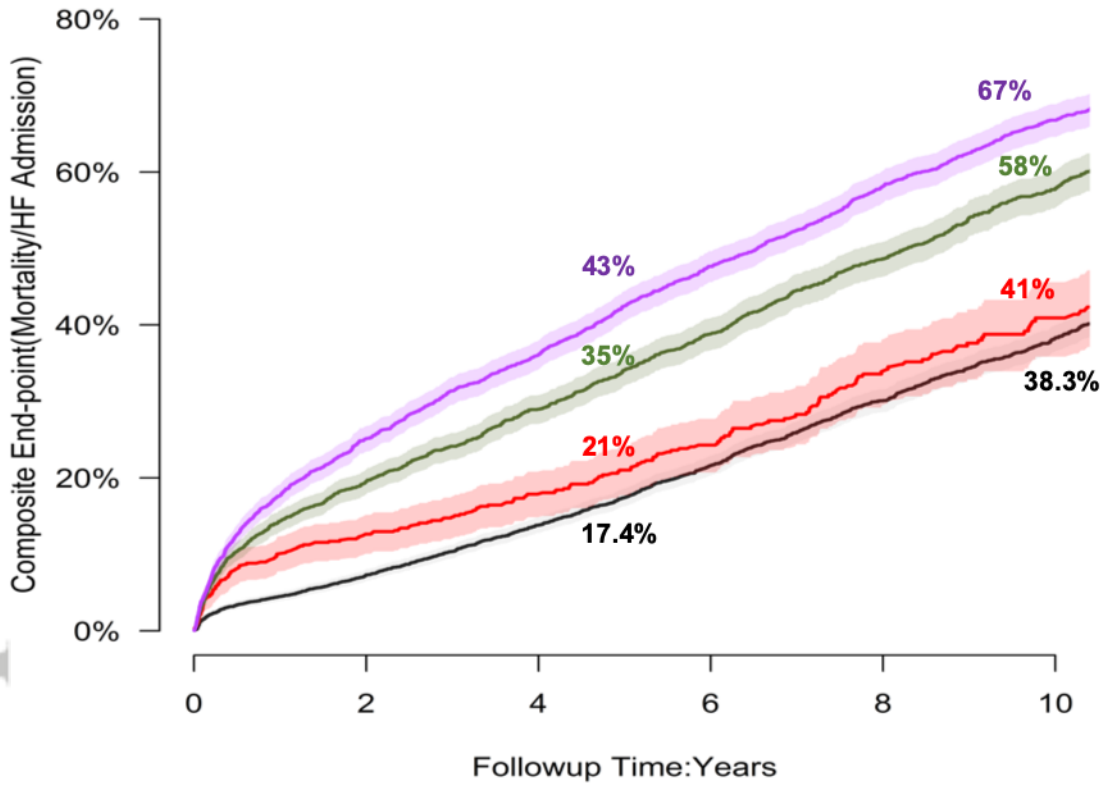


Figure 6.tiff

Outcomes following CABG stratified by heart failure phenotypes



Patients at risk			
No HF	4740	3115	1254
HFpEF	667	377	128
HFmEF	2370	1208	446
HFrEF	2619	1218	441

Graphical abstract.tiff

Permission Note:

All materials, including manuscript, tables, and figures, are original to this submission and have been neither published elsewhere nor submitted for publication simultaneously.

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	No HF	HFpEF	HFmrEF	HFrEF	P-value
N	4,740	667	2,370	2,619	
Demographics					
Age (median [IQR])	65.0 [61.0, 71.0]	66.0 [62.0, 71.0]	65.0 [60.0, 72.0]	65.0 [60.0, 71.0]	0.03
Female, n (%)	46 (1.0)	7 (1.0)	22 (0.9)	17 (0.6)	0.51
Race, n (%)					<0.001
Black	357 (7.5)	51 (7.6)	220 (9.3)	296 (11.3)	
Others	958 (20.2)	102 (15.3)	423 (17.8)	515 (19.7)	
White	3425 (72.3)	514 (77.1)	1727 (72.9)	1808 (69.0)	
Co-morbidities, n (%)					
Diabetes	1,784 (37.6)	320 (48.0)	1,210 (51.1)	1,207 (46.1)	<0.001
Prior stroke	94 (2.0)	10 (1.5)	31 (1.3)	28 (1.1)	0.014
Prior MI	1,483 (31.3)	235 (35.2)	1,231 (51.9)	1,569 (59.9)	<0.001
Prior PCI	211 (4.5)	32 (4.8)	75 (3.2)	69 (2.6)	<0.001
CKD	693 (14.6)	107 (16.1)	500 (21.2)	636 (24.3)	<0.001
Obese	1,811 (38.2)	364 (54.6)	1,169 (49.3)	972 (37.1)	<0.001
Anemia	1,441 (30.4)	252 (37.8)	1,008 (42.6)	1,152 (44.0)	<0.001
Peripheral vascular disease	1,088 (23.0%)	169 (25.4%)	732 (30.9%)	820 (31.3%)	<0.001
NYHA (mean (SD))	1.51 (0.50)	2.31 (0.92)	2.43 (0.97)	2.55 (0.97)	<0.001
Smoking	3,897 (82.2)	554 (83.1)	1,999 (84.3)	2,269 (86.6)	<0.001
Atrial Fibrillation	990 (20.9)	165 (24.7)	546 (23.0)	592 (22.6)	0.039
Mitral regurgitation severity					<0.001
0	3,324 (79.6)	429 (70.7)	1,292 (62.1)	1,100 (46.9)	
1+	851 (20.4)	138 (22.7)	575 (27.6)	830 (35.4)	
2+	0 (0.0)	23 (3.8)	136 (6.5)	342 (14.6)	
3+	0 (0.0)	17 (2.8)	78 (3.7)	71 (3.0)	
Baseline measurements					
BMI (median [IQR])	28.0 [25.6, 31.9]	30.7 [27.4, 34.8]	29.9 [26.3, 33.9]	28.3 [24.7, 31.9]	<0.001
HBA1c (mean (SD))	6.6 (1.4)	6.8 (1.3)	6.9 (1.5)	6.9 (1.6)	<0.001
Creatinine (median [IQR])	1.00 [0.9, 1.2]	1.1 [0.9, 1.3]	1.1 [0.9, 1.3]	1.1 [0.9, 1.3]	<0.001
eGFR (mean (SD))	90.7 (31.4)	90.4 (35.8)	88.2 (36.9)	83.7 (35.5)	<0.001
Hemoglobin (median [IQR])	13.8 [12.6, 14.8]	13.4 [12.2, 14.5]	13.3 [12.0, 14.4]	13.2 [11.8, 14.4]	<0.001
Serum albumin (median [IQR])	3.9 [3.6, 4.2]	3.9 [3.5, 4.2]	3.8 [3.40, 4.10]	3.7 [3.4, 4.1]	<0.001
Serum bilirubin (mean (SD))	0.6 (0.3)	0.6(0.3)	0. (0.32)	0.7 (0.4)	<0.001
Medications prior to surgery, n (%)					
Loop diuretic	0	667 (100%)	1,793 (75.7%)	1,260 (48.1%)	<0.001
Preoperative IABP use	67 (1.4)	9 (1.3)	64 (2.7)	200 (7.6)	<0.001
Number of bypass grafts					
All Grafts, n (%)					0.089
1	363 (10.0)	55 (12.5)	195 (11.1)	189 (9.3)	
2	910 (24.9)	114 (26.0)	438 (24.9)	517 (25.5)	
3	1,614 (44.2)	188 (42.8)	716 (40.7)	865 (42.6)	

>3	761 (20.9)	82 (18.7)	409 (23.3)	459 (22.6)	
Medications at Discharge, n (%)					
ACEI/ARB	1,245 (26.3)	183 (27.4)	742 (31.3)	1,018 (38.9)	<0.001
Betablockers	4,584 (96.7)	643 (96.4)	2,267 (95.7)	2,511 (95.1)	0.105
Spironolactone	96 (2.0)	27 (4.0)	137 (5.8)	225 (8.6)	<0.001

Table 1. Baseline characteristics of patients undergoing CABG stratified by heart failure status and phenotype

IQR: Interquartile range; Prior MI: Prior myocardial infarction; Prior PCI: Prior percutaneous intervention; CKD: Chronic Kidney Disease > Stage 3; NYHA: New York Heart Association; BMI: body mass index in kg/m2; HBA1C: haemoglobin A1C in %; eGFR: estimated glomerular filtration rate in ml/min/1.73m2; ACEI/ARB; Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers; HFpEF: Heart Failure with preserved ejection fraction; HFmrEF: Heart Failure with mid-range ejection fraction; HFrEF: Heart Failure with reduced ejection fraction; IABP: Intra-aortic balloon pump

**The numbers in HFpEF and no HF group could be biased as the diagnosis of HFpEF included the use of diuretics and patients on diuretics were excluded from the control group (i.e., no HF group)*

Table 2 Factors influencing primary outcome, composite of heart failure hospitalization and all-cause mortality, in the entire cohort. Multisegmented Cox model for 3 time periods (0-1 year, 1-5 years, 5-10 years), Hazard Ratios, 95% CI

Variables	0-1 year	1-5 years	5-10 years
Heart Failure Phenotypes			
HFpEF	1.9 (1.5 - 2.6)	0.8 (0.6 - 1.0)	0.9 (0.7 - 1.1)
HFmrEF	2.6 (2.1 - 3.1)	1.5 (1.3 - 1.7)	1.3 (1.2 - 1.5)
HFrEF	3.2 (2.7 - 3.7)	2.0 (1.8 - 2.2)	1.6 (1.4 - 1.8)
Demographics			
Age	1.0 (0.9 - 1.1)	1.1 (1.0 - 1.2)	1.1 (1.0 - 1.2)
Caucasian race	0.9 (0.7 - 1.1)	0.9 (0.8 - 1.1)	1.0 (0.9 - 1.2)
Co-morbidities			
Diabetes Mellitus	1.4 (1.2 - 1.6)	1.8 (1.6 - 2.0)	1.7 (1.5 - 1.9)
CKD	1.4 (1.2 - 1.7)	1.4 (1.2 - 1.6)	1.4 (1.2 - 1.6)
Prior Myocardial Infarction	1.2 (1.1 - 1.4)	1.1 (1.0 - 1.2)	1.0 (0.9 - 1.1)
Prior Stroke	0.9 (0.5 - 1.6)	0.9 (0.6 - 1.4)	0.6 (0.3 - 1.1)
Atrial Fibrillation	1.1 (1.0 - 1.3)	1.3 (1.1 - 1.4)	1.2 (1.1 - 1.3)
COPD	1.5 (1.3 - 1.7)	1.4 (1.3 - 1.6)	1.4 (1.3 - 1.5)
Anemia	1.5 (1.3 - 1.7)	1.6 (1.5 - 1.8)	1.3 (1.1 - 1.4)
Smoking	1.1 (0.9 - 1.3)	1.1 (1.0 - 1.3)	1.3 (1.1 - 1.4)
Body Mass Index	1.1 (1.0 - 1.1)	1.0 (0.9 - 1.1)	0.9 (1.0 - 1.1)
Prior PCI	1.0 (0.7 - 1.5)	0.9 (0.7 - 1.2)	0.9 (0.7 - 1.2)

** Model was adjusted for age at surgery, sex, race, prior history of myocardial infarction, prior percutaneous intervention, prior stroke, chronic kidney disease, prior heart surgery, prior atrial fibrillation, peripheral vascular disease, and preoperative dialysis dependence*

** Group with no heart failure was used as the reference group*

Prior PCI: Prior percutaneous intervention; CKD: Chronic Kidney Disease > Stage 3; COPD: Chronic Obstrutive Pulmonary Disease; HFpEF: Heart Failure with preserved ejection fraction; HFmrEF: Heart Failure with mid-range ejection fraction; HFrEF: Heart Failure with reduced ejection fraction