Initial Invasive versus Conservative Management of Stable Ischemic Heart Disease Patients with a History of Heart Failure or Left Ventricular Dysfunction: Insights from the ISCHEMIA Trial

Running Title: Managing Ischemic Heart Disease and Heart Failure

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Abstract

Background: Ischemic heart disease is a common cause of heart failure (HF). Coronary artery bypass graft surgery (CABG) reduces long-term mortality in patients with left ventricular ejection fraction (LVEF) ≤ 35% compared with medical therapy alone. However, it is unknown whether an initial invasive strategy in patients with stable ischemic heart disease and at least moderate ischemia improves outcomes in patients with a history of HF or LV dysfunction (LVD) when EF ≥35%, but <45%.

Methods: Among 5179 participants randomized into the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA), all of whom had LVEF ≥35%, we compared cardiovascular outcomes by treatment strategy in those with a history of HF or LV dysfunction (HF/LVD) at baseline versus those without HF/LVD. Median follow-up was 3.2 years.

Results: There were 398 (7.7%) participants with HF/LVD at baseline of whom 221 (55.5%) had LVEF <45% and 205 (51.5%) had a prior clinical diagnosis of HF. HF/LVD was associated with more comorbidities at baseline, particularly prior myocardial infarction (MI), stroke and hypertension. Compared to those without HF/LVD, those with HF/LVD were more likely to experience a primary outcome composite of cardiovascular death, nonfatal MI, or hospitalization for unstable angina, HF, or resuscitated cardiac arrest; four-year cumulative incidence rate (22.7% vs. 13.8%), cardiovascular death or MI (19.7% vs. 12.3%), and all-cause death or HF (15.0% vs. 6.9%). Those with HF/LVD randomized to the invasive versus conservative strategy had a lower rate of the primary outcome (17.2% vs. 29.3%, difference in 4-year event rate -12.1%; 95% CI: -22.6, -1.6%), whereas those without HF/LVD did not (13.0% vs. 14.6%, difference in 4-year event rate -1.6%; 95% CI: -3.8%, 0.7%; p-interaction = 0.055). A similar

differential effect was seen for the primary outcome, all-cause mortality, and CV mortality when invasive versus conservative strategy associated outcomes were analyzed with LVEF as a continuous variable for those with and without prior HF.

Conclusion: ISCHEMIA trial participants with stable ischemic heart disease and at least moderate ischemia with a history of HF or LVD were at increased risk for the primary outcome. Although the number of patients was relatively small, an initial invasive approach in this high-risk subgroup may improve event-free survival and should be considered hypothesis generating.

Clinical Perspective

What is new:

- This is a contemporary study comparing an initial invasive versus conservative strategy in patients with stable ischemic heart disease and history of heart failure and/or left ventricular dysfunction (HF/LVD).

- We found a lower rate of the primary outcome and secondary outcome (CV death or MI) for participants with HF/LVD randomized to the invasive strategy. These results were primarily driven by left ventricular dysfunction (EF<45%) in the HF/LVD group.

- In participants without HF/LVD we found no difference between the strategies in the primary outcome and secondary outcome (CV death or MI).

What are the clinical implications?

- Patients with stable ischemic heart disease and at least moderate ischemia with a history of HF or LVD are at increased risk for cardiovascular events and deserve diligent efforts to optimize evidence-based medical therapy.

- Despite the relatively small number of patients and events in the HF/LVD group, an initial invasive approach in this high-risk subgroup seems to improve event-free survival and should be interpreted as hypothesis generating.

- Caution should be taken with an initial invasive approach for patients with HF and normal EF.

Ischemic heart disease is a common underlying cause of heart failure (HF) due to left ventricular dysfunction (LVD) arising from myocardial ischemia or infarction as well as common risk factors such as hypertension and diabetes.[1] The prognosis of patients with HF and flow-limiting obstructive coronary artery disease is also poor.[2] Prior studies failed to demonstrate any significant difference in all-cause mortality between medical therapy alone and surgical revascularization in patients with severe left ventricular LVD (LV ejection fraction [EF] ≤35%. [3, 4] Long-term follow-up of STICH found surgical revascularization in addition to medical therapy in patients with HF and severe left ventricular LVD improved long-term survival as well as angina symptoms.[5, 6] Nevertheless, the optimal management of patients with coronary disease and HF or LVD without markedly reduced LVEF remains uncertain.

Specifically, whether or not an invasive strategy with initial angiography and percutaneous coronary intervention (PCI)[7] or coronary artery bypass graft (CABG) surgery if appropriate is superior to a conservative treatment with guideline-directed medical therapy (GDMT) alone for patients with stable ischemic heart disease and a history of HF or LVD is unknown.

The ISCHEMIA trial found no significant differences at 4 years in the occurrence of cardiovascular events among participants with at least moderate or severe ischemia randomized to a routine invasive therapy or a conservative approach with revascularization reserved for failure of medical treatment. [8] Importantly, patients with LVEF <35% or New York Heart Association (NYHA) functional class III or IV symptoms were excluded from ISCHEMIA. However, those with history of heart failure or mild-to-moderate LV dysfunction (EF 35%-45%) were included, providing a unique opportunity to explore the benefit of an invasive strategy in this subgroup. The objectives of our study were to: a) summarize baseline patient characteristics by history of HF or LVD; b) determine the association between history of HF or LVD and

clinical outcomes; c) compare primary outcomes between initial invasive or conservative strategy according to whether history of HF or LVD was present at baseline; and d) explore hospitalization for HF during follow-up in the subgroups according to treatment.

Methods

The ISCHEMIA Trial

Deidentified participant data and data dictionary will be available starting June 30, 2022. Methods of data sharing to be determined based on National Institute of Health data sharing policy and in discussion with the National Institute of Health and National Heart, Lung and Blood Institute trial officer. The design and results of the ISCHEMIA trial have been published.[8,9] In summary, ISCHEMIA was a randomized, controlled trial that included 5179 participants with at least moderate ischemia on noninvasive stress testing who were randomized 1:1 to a routine invasive strategy or conservative strategy with angiography reserved for failure of medical therapy. Participants were followed for a median of 3.2 years. Key exclusion criteria were >50% unprotected left main stenosis or non-obstructive CAD on blinded coronary computed tomography angiography, estimated glomerular filtration rate (eGFR) <30 ml/min, recent MI (within 2 months prior enrollment), LVEF <35% by any imaging modality, NYHA Class III or IV, unacceptable angina on medical therapy at baseline, or PCI or CABG within 1 year prior to enrollment. Overall, cardiac catheterization was performed in 96% of the invasive group and 26% of the conservative group, and revascularization was performed in 80% of the invasive group and 21% of the conservative group (15% prior to sustaining a primary outcome). This subgroup analysis of patients with HF/LVD was prespecified and the statistical analysis plan was finalized before the main trial database was locked. All patients provided informed consent for participation in the ISCHEMIA trial. The protocol was approved by the institutional

review board at New York University Grossman School of Medicine (the clinical coordinating center) and by the institutional review board and ethics committee at each participating site (see the Supplementary Appendix).

Definition of Heart Failure

History of HF was defined as having been diagnosed with HF prior to randomization regardless of LVEF. LVD was defined as LVEF ≥35% and <45% assessed by the ISCHEMIA core laboratory on the medical history/medical status form at randomization regardless of a history of HF. Participants were then categorized as HF with reduced ejection fraction (HFrEF) if LVEF <45% or HF with preserved ejection fraction (HFpEF) if LVEF ≥45%. These cut points for EF were chosen partly due to aspects of data collection. Specifically, when exact EF was unknown, the category "abnormal—moderate (LVEF 35%-44%)" on the case report form was used to classify patients as having LVD. [10-13] For the analyses using continuous EF, multiple imputation (average value across 100 imputed datasets) was used to assign an EF within the category for those without continuous EF value (**Supplemental Methods**, *Imputation of LVEF*). Continuous LVEF was available for 4633 of 5174. The remaining 541 had ejection fraction entered only as "Normal (EF>=55%)," "Abnormal - mild (45-54%)," or "Abnormal – moderate (35-44%)." Sensitivity analyses were performed using LVEF <50% to define LVD based on guidelines definition. [14] For the sensitivity analyses using a 50% cutoff to define LV dysfunction, 36 patients without prior HF and EF between 45-54% were not included since specific LV function was unknown.

Study Outcomes

The primary outcome was the composite of cardiovascular death, MI, resuscitated cardiac arrest, or hospitalization for unstable angina or HF. Other outcomes were all-cause death, cardiovascular death, MI, hospitalization for UA, hospitalization for HF.[9] Outcomes of special interest were the composite of all-cause death or HF hospitalization, Rose dyspnea questionnaire score ≥ 2[15] assessed at baseline and at every study visit, and HF symptoms defined as NYHA II or more among those without NYHA II or more at baseline.

Statistical analysis

Continuous variables are summarized with median (25th, 75th percentile) and categorical variables with number (percentage). Summary statistics are provided for those with and without prior HF or LVD and are shown separately for the HFpEF and HFrEF in the subset with HF or LVD. The history of HF or LVD groups (yes versus no) are compared with Wilcoxon rank sum, chi-square, and Fisher's exact tests as appropriate. No testing was done to compare HFrEF and HFpEF.

Cox proportional hazards regression models were fit for each outcome where prior HF or LVD was the independent variable of interest**.** Models were run without adjustment and were repeated adjusting for the same adjustment covariates as those in the primary manuscript with the exception of LVEF (age, sex, eGFR, and diabetes). The same transformations and inclusion of cubic restricted splines for covariates needed in the primary analysis were used. Results are presented as hazard ratio (95% CI) and p-value for the unadjusted and adjusted analyses as well as the cumulative incidence rate (95% CI) and number of events.

The analyses in the second objective were repeated where the independent variable of interest was HF type. HF type had three levels to preserve the sample size (no prior HF and

LVEF ≥ 45, LVEF <45 with or without prior HF, and prior HF with LVEF ≥ 45). Even so,

statistical power is limited, and the HF type groups are small given that the trial excluded

patients with LVEF <35%. Restricted cubic splines were used to test whether there was a non-

linear association between continuous LVEF and each outcome in Cox proportional hazards

regression models. No outcomes had non-linear relationships with EF so a hazard ratio and 95%

CI corresponding to a 10 unit increase in LVEF was given for each outcome. The results are

presented unadjusted and adjusted as described above. Sensitivity analyses were also performed

using EF <50% to define LVD.

For assessing the presence of a treatment interaction with HF/LVD, we focused on 4-year

cumulative event rates and assessed whether differences in 4-year event rates for invasive minus

conservative were consistent for those with and without HF/LVD (Supplemental Methods,

Calculating 95% confidence intervals for the differences in the CIF estimates).A forest plot was

used to show those differences for those with and without prior HF or LVD for each outcome

along with interaction p-values (Supplemental Methods, *Calculation of interaction p-values for*

the test of differences in CIF differences). Predicted primary outcome rates at 4 years across

continuous EF values were calculated for each prior HF and treatment group using Cox

proportional hazards models where LVEF was included as a restricted cubic spline. These

predicted rates were plotted along with the half width 95% confidence interval for the event rate

difference between treatment groups. At any point on the x axis where neither line touches the

shaded area indicates a confidence interval that does not include zero at that point.

A Cox proportional hazards regression model was fit for the all-cause mortality outcome.

The model includes prior HF, age, sex, eGFR, diabetes, and baseline LVEF as adjustment

variables and hospitalization for HF as a time dependent covariate. Hospitalization for HF was

defined as a time dependent variable that takes the value of zero for participants who never had a hospitalization for HF event. For those having hospitalization for heart failure, it takes the value of zero before the hospitalization for HF and one in the time after hospitalization for HF.

Results

Study Participants

A total of 5174 out of 5179 participants randomized into the main ISCHEMIA trial were included in this analysis. Five participants were excluded: 4 had an LVEF <35% and in 1 the LVEF was missing. HF/LVD was present in 398/5174 (7.7%) participants of whom 221 (55.5%) had LVEF <45% and 205 (51.5%) had a prior clinical diagnosis of HF; 28 patients (0.6%) had prior heart failure and LVEF <45%. Baseline characteristics according to HF classification are presented in **Table 1 (Supplemental Table 1)**. Overall, participants with HF/LVD were slightly older, with more prior MI, revascularization, and comorbidities than participants without HF/LVD. At baseline, 50% had NYHA class II symptoms while only 17% without HF/LVD had class II symptoms. Participants with HF/LVD had similar use of statins, but more ACE/ARB, diuretics, beta blockers, and anticoagulation at baseline than those without HF/LVD. Similar results were seen when LVD was defined as LVEF<50% (**Supplemental Table 2**).

HF/LVD *and clinical outcomes*

Participants with HF/LVD had a higher rate of the primary composite outcome of cardiovascular death, nonfatal MI, or hospitalization for unstable angina, HF, or resuscitated cardiac arrest than participants without HF/LVD (adjusted HR 1.42; 95%CI: 1.12 - 1.80). Similar results were seen for cardiovascular death or MI, and hospitalization for HF (**Table 2**) and also when LVD was defined as LVEF<50% (**Supplemental Table 3**). These results were primarily noted in the

subgroup with reduced LVEF (**Supplemental Table 4**). The associations between baseline

LVEF as a continuous variable and trial outcomes are shown in **Supplemental Table 5**.

Clinical Outcomes by HF/LVD *with an Invasive or Conservative Strategy*

In participants without HF/LVD, there was no observed difference between the invasive and

conservative strategies for the primary outcome (difference in 4-year event rate -1.6%; 95% CI: -

3.8%, 0.7%) (**Figure 1**). However, for the subgroup with HF/LVD, those assigned to the

invasive strategy had lower rates of the primary outcome when compared with those assigned to

the conservative strategy (difference in 4-year event rate -12.1%; 95%CI: -22.6, -1.6%; p-

interaction: 0.055) (**Figure 2, Supplemental Table 6**). Similar results were seen for

cardiovascular death or MI. Similar patterns were seen when LVD was defined as LVEF<50%

(**Supplemental Figures 1 and 2**). When adjusted proportional hazards regression models were

used to test for a differential treatment effect in those with and without HF/LVD, findings were

consistent with those testing for a difference in CIF differences (Supplemental, Figure 3). The

probabilities of the primary outcome, all-cause mortality and CV mortality according to baseline

LVEF analyzed as a continuous variable are presented in **Figure 3** for those with and without a

history of HF. In patients without history of heart failure, there were no observed differences in

the primary outcome, all-cause mortality and CV mortality between treatment groups across the

spectrum of LVEF (**Figure 3 A, C, E**). However, patients with a history of heart failure and

LVD treated with the initial invasive strategy had lower observed rates of the primary outcome,

all-cause mortality and CV mortality than patients treated initially with the conservative strategy

(**Figure 3 B, D, F**). For the primary outcome in patients with a history of HF (Fig 3B) the lack

of overlap with the between group confidence interval for a segment of the EF curve compared

to complete overlap in fig 3A, is consistent with the overall test of interaction (p=.055) noted

above. In participants without HF/LVD, the invasive strategy was associated with higher rates of hospitalization for HF (**Figure 1**), which was not seen in patients with HF/LVD assigned to the invasive strategy. Of the 51 patients randomized to the invasive group who were hospitalized for HF, 38 (75%) had revascularization prior to hospitalization for HF, 25 (66%) with PCI and 13 (34%) with CABG.

Association between hospitalization for HF during follow-up and all-cause death

Participants who were hospitalized for HF during the study also had a higher rate of death than those who did not. There were 263 deaths (1.6 deaths per 100 patient years of follow-up) in the time without hospitalization for HF and 26 deaths (24.8 deaths per 100 patient years of follow-up) after hospitalization for HF. By multivariable analysis, hospitalization for HF was an independent predictor of mortality (adjusted HR 7.11. 95% CI 4.57-11.06, p<0.0001).

Discussion

Among patients with stable ischemic heart disease and at least moderate ischemia enrolled in the ISCHEMIA trial, participants with HF/LVD had higher rates of cardiovascular events than those without HF/LVD. In addition, there was a lower rate of the primary outcome as well as CV death or MI for participants with HF/LVD randomized to the initial invasive strategy, but no difference between strategies in patients without HF/LVD. When outcomes for invasive versus conservative strategy were compared using LVEF as a continuous variable, this similar differential effect was noted for the primary outcome, all-cause mortality, and CV mortality for those with prior HF vs those without prior HF. Finally, regardless of baseline HF/LVD, participants who were hospitalized for HF during the study had a higher subsequent risk of death than those who did

not. Our study confirms the higher risk of patients with ischemic heart disease and HF/LVD and provides important new insights into the management approach for such patients with mid-range LVEF 35% to 44%. Our results were generally consistent when LVD was defined as LVEF <50%.

In the past decade, several trials have addressed whether an invasive strategy or a conservative strategy with initial optimal medical therapy was the best approach for the management of patients with stable ischemic heart disease. [16-18] Optimal medical therapy with lifestyle and pharmacologic interventions reduces the risk of myocardial infarctions and resulting damage to the myocardium. Medical therapy also treats hypertension and other risk factors thereby reducing their contribution to left ventricular hypertrophy and dilation. In the Surgical Treatment for Ischemic Heart Failure (STICH) trial, surgical revascularization was compared with medical therapy alone in 1212 randomized patients with ischemic cardiomyopathy and LVEF <35%.[5] After a median follow-up of 56 months, there was no significant difference in mortality between treatment groups.[5, 19] Similar results were seen in the HEART study[4], although the study was small and underpowered. However, patients undergoing surgical revascularization had significantly lower rates of cardiovascular death and the combined outcome of all-cause death or hospitalization for cardiovascular causes compared with the medical therapy group after 10 years of follow-up, especially if age less than 60 .[5] These results support surgical therapy in patients with LVEF<35%. On the other hand, non-randomized studies have shown that PCI with newer generation drug-eluting stents might be an alternative to CABG in patients with multi-vessel disease and LVEF ≤35%.[20] Less is known about percutaneous intervention in this setting or in those with LVEF >35% but <50%. The COURAGE trial randomized 2287 patients with stable coronary disease, whom only 5% had prior HF, to PCI plus medical therapy or medical

therapy alone and found similar rates of all-cause death and non-fatal myocardial infarction between groups.[17,21] BARI-2D found no differences between groups of patients with coronary artery disease and type 2 diabetes assigned to either prompt revascularization (PCI and CABG strata) or medical therapy alone in the rates of all-cause death and cardiovascular events.[18] However, in high-risk patients, including those with LVEF<50% and more extensive coronary disease, the rates of death, MI, and stroke at 5 years were significantly lower among those undergoing CABG when compared with the group receiving medical therapy alone.[22]

There are a number of pathophysiologic reasons why those with a mild-moderate LVD may benefit from revascularization. First, performing revascularization improves blood flow to ischemic myocardium, either reducing dysfunction or recruiting segments previously hibernating.[23] Revascularization is a key strategy to improve cardiac reserve in HF. Coronary artery disease (CAD) is common in patients with HFpEF and is associated with increased mortality and greater deterioration in ventricular function.[24-27] Although revascularization can lead to myocardial injury as evidenced by cardiac magnetic resonance,[28] it may be associated with preservation of cardiac function and improved outcomes in patients with CAD.[26] Our results suggest that when myocardial ischemia is associated with known functional impairment of the myocardium, patients are more likely to derive benefit from revascularization. CAD is the only therapeutic target in HFpEF. We observed no benefit and a possible higher rate of death in participants with a prior history of HF with normal EF, although the numbers were quite small. Thus, treating ischemia more aggressively in patients with LVD might provide incremental benefit from recruitment of hibernating myocardium and/or symptom relief more pronounced than in patients without HF.

Interestingly, we observed higher rates of subsequent HF diagnoses and hospitalizations among

those without HF/LVD at baseline randomized to an invasive strategy. This finding was unexpected and deserves further investigation.

Our findings should be interpreted in light of several limitations. First, there were a small number of patients with clinical events in the HF/LVD, including only 28 patients with prior history of HF and LVD, and therefore, our results should be interpreted as hypothesis-generating. LVEF has inherent measurement variation, so although all measurements were performed in core laboratories, LVEF recorded at trial inclusion may have varied around the somewhat arbitrary cut point of >35%. HF is the result of factors other than ischemia even in a high-risk population such as this one, so the strength of association between an initial invasive approach and HF outcomes may be lessened by other HF etiologies over time. We instructed sites to record NYHA class only if HF was present, but instructions may not have been followed perfectly. The median age of the HF/LVD group in our study was 67 years, which is slightly younger than the typical HF population, so caution should be taken when applying our results to older adults. We may also underestimate the benefit of revascularization due to incomplete revascularization in the invasive arm as well as use of revascularization for refractory symptoms in the conservative arm. Unfortunately, the type of diuretic was not collected in our study and therefore the differentiation between thiazides (usually used for hypertension) and loop diuretic (generally used for HF) could not be made. Finally, revascularization in the invasive strategy was a mixture of CABG and PCI, which differ fundamentally in their acute risks and benefits as well as in their long-term protection from future events.[32] Further follow-up should provide additional information regarding the robustness of our findings and whether there are longer-term benefits of the invasive approach in patients with prior HF/LVD.

Conclusions

In ISCHEMIA, patients with stable ischemic heart disease and HF/LVD had worse outcomes than patients without HF/LVD. Patients with HF/LVD assigned to an initial invasive treatment strategy had improved clinical outcomes when compared with a conservative strategy, whereas no such difference was present in those without HF/LVD. Our results suggest that an invasive approach may benefit high-risk patients with moderate to severe ischemia and HF/LVD.

Table 1. Baseline Patient Characteristics According to Prior Heart Failure or Low Systolic Left Ventricular Function

| | No History of HF/LVD (N=4,776) | History of HF/LVD | | | p* |
		Overall (N=398)	HFrEF (n=221)	HFpEF (n=177)	
Demographics					
Age, years					0.004
n	4776	398	221	177	
Median (Q1, Q3)	65 (58, 71)	66 (59, 72)	64 (57, 71)	67 (61, 74)	
Female sex	1085/4776 (22.7%)	83/398 (20.9%)	28/221 (12.7%)	55/177 (31.1%)	0.393
Race					<.001
White	3083/4728 (65.2%)	315/396 (79.5%)	153/220 (69.5%)	162/176 (92.0%)	
Asian	1431/4728 (30.3%)	54/396 (13.6%)	46/220 (20.9%)	8/176 (4.5%)	
Black or African American	178/4728 (3.8%)	26/396 (6.6%)	20/220 (9.1%)	6/176 (3.4%)	
Other	36/4728 (0.8%)	1/396 (0.3%)	1/220 (0.5%)	0	
NYHA Class					<.001
None	3049/4776 (63.8%)	112/398 (28.1%)	94/221 (42.5%)	18/177 (10.2%)	
I	910/4776 (19.1%)	86/398 (21.6%)	45/221 (20.4%)	41/177 (23.2%)	
II	817/4776 (17.1%)	200/398 (50.3%)	82/221 (37.1%)	118/177 (66.7%)	
Medical history					
Angina	4276/4776 (89.5%)	362/398 (91.0%)	194/221 (87.8%)	168/177 (94.9%)	0.370
MI	844/4762 (17.7%)	146/395 (37.0%)	77/219 (35.2%)	69/176 (39.2%)	<.001
PCI	912/4772 (19.1%)	137/398 (34.4%)	65/221 (29.4%)	72/177 (40.7%)	<.001
CABG	172/4776 (3.6%)	31/398 (7.8%)	13/221 (5.9%)	18/177 (10.2%)	<.001
PVD	177/4765 (3.7%)	26/398 (6.5%)	10/221 (4.5%)	16/177 (9.0%)	0.005
Stroke	129/4775 (2.7%)	22/398 (5.5%)	13/221 (5.9%)	9/177 (5.1%)	0.001
Hypertension	3464/4761 (72.8%)	322/395 (81.5%)	167/218 (76.6%)	155/177 (87.6%)	<.001
Diabetes	1978/4776 (41.4%)	184/398 (46.2%)	106/221 (48.0%)	78/177 (44.1%)	0.061
Chronic lung disease	261/4765 (5.5%)	37/396 (9.3%)	14/220 (6.4%)	23/176 (13.1%)	0.002
Hospitalization for heart failure	0	56/398 (14.1%)	12/221 (5.4%)	44/177 (24.9%)	<.001
Medical Therapy at Randomization					
Aspirin	4305/4772 (90.2%)	338/398 (84.9%)	189/221 (85.5%)	149/177 (84.2%)	<.001
Statin	4525/4771 (94.8%)	374/398 (94.0%)	209/221 (94.6%)	165/177 (93.2%)	0.452
High intensity statin	1766/4771 (37.0%)	144/398 (36.2%)	86/221 (38.9%)	58/177 (32.8%)	0.740
ACE/ARB	3085/4772 (64.6%)	328/398 (82.4%)	170/221 (76.9%)	158/177 (89.3%)	<.001
Beta blockers	3805/4772 (79.7%)	351/398 (88.2%)	190/221 (86.0%)	161/177 (91.0%)	<.001
Aldosterone antagonist	79/4772 (1.7%)	36/398 (9.0%)	18/221 (8.1%)	18/177 (10.2%)	<.001
Diuretic	935/4772 (19.6%)	146/398 (36.7%)	65/221 (29.4%)	81/177 (45.8%)	<.001
Antiarrhythmics	58/4740 (1.2%)	10/392 (2.6%)	1/218 (0.5%)	9/174 (5.2%)	0.027
Anticoagulants	155/4729 (3.3%)	48/397 (12.1%)	25/220 (11.4%)	23/177 (13.0%)	<.001
Dual antiplatelet	1149/4772 (24.1%)	78/398 (19.6%)	48/221 (21.7%)	30/177 (16.9%)	0.044
QOL					
SAQ Angina Frequency Score					0.902
n	4262	380	204	176	

	No History of HF/LVD (N=4,776)	History of HF/LVD			
		Overall (N=398)	HFrEF (n=221)	HFpEF (n=177)	p*
Median (Q1, Q3)	90 (70, 100)	90 (70, 100)	90 (70, 100)	85 (65, 100)	
Stress imaging and ETT detail					
Degree of ischemia[†]					0.015
None	225/4764 (4.7%)	29/398 (7.3%)	14/221 (6.3%)	15/177 (8.5%)	
Mild	327/4764 (6.9%)	25/398 (6.3%)	13/221 (5.9%)	12/177 (6.8%)	
Moderate	1550/4764 (32.5%)	150/398 (37.7%)	74/221 (33.5%)	76/177 (42.9%)	
Severe	2601/4764 (54.6%)	193/398 (48.5%)	119/221 (53.8%)	74/177 (41.8%)	
Uninterpretable	61/4764 (1.3%)	1/398 (0.3%)	1/221 (0.5%)	0	
Anterior ischemia	1183/3525 (33.6%)	106/357 (29.7%)	70/201 (34.8%)	36/156 (23.1%)	0.139
Duke Prognostic Score					0.055
n	2791	195	111	84	
Median (Q1, Q3)	5 (5, 6)	5 (5, 6)	5 (5, 6)	5 (5, 6)	
Number of 50% Diseased Vessels by CCTA[†]					0.361
0	4/2789 (0.1%)	0	0	0	
1	659/2789 (23.6%)	38/195 (19.5%)	22/111 (19.8%)	16/84 (19.0%)	
2	875/2789 (31.4%)	62/195 (31.8%)	33/111 (29.7%)	29/84 (34.5%)	
3	1251/2789 (44.9%)	95/195 (48.7%)	56/111 (50.5%)	39/84 (46.4%)	
LM ≥ 50% Stenosis by CCTA	37/3586 (1.0%)	3/255 (1.2%)	2/150 (1.3%)	1/105 (1.0%)	0.747
Proximal LAD ≥ 50% Stenosis by CCTA	1649/3487 (47.3%)	98/249 (39.4%)	57/147 (38.8%)	41/102 (40.2%)	0.015
Number of 70% Diseased Vessels by CCTA					0.165
0	288/2383 (12.1%)	13/175 (7.4%)	7/99 (7.1%)	6/76 (7.9%)	
1	960/2383 (40.3%)	66/175 (37.7%)	42/99 (42.4%)	24/76 (31.6%)	
2	673/2383 (28.2%)	58/175 (33.1%)	28/99 (28.3%)	30/76 (39.5%)	
3	462/2383 (19.4%)	38/175 (21.7%)	22/99 (22.2%)	16/76 (21.1%)	
Proximal LAD ≥ 70% Stenosis by CCTA	762/3478 (21.9%)	43/249 (17.3%)	28/147 (19.0%)	15/102 (14.7%)	0.086

ACE/ARB indicates angiotensin-converting enzyme/ angiotensin II receptor blocker; CABG, coronary artery bypass graft; CCTA, coronary computed tomography angiography; ETT, exercise tolerance testing; HF/LVD, Heart Failure/ Left ventricular dysfunction; HFrEF, Heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LAD, left anterior descending; LM, left main ; NYHA, New York Heart Association; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease ;Q1, first quartile; Q3, third quartile; QOL, Quality of Life; SAQ, Seattle Angina Questionnaire;

* P-values comparing **any history of HF/LVD** versus none (first 2 columns)

† Uninterpretable degree of ischemia set to missing for chi-square test; Zero vessels with 50% stenosis is combined with one vessel for chi-square test.

Table 2. Association between history of HF/LVD at baseline and outcomes

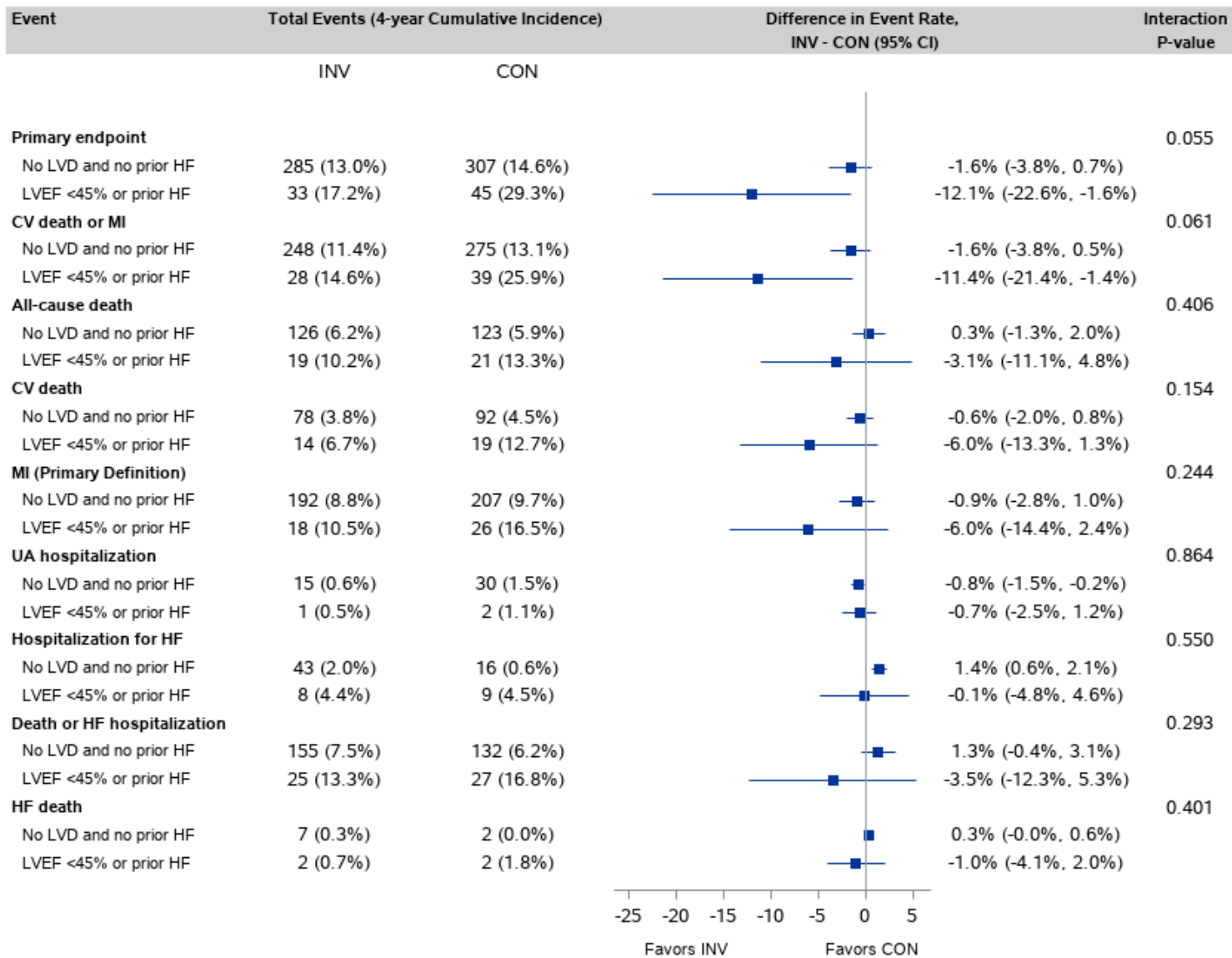| Variable Label	History of HF/LVD		No History of HF/LVD		Unadjusted HR (95% CI)	Unadjusted p	Adjusted* HR (95% CI)	Adjusted* p
	N events	CIF	N events	CIF				
Primary outcome	78	22.68 (17.79, 27.95)	592	13.78 (12.67, 14.93)	1.68 (1.32, 2.12)	<0.001	1.43 (1.12, 1.82)	0.004
CV death/MI	67	19.74 (15.11, 24.82)	523	12.26 (11.20, 13.37)	1.61 (1.25, 2.08)	<0.001	1.37 (1.06, 1.78)	0.016
All-cause Death	40	11.60 (8.05, 15.85)	249	6.05 (5.25, 6.92)	2.00 (1.43, 2.79)	<0.001	1.58 (1.13, 2.22)	0.008
CV Death	33	9.51 (6.35, 13.44)	170	4.15 (3.50, 4.88)	2.42 (1.67, 3.52)	<0.001	1.89 (1.30, 2.77)	<0.001
Primary Definition of MI	44	13.25 (9.48, 17.65)	399	9.26 (8.35, 10.23)	1.38 (1.01, 1.89)	0.041	1.22 (0.89, 1.67)	0.223
Unstable Angina	3	0.78 (0.22, 2.14)	45	1.05 (0.77, 1.42)	0.84 (0.26, 2.70)	0.771	0.83 (0.26, 2.69)	0.758
Hospitalization for Heart Failure	17	4.46 (2.50, 7.25)	59	1.30 (0.96, 1.73)	3.61 (2.10, 6.20)	<0.001	2.73 (1.57, 4.75)	<0.001
All-cause death or HF Hosp	52	14.95 (10.91, 19.59)	287	6.88 (6.04, 7.80)	2.29 (1.70, 3.08)	<0.001	1.80 (1.33, 2.43)	<0.001
HF death	4	1.22 (0.31, 3.44)	9	0.18 (0.07, 0.40)	5.61 (1.72, 18.26)	0.004	4.19 (1.25, 14.08)	0.021
NYHA Class II or greater[†]	62	34.43 (27.10, 41.87)	984	27.77 (26.18, 29.38)	1.31 (1.01, 1.70)	0.038	1.32 (1.02, 1.70)	0.038
Rose Dyspnea Scale 2 or more[‡]	91	40.63 (33.56, 47.58)	1026	33.77 (31.91, 35.64)	1.28 (1.03, 1.58)	0.026	1.23 (0.99, 1.53)	0.064

CV indicates cardiovascular; CIF, Cumulative incidence function; HF/LVD, heart failure/ left ventricular dysfunction; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association

* Adjusted for age (restricted cubic spline), sex, eGFR (restricted cubic spline), and diabetes.

†NYHA Class II or greater outcome assessed at baseline and in each study visit is restricted to 4158 participants without NYHA Class II or greater at baseline.

‡Rose Dyspnea Scale 2 or more outcome assessed at baseline and in each study visit is restricted to 3566 participants without Rose Dyspnea Scale 2 or more at baseline.

Figure 1. Association between randomized treatment and outcomes for patients with and without HF/LVD at baseline

Event	Total Events (4-year Cumulative Incidence)		Difference in Event Rate, INV - CON (95% CI)	Interaction P-value
	INV	CON		
Primary endpoint				0.055
No LVD and no prior HF	285 (13.0%)	307 (14.6%)	-1.6% (-3.8%, 0.7%)	
LVEF <45% or prior HF	33 (17.2%)	45 (29.3%)	-12.1% (-22.6%, -1.6%)	
CV death or MI				0.061
No LVD and no prior HF	248 (11.4%)	275 (13.1%)	-1.6% (-3.8%, 0.5%)	
LVEF <45% or prior HF	28 (14.6%)	39 (25.9%)	-11.4% (-21.4%, -1.4%)	
All-cause death				0.406
No LVD and no prior HF	126 (6.2%)	123 (5.9%)	0.3% (-1.3%, 2.0%)	
LVEF <45% or prior HF	19 (10.2%)	21 (13.3%)	-3.1% (-11.1%, 4.8%)	
CV death				0.154
No LVD and no prior HF	78 (3.8%)	92 (4.5%)	-0.6% (-2.0%, 0.8%)	
LVEF <45% or prior HF	14 (6.7%)	19 (12.7%)	-6.0% (-13.3%, 1.3%)	
MI (Primary Definition)				0.244
No LVD and no prior HF	192 (8.8%)	207 (9.7%)	-0.9% (-2.8%, 1.0%)	
LVEF <45% or prior HF	18 (10.5%)	26 (16.5%)	-6.0% (-14.4%, 2.4%)	
UA hospitalization				0.864
No LVD and no prior HF	15 (0.6%)	30 (1.5%)	-0.8% (-1.5%, -0.2%)	
LVEF <45% or prior HF	1 (0.5%)	2 (1.1%)	-0.7% (-2.5%, 1.2%)	
Hospitalization for HF				0.550
No LVD and no prior HF	43 (2.0%)	16 (0.6%)	1.4% (0.6%, 2.1%)	
LVEF <45% or prior HF	8 (4.4%)	9 (4.5%)	-0.1% (-4.8%, 4.6%)	
Death or HF hospitalization				0.293
No LVD and no prior HF	155 (7.5%)	132 (6.2%)	1.3% (-0.4%, 3.1%)	
LVEF <45% or prior HF	25 (13.3%)	27 (16.8%)	-3.5% (-12.3%, 5.3%)	
HF death				0.401
No LVD and no prior HF	7 (0.3%)	2 (0.0%)	0.3% (-0.0%, 0.6%)	
LVEF <45% or prior HF	2 (0.7%)	2 (1.8%)	-1.0% (-4.1%, 2.0%)	

-25 -20 -15 -10 -5 0 5

Favors INV   Favors CON

Of 2586 INV participants, 214 had prior HF/LVD. Of 2588 CON participants, 184 had prior HF/LVD

Figure 2. Cumulative incidence curves for the primary outcomes according to randomized treatment and history of HF/LVD
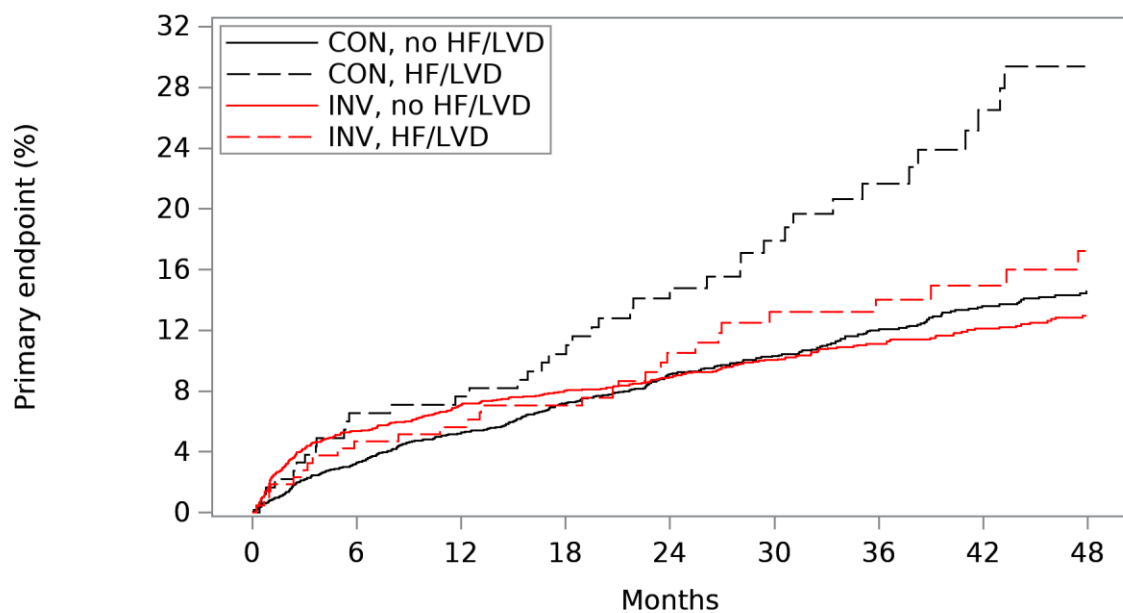
Subjects at Risk								
CON, no HF/LVD	2404	2311	2260	2114	1781	1469	1222	947	690
CON, HF/LVD	184	172	169	156	124	98	77	56	43
INV, no HF/LVD	2372	2218	2164	2040	1764	1455	1189	913	670
INV, HF/LVD	214	203	199	185	143	121	103	84	63

Figure 3. Predicted probability of primary outcome, all-cause mortality, and CV mortality according to baseline LVEF. A, C, E) In those without prior HF indicated on medical history form. B, D, F) In those with prior HF indicated on medical history form. The blue shading indicates the half-width confidence intervals for the difference in event rates for invasive and conservative strategies.

A) *In those without prior HF indicated on medical history form (N=2495 CON and 2474 INV)*
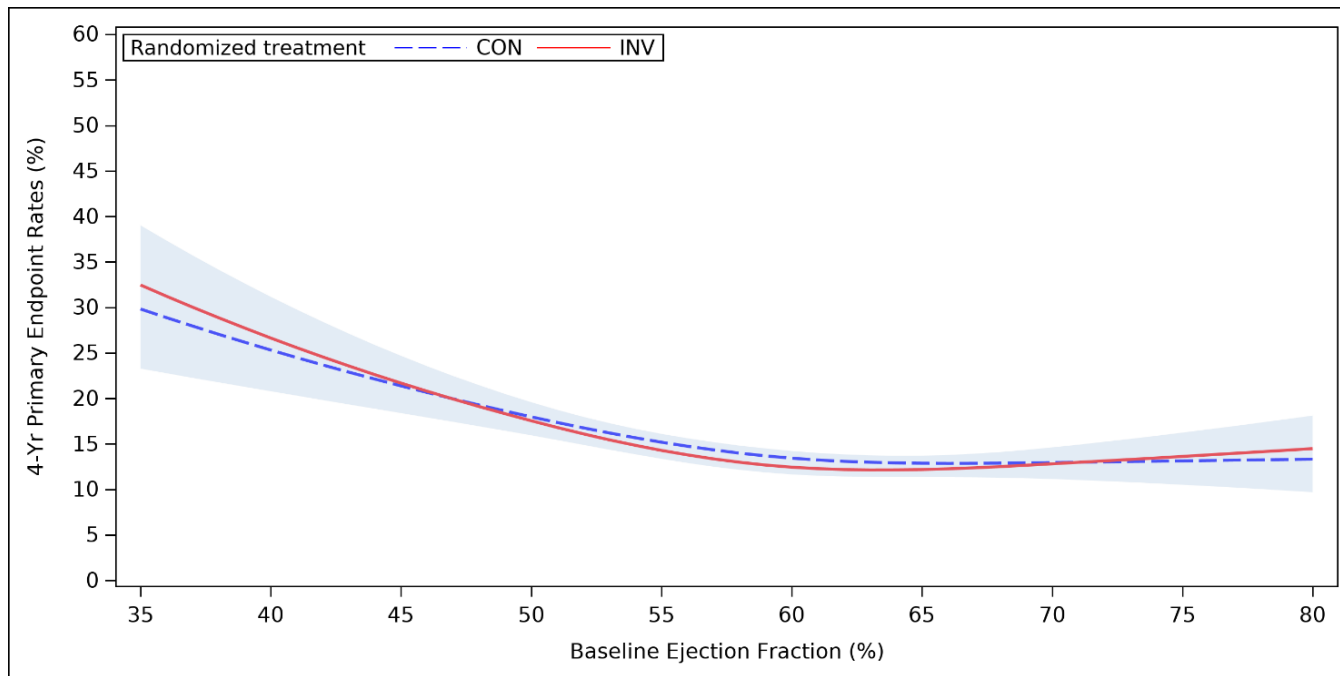
CON	29	62	146	266	1992
INV	20	82	114	243	2015

B) In those with prior HF indicated on medical history form (N=93 CON and 112 INV)
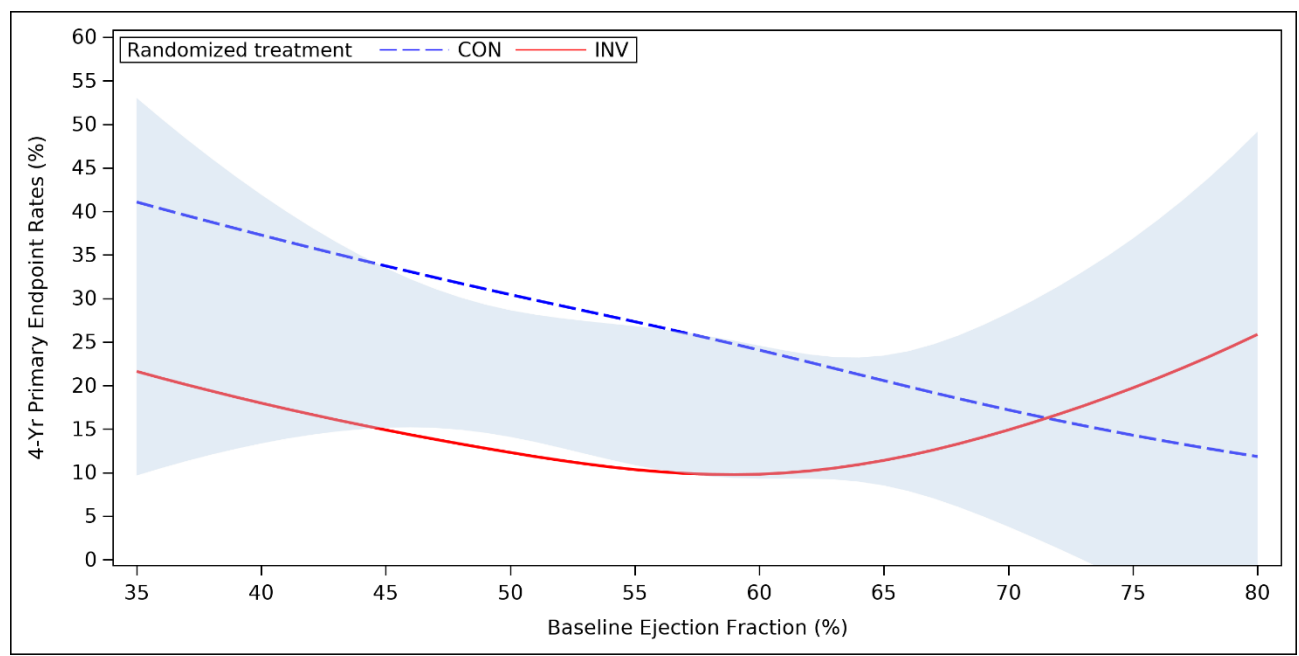
| CON | 8 | 8 | 9 | 14 | 54 |
| INV | 2 | 10 | 11 | 11 | 78 |

C) In those without prior HF indicated on medical history form (N=2495 CON and 2474 INV)
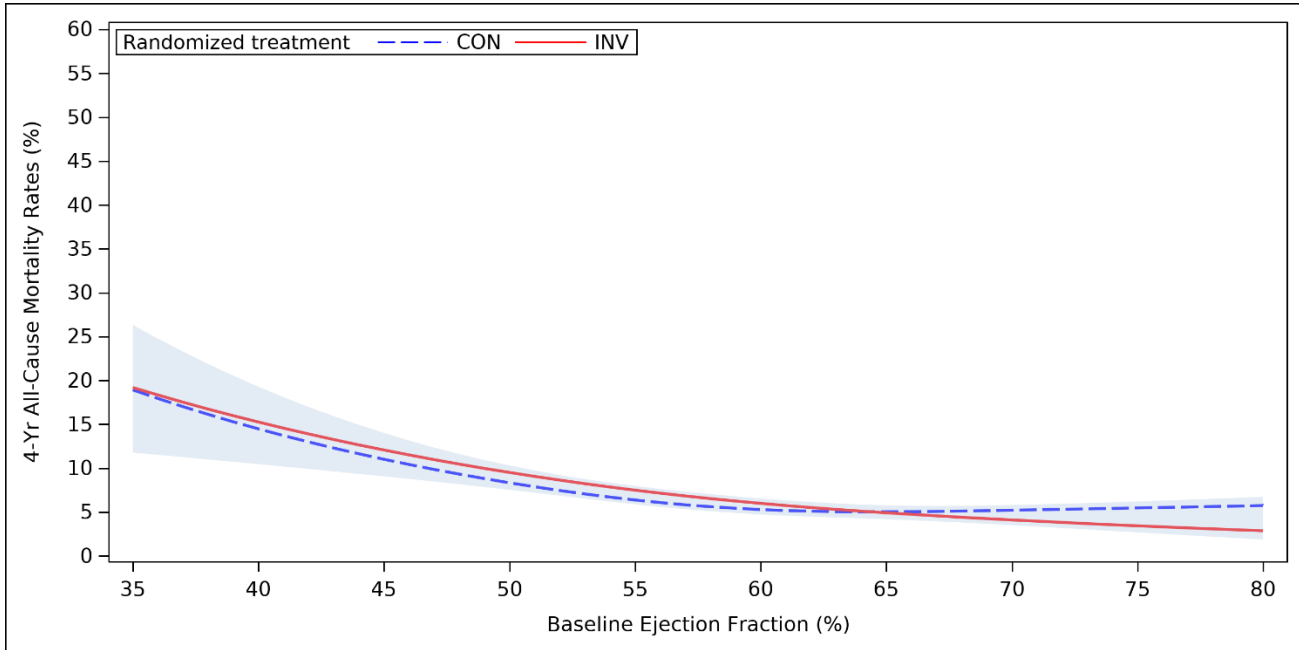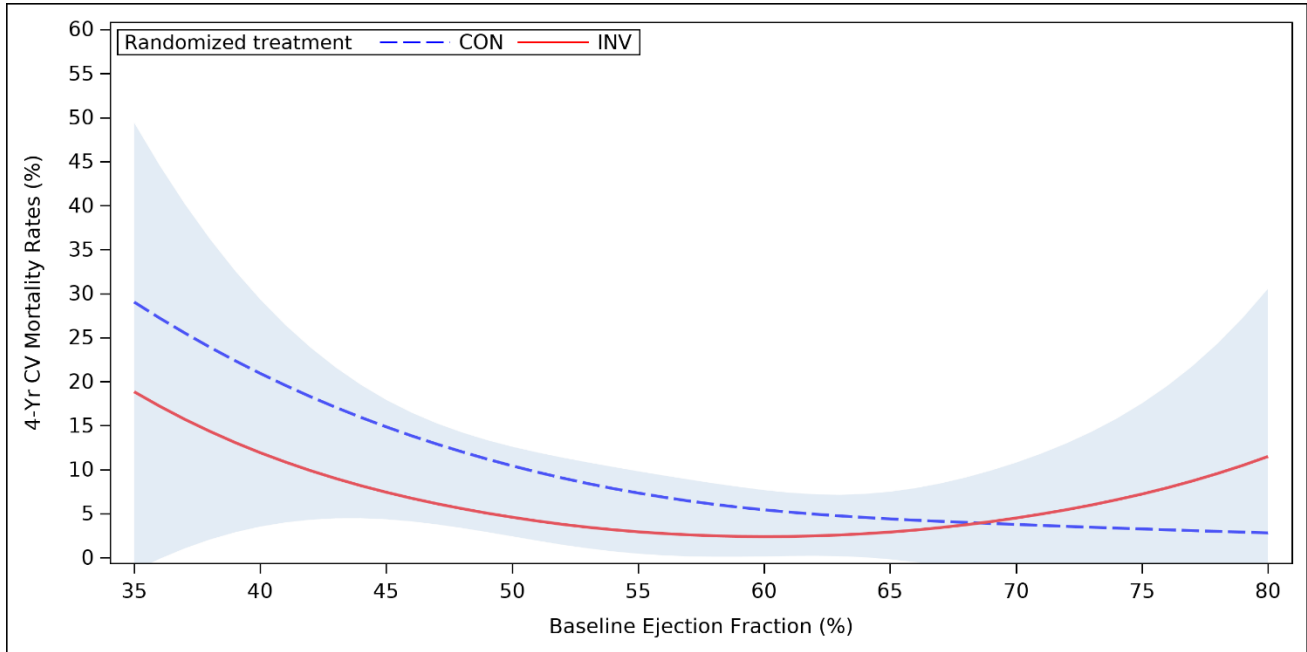

CON	29	62	146	266	1992
INV	20	82	114	243	2015

D) *In those with prior HF indicated on medical history form (N=93 CON and 112 INV)*
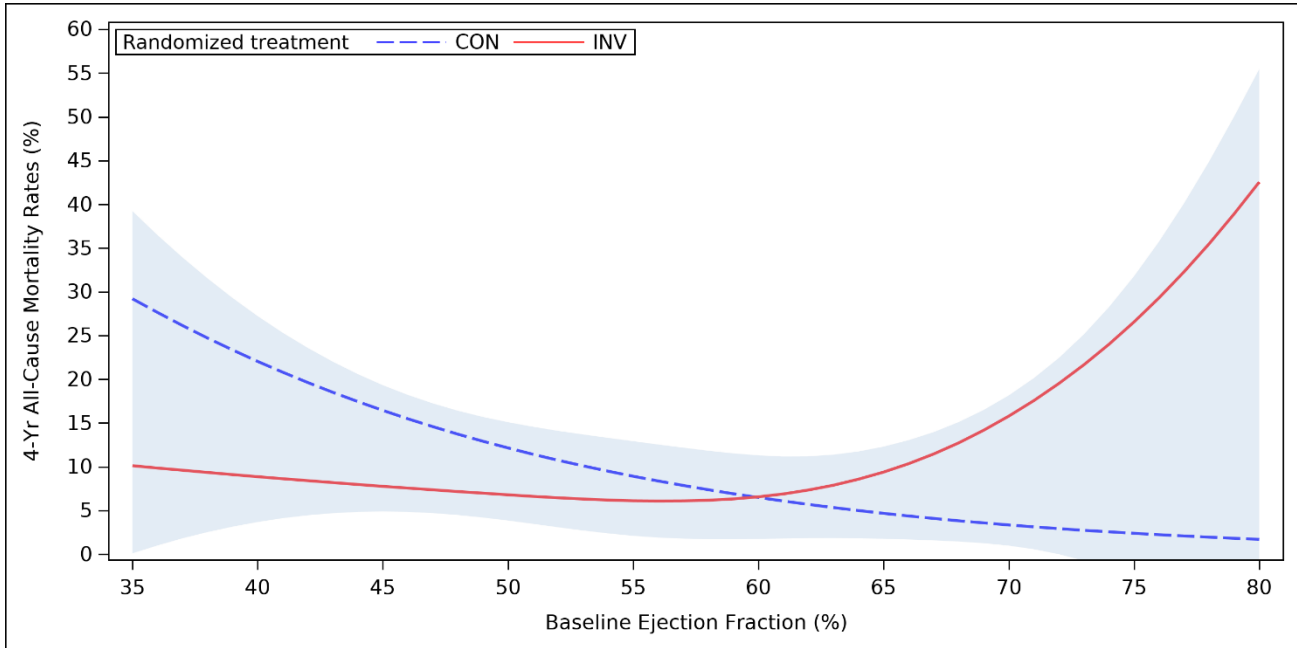
CON	8	8	9	14	54
INV	2	10	11	11	78

E) In those without prior HF indicated on medical history form (N=2495 CON and 2474 INV)
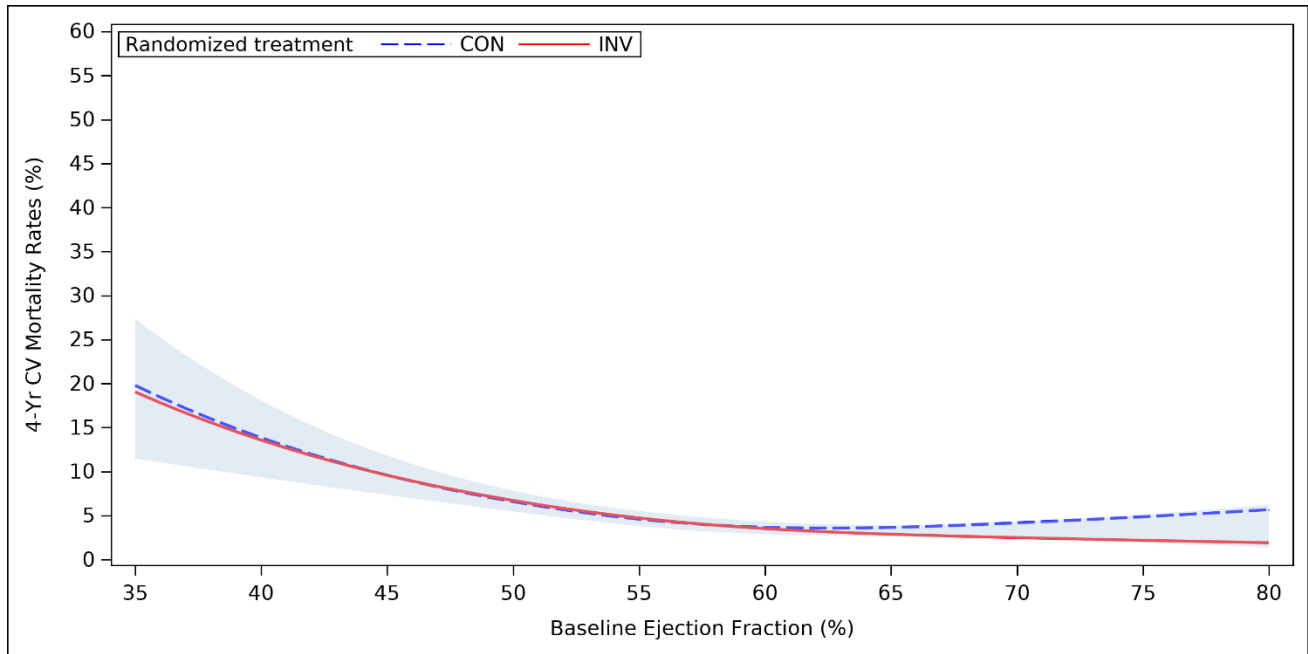
| CON | 29 | 62 | 146 | 266 | 1992 |
| INV | 20 | 82 | 114 | 243 | 2015 |

F) In those with prior HF indicated on medical history form (N=93 CON and 112 INV)

CON	8	8	9	14	54
INV	2	10	11	11	78

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