Impact of left ventricular function on clinical outcomes among patients with coronary artery disease

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ABSTRACT

Aims: To investigate the clinical relevance of contemporary cutoffs of left ventricular ejection fraction (LVEF) including an intermediate phenotype with mid-range reduced ejection fraction (EF) among patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI).

Methods and Results: Patient-level data were summarized from five randomized clinical trials in which 6,198 patients underwent clinically indicated PCI in different clinical settings. We assessed all-cause mortality as primary endpoint at 5-year follow-up. According to the proposed LVEF cutoffs, 3,816 patients were included in the preserved LVEF group (LVEF≥50%), 1,793 in the mid-range reduced LVEF group (LVEF 40-49%), and 589 patients in the reduced LVEF group (LVEF<40%). Patients in the reduced LVEF group were at increased risk for the primary outcome of all-cause mortality compared with both, preserved and mid-range LVEF throughout 5 years of follow-up (adjusted HR 2.39 (95%CI 1.75-3.28, p<0.001) and 1.68 (95%CI 1.34-2.10, p<0.001), respectively). The risk of cardiac death and the composite endpoint of cardiac death, myocardial infarction, or stroke were higher for patients in the reduced LVEF group compared with the preserved and mid-range reduced LVEF groups, but also for the mid-range LVEF compared to preserved LVEF group (adjusted p<0.05 for all comparisons) throughout 5 years. Irrespective of clinical presentation at baseline (stable CAD or acute coronary syndrome), patients with reduced or mid-range LVEF were at increased risk of all-cause mortality and cardiac death up to 5-years compared to the other group (adjusted p<0.05 for all comparisons).

Conclusion: Patients with reduced LVEF<40% or mid-range LVEF 40-49% in the context of CAD undergoing clinically indicated PCI are at increased risk of all-cause mortality, cardiac death and the composite of cardiac death, stroke and myocardial infarction throughout 5 years of follow-up. The recently proposed LVEF cut-offs contribute to the differentiation and risk stratification of patients with ischemic heart disease.

Keywords: heart failure, left ventricular ejection fraction, heart failure reduce ejection fraction, myocardial infarction, risk stratification.

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INTRODUCTION

Left ventricular dysfunction due to coronary artery disease (CAD) remains a major cause of morbidity and mortality with considerable burden of disease worldwide.[1] Patients with left ventricular dysfunction and symptoms of heart failure (HF) represent a clinical challenge because of the complex pathophysiological substrate and comorbidity interplay.[2] Previous studies of patients with CAD and reduced left ventricular ejection fraction (LVEF) (LVEF<40%) have shown favourable results of coronary revascularization (either with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)) compared with a medical management alone.[3, 4] However, the most recent guidelines of the American College of Cardiology Foundation (ACCF)/AHA and European Society of Cardiology are not uniform with respect to the class and level of treatment recommendations for patients with HF and CAD suitable for revascularization. The European Society of Cardiology (ESC) guidelines recommend any intervention that would achieve complete revascularization (CABG or PCI) for patients with HF and significant CAD in the presence of symptoms of angina and the presence of viable myocardium.[5] The American College of Cardiology Foundation (ACCF)/AHA guidelines recommend CABG or PCI in patients with left main or multivessel disease in case of symptomatic patients without requiring evidence of ischemia.[6] Recently, the ESC guidelines on acute and chronic HF suggested an additional intermediate phenotype in addition to the existing reduced LVEF of <40% and preserved LVEF of ≥50% referred to as heart failure with mid-range ejection fraction (LVEF 40-49%).[7] Nevertheless, the chosen cutoff of 40% has been disputed as its prognostic relevance is under question and trials on neurohormonal antagonism have used different inclusion criteria.[8]

Against this background, we sought to investigate the impact of left ventricular systolic function by applying the recently proposed LVEF cutoffs[7] in a large sample of patients with CAD undergoing PCI in the context of different clinical settings.

METHODS

Data sources, study population and interventions

We summarized patient-level data from five randomized clinical trials (SIRTAX (NCT00297661)[9], LEADERS (NCT00389220)[10, 11], RESOLUTE (NCT00617084)[12, 13], COMFORTABLE (NCT00962416)[14] and BIOSCIENCE (NCT01443104)[15, 16]) with long-term follow-up conducted from 2004 to 2014 at European institutions. Detailed individual study design and trial results are available in the individual publications of the trials (**Supplementary Table 1**).[9-16] Briefly, all studies included patients with CAD referred for clinically indicated PCI in different clinical setting (corresponding to stable CAD, non-ST-elevation acute coronary syndrome (NSTE-ACS), or ST-elevation myocardial infarction (STEMI)) that were amendable to coronary stent implantation. In the individual trials, patients were randomly assigned to one of two different stent platforms (either bare-metal (BMS) or drug-eluting stents (DES)) following pre-specified protocols (**Supplementary Table 1**). For the purpose of this study, we included all patients with available information on left ventricular (LV) function. LV function was determined at baseline prior to the index intervention by left ventricular angiography or transthoracic echocardiography as reported in the case record form.

All studies complied with the Declaration of Helsinki and were approved by the ethical review board in each institution. All patients in the individual trials had provided written informed consent to be prospectively followed. The case report forms were verified or checked for plausibility by an independent monitoring provider in the individual studies. The databases used in this study only contained anonymous patient records.

Outcomes definitions and follow-up

Assessed outcomes across the trials were adjudicated with similar standardized definitions as has been previously reported.[17] The primary outcome in our analysis was all-cause mortality. Secondary outcomes included cardiac death, myocardial infarction (MI), composite of cardiac

death, MI or stroke, Q-wave MI, non Q-Wave MI, stroke, any target lesion revascularization (TLR), any target-vessel revascularization (TVR), and any revascularization up to 5-years follow-up. Follow-up in individual trials was prospectively performed at 30-days, 1-year and annually thereafter throughout 5-years. For this analysis, 5-year follow-up data were available for all trials. Individual patients were censored at the valid contact in case of lost-to-follow-up or withdrawal of the consent.

Statistical analysis

We stratified the study population according to the recently proposed LVEF cutoffs[7] into three groups of ≥50%, 40-49%, and <40%. Descriptive statistics of baseline continuous variables were presented as mean ± standard deviation (SD) and compared with independent samples Student t-test; categorical variables were expressed as frequencies and percentages and compared with Fisher's exact or chi-squared test. We evaluated different cut-offs in our dataset comparing them with the Harrel's C index. Clinical outcomes at 5 years were expressed as counts with percentage for the overall population, and stratified according to clinical presentation (stable CAD or ACS). We performed additional analyses by breaking down the ACS group into two subgroups (NSTE-ACS and STEMI). We performed a survival parametric model with Weibull distribution, PH model, for the overall population and the stratified population to calculate hazard ratios (HRs) with accompanied 95% confidence intervals (CIs). We considered the different trials as random effect and we derived adjusted HRs performing maximum likelihood estimation from multivariable survival parametric models for the overall population and stratified groups for all the endpoints. We obtained adjusted HRs by considering baseline characteristics, excluding PCI related information and those variables with ≥30% of missing values or those variables not available in a particular study. Adjustment was performed for age, gender, body-mass index, diabetes mellitus, insulin-treatment, diabetes diet or oral treatment at baseline, hypertension, current smoker, family history of coronary artery disease, previous myocardial infarction,

previous percutaneous coronary interventions, previous coronary artery bypass-graft, acute coronary syndrome group, renal failure, and glycoprotein IIb/IIIa antagonist use at procedure. We imputed the missing values by using multiple imputation to obtain the final model. The Kaplan-Meier curves, were obtained for the endpoints of all-cause mortality, cardiac death and the composite of cardiac death, MI and stroke; and stratified according to the specified LVEF groups. We considered a landmark analysis using a time point at 30-days, with HRs computed separately for events up to 30-days and from 30-days to 5-years. Finally, we used fractional polynomial to analyze the LVEF versus all-cause mortality. In the latter case, fractional polynomials with one degree were used to obtain the estimation of the effect of LVEF versus log hazard of all-cause mortality and the values were centered at the value of 50. HRs are considered statistically significant at 5% level. All statistical analyses were performed with Stata version 15.0 (StataCorp. 2017, College Station, TX).

RESULTS

Study population and baseline clinical characteristics

A total of 8,287 patients were enrolled into 5 trials of whom 6,198 patients fulfilled the eligibility criteria and were included in this pooled analysis (**Figure 1, Table 1**). The Harrel's C comparison in the study population confirms that for an unadjusted model the best cut-offs of LVEF for the mid-range reduced LVEF group are those proposed by the recent ESC guidelines (LVEF 40-49%), while for the adjusted model, the best lower cut-off value would be a LVEF of 35% (**Supplementary Table 2**). According to the proposed LVEF cutoffs[7], 3,816 patients were included in the preserved LVEF (≥50%) group, 1,793 mid-range reduced LVEF (40-49%) group, and 589 in the reduced LVEF (<40%) group. **Table 1** and **Supplementary Tables 3 and 4** summarize baseline demographics and procedural characteristic of the study population. Baseline characteristics differed considerably across the three groups with patients in LVEF<40% group featuring a more severe cardiovascular-risk profile and a higher proportion of advanced Killip Class (III or IV) at presentation (**Table 1**). In our study sample, 60% of patients presented with acute coronary syndromes (ACS) (29% NSTE-ACS and 31% STEMI). Multivessel revascularization was performed in 30% of the overall population and was equally represented across the three groups of LVEF.

Clinical outcomes

Clinical outcomes throughout 5 years are summarized in **Supplementary Table 4** for the overall study population stratified according to LVEF group and clinical presentation. In crude analyses, patients with reduced LVEF<40% experienced higher rates of all-cause mortality compared with both, the preserved and mid-range reduced LVEF group (24% versus 8% and 13%, respectively) with unadjusted hazard ratios of 1.56 (95%CI, 1.36 to 1.80) for mid-range vs. preserved LVEF group, 3.32 (95%CI, 2.81 to 3.93) for reduced vs. preserved LVEF group, and 2.13 (95%CI, 1.78 to 2.54) for reduced vs. mid-range reduced LVEF group (**Supplementary Table 5**) at 5 years of follow-up. Following multivariable adjustment, patients in the reduced

LVEF<40% group remained at increased risk for all-cause mortality compared with preserved LVEF≥50% (adjusted HR 2.39 (95%CI 1.75 to 3.28), p<0.001) or mid-range LVEF 40-49% (adjusted HR 1.68 (95%CI 1.34 to 2.10), p<0.001) throughout 5 years of follow-up (**Table 2** and **Figure 2**). The risk of cardiac death and the composite endpoint of cardiac death, myocardial infarction, or stroke remained higher for patients in the reduced LVEF group compared with either the preserved or mid-range LVEF group (adjusted p<0.05 for all comparisons). In a landmark analysis at 30 days of follow-up, the risk of all-cause mortality was higher for the reduced LVEF group compared with the preserved LVEF group (adjusted HR of 8.82 (95%CI, 2.02 to 38.60), p<0.001). The mid-range LVEF group remained at increased risk of all-cause mortality and cardiac death compared to the preserved LVEF group during the first 30 days and continued to be at increased risk up to 5 years (adjusted p<0.05 for all comparisons) (**Table 2** and **Figure 2**). The trend of risk over time for cardiac death was consistent with that for all-cause mortality with a higher risk for the reduced LVEF group compared with either the preserved LVEF (adjusted HR 3.07 (95%CI, 2.14 to 4.42), p<0.001) or the mid-range LVEF group (adjusted HR 1.74 (95%CI, 1.22 to 2.50), p=0.002) throughout five years of follow-up.

Outcomes according to initial clinical setting

The clinical indication for PCI at baseline was ACS in 60% of the participants (either NSTE-ACS (29%) or STEMI (31%)), while 40% of the participants presented with stable CAD (**Table 1**). Detailed outcomes stratified according to initial clinical presentation and LVEF group at baseline are provided in **Supplementary Table 4**. The unadjusted analyses indicated an increased risk of all-cause mortality, cardiac death and the composite endpoint of cardiac death, MI, or stroke (p<0.05 for all comparisons of subgroups) across the entire spectrum of clinical presentations for reduced over preserved and mid-range LVEF group, and also for mid-range over preserved LVEF group (**Supplementary Table 6 and 7**). After adjusting for differences in baseline characteristics, patients with reduced LVEF (<40%) presenting with either stable CAD or ACS

remained at increased risk of all-cause mortality and cardiac death compared to both preserved and mid-range LVEF group throughout 5 years of follow-up ($p<0.05$ for all comparisons) (**Table 3, Figure 3**). Patients initially presenting with either stable CAD or ACS and reduced LVEF<40% were at increased risk of cardiac death compared with preserved LVEF≥50% (adjusted HR of 2.64 (95%CI 1.71 to 4.06, $p<0.001$) and 3.48 (95%CI 2.27 to 5.33, $p<0.001$) respectively) (**Supplementary Table 8** and **Supplementary Figure**). Patients with mid-range LVEF 40-49% were well differentiated and at higher risk of all-cause mortality and cardiac death compared to preserved LVEF≥50% in both clinical settings (adjusted $p<0.001$ for all comparisons) (**Table 3**). In a spline analysis using fractional polynomial stratified according to clinical setting at baseline (**Figure 4)** patients with lower LVEF had a higher hazard of all-cause mortality, particularly in the group of ACS patients.

DISCUSSION

The present study provides comprehensive evidence applying the recently proposed LVEF cutoffs to a large group of patients with CAD undergoing clinically indicated PCI followed throughout 5 years of follow-up with adjudicated clinical endpoint assessment in the context of carefully conducted randomized clinical trials. The salient findings of our analysis can be summarized as follows:

- Patients with reduced LVEF<40% are at increased risk of all-cause mortality and cardiac death compared with those with preserved and mid-range LVEF throughout 5 years.
- The difference in mortality emerges early (within 30 days) and continues to increase over time (throughout 5 years).
- Patients with mid-range LVEF 40-49% are well differentiated and at increased risk of all-cause mortality and cardiac death compared with those with preserved LVEF≥50% throughout 5 years.
- The risk of all-cause mortality and cardiac death is higher for patients with reduced LVEF<40% irrespective of clinical indication (stable CAD or ACS) compared to preserved and mid-range reduced LVEF.

The prognostic relevance of LVEF to appropriately risk stratify patients over the whole spectrum of LV function and heart failure phenotype remains subject of debate. In a post-hoc analysis of the CHARM trial, LVEF was shown to function as a good predictor of cardiovascular outcomes only for patients with heart failure and LVEF<45%.[18] The findings of the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) indicated no significant increase in the risk of all-cause mortality or cardiovascular death in patients with either LVEF 50–59% or 40-49% compared with patients with LVEF of 60% or above, whereas the hazard for death increased steadily below a LVEF of 40%.[19] However, in our study sample, the proposed LVEF cut-offs did appropriately risk discriminate the patients among the spectrum of mid-range and preserved LV

function. These findings are in concordance with recently published large scale meta-analysis, highlighting the distinct prognostic role of mid-range LVEF group.[20, 21]

We were able to demonstrate that patients with impaired LVEF at baseline irrespective of initial clinical presentation (stable CAD or ACS) remain at increased risk of death compared to patients with either preserved or mid-range impaired LV function throughout 5 years. Most studies, of heart failure with depressed systolic function, report only a single LVEF measurement, generally obtained at baseline. Notwithstanding, the heart failure syndrome includes multiple diverging patient-specific phenotypes, resulting in a wide spectrum of LVEF trajectories over time depending on underlying aetiology, duration, and gender.[22, 23] In a large prospective cohort of patients with heart failure and echocardiographic assessment of LV function at several time points (mean 3.6±1.7) over 15 years, LV function in patients with ischemic heart failure improved to a lesser degree compared with patients with non-ischemic heart failure within the first year of initial assessment followed by a relative plateau thereafter. Of note a decline in LVEF as compared to the preceding period was associated with higher mortality.[22] The findings of our study corroborate those of the HORIZONS-AMI trial, where severe LV dysfunction (LVEF<40%) determined during the acute phase of STEMI patients undergoing primary PCI was a powerful independent predictor of adverse clinical outcomes during 3 years follow-up.[24] Similarly, a retrospective analysis of the CADILLAC trial reported an increased risk of all-cause mortality at 1 year of follow-up among STEMI patients with baseline LVEF<40% as compared to those with baseline LVEF>40%.[25] The present study extends these findings suggesting that baseline LV dysfunction impacts on survival up to 5 years. However, a recently published meta-analysis highlighted the prognostic importance and favourable outcomes of heart failure patients with improved ejection fraction under optimal medical therapy, compared to those with persistently reduced ejection fraction.[26] The role of ejection fraction improvement and appropriate identification of patients at higher risk should be evaluated in dedicated prospectively designed studies.

Nevertheless, no specific heart failure treatment has been shown to improve prognosis among patients with preserved or mid-range reduced LVEF, and the management is mainly directed to the underlying disease entity (i.e. CAD in the present cohort), symptom relief and treatment of comorbidities. The lack of benefit of established medical treatment for patients with mid-range reduced or preserved LVEF can be partially explained by the heterogeneous phenotypes of patients, the absence of dedicated trials to investigate therapeutic strategies, and the lack of established surrogate end points for these group of patients.[27] At 5 years of follow-up, the patients with reduced LVEF remained at increased risk for all-cause mortality, cardiac death and the composite of cardiac death, stroke and myocardial infarction compared with both preserved and mid-range LVEF group in the present study. Previous studies have evaluated the prognostic impact of non-invasive diagnostic tests (e.g. cardiopulmonary exercise testing), invasive measurements (e.g. wedge pressure), and biomarkers across the entire spectrum of heart failure patients.[28-30] However, it remains unclear whether such tools result in modification of therapeutic strategies and cost-effective improvement in patient outcomes.

Consistent with a previous study[31], we found that a lower cut-off of LVEF 35% discriminates more precisely those patients with more severe systolic dysfunction and impaired prognosis, than the guideline proposed cut-off of <40%. However, in our study a small proportion of patients (8% of the group of LVEF<40%, corresponding to 0.8% of the whole study cohort with LVEF between 35%-40%) would influence the prognostic significance of the 40% cut-off, which possibly explains the slightly suboptimal discriminatory ability. Prospective large-scale studies should evaluate the clinical relevance of such differences in discriminatory performance.

Limitations

Several limitations should be acknowledged in the present study. First, this is a non-prespecified retrospective analysis of prospectively ascertained clinical data and therefore exploratory in nature. However, we analyzed data of a carefully documented series of patients that had been

fully characterized in terms of baseline characteristics in the framework of RCTs and correlated LVEF in the context of different clinical settings with fully adjudicated long-term clinical outcomes up to 5-years follow-up. Second, values for LVEF are continuously distributed but measurement precision is known to be imperfect and differences up to 10% in individual patients may be attributed to measurement errors.[32] Third, LVEF was available only at baseline and changes in LV function at follow-up were not ascertained; therefore we were unable to consider this parameter and its impact on long-term analysis in the present study. Forth, we were unable to correlate clinical heart failure status with objective parameters of left ventricular function. Finally, in any individual trial, there is always concerns about whether the study populations enrolled reflect the patients encountered in clinical practice due to selection criteria, and in toward to this aspect this analysis is not different. However, our dataset represents the vast majority of patients enrolled in RCTs PCI trials.

Conclusions

Patients with reduced LVEF<40% or mid-range LVEF 40-49% in the context of CAD undergoing clinically indicated PCI are at increased risk of all-cause mortality, cardiac death and the composite of cardiac death, stroke and myocardial infarction throughout 5 years of follow-up. The recently proposed LVEF cut-offs contribute to the differentiation and risk stratification of patients with ischemic heart disease.

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Contributions

GCMS, MB, DH, SW, and LH conceived and designed the study. MB and DH performed the statistical analyses. All authors interpreted the results. GCMS, SW, and LH drafted the first draft of the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy. All authors had full access to all of the data. LH is the guarantor.

Conflicts of interest

MB and DH are affiliated with CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest see http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html. PWS reports consultancy fees from Abbott, Biosensors, Medtronic, Micell, Qualimed, Sinomedical Sciences, St. Jude Medical, Stentys, Svelte Medical Systems, Philips/Volcano, Xeltis, StentIt and HeartFlow. TP has received research grants to the institution from Biotronik, Boston Scientific, and Edwards Lifesciences; and speaker fees from Biotronik and Boston Scientific. SW reports research grants to the institution from Amgen, Abbott, Biotronik, Boston Scientific, Medtronic, Edwards, St Jude and Terumo. The other authors have nothing to disclose relevant to this study.

FIGURES

FIGURE 1: Flowchart of patients' selection process and group distribution according to LVEF in study population.

Abbreviations: RCTs, randomized controlled trials; LVEF, left ventricular ejection fraction.

FIGURE 2: Time-to-first event curves for patients across the three groups with preserved (≥50%), mid-range (40-49%) and reduced (<40%) LVEF.

Panel A and B: All-cause mortality; Panel C and D: Composite outcome of cardiac death, MI, and stroke; Panel E and F: Cardiac death. Estimates are shown as adjusted hazard ratios (HRs) with accompanied 95% confidence intervals (CIs). A landmark analysis at time-point of 30 days is shown in Panels B, D, and F.

Abbreviations: MI, myocardial infarction.

FIGURE 3: Time-to-first event curves for patients across the three groups with preserved (≥50%), mid-range (40-49%) and reduced (<40%) LVEF stratified according to clinical presentation.

Panels A, B, and C: for the primary outcome of all-cause mortality; Panels D, E, and F: for the composite endpoint of cardiac death, myocardial infarction, or stroke; Panels G, H, and I: for the outcome of cardiac death. Estimates are shown as adjusted hazard ratios (HRs) with accompanied 95% confidence intervals (CIs).

Abbreviations: MI, myocardial infarction; CAD, coronary artery disease; ACS, acute coronary syndrome.

FIGURE 4: Fractional polynomial stratified according to clinical setting at baseline for all-cause mortality.

Panel A: Overall; Panel B: Stable CAD; Panel C: ACS.

Abbreviations: HR, hazard ratio; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; ACS, acute coronary syndrome.

TABLES

TABLE 1: Baseline clinical characteristics.

Data are shown as n, count (%) and mean±SD as appropriate.

Abbreviations: LVEF, left ventricular ejection fraction; BMI, body mass index; GFR, glomerular filtration rate; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; NSTE-ACS, non-ST elevation acute coronary syndrome; STEMI, ST elevation myocardial infarction.

TABLE 2: Clinical outcomes at 5 years of follow-up across the three groups of preserved (≥50%), mid-range (40-49%) and reduced (<40%) LVEF.

Data shown are adjusted hazard rations (HR) with 95% confidence intervals (CI). Adjustment was performed for age, gender, body-mass index, diabetes mellitus, insulin-treatment, diabetes diet or oral treatment at baseline, hypertension, current smoker, family history of coronary artery disease, previous myocardial infarction, previous percutaneous coronary interventions, previous coronary artery bypass-graft, acute coronary syndrome group, renal failure, glycoprotein IIb/IIIa antagonist use at procedure.

Abbreviations: LVEF, left ventricular ejection fraction; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; TLR, target lesion revascularisation; TVR, target vessel revascularisation.

TABLE 3: Clinical outcomes at 5 years of follow-up across the three groups of preserved (≥50%), mid-range (40-49%) and reduced (<40%) LVEF according to clinical presentation.

Data shown are adjusted hazard rations (HR) with 95% confidence intervals (CI). Adjustment as reported in Table 2.

Abbreviations: LVEF, left ventricular ejection fraction; HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; ACS, acute coronary syndrome; MI, myocardial infarction; TLR, target lesion revascularisation; TVR, target vessel revascularisation.

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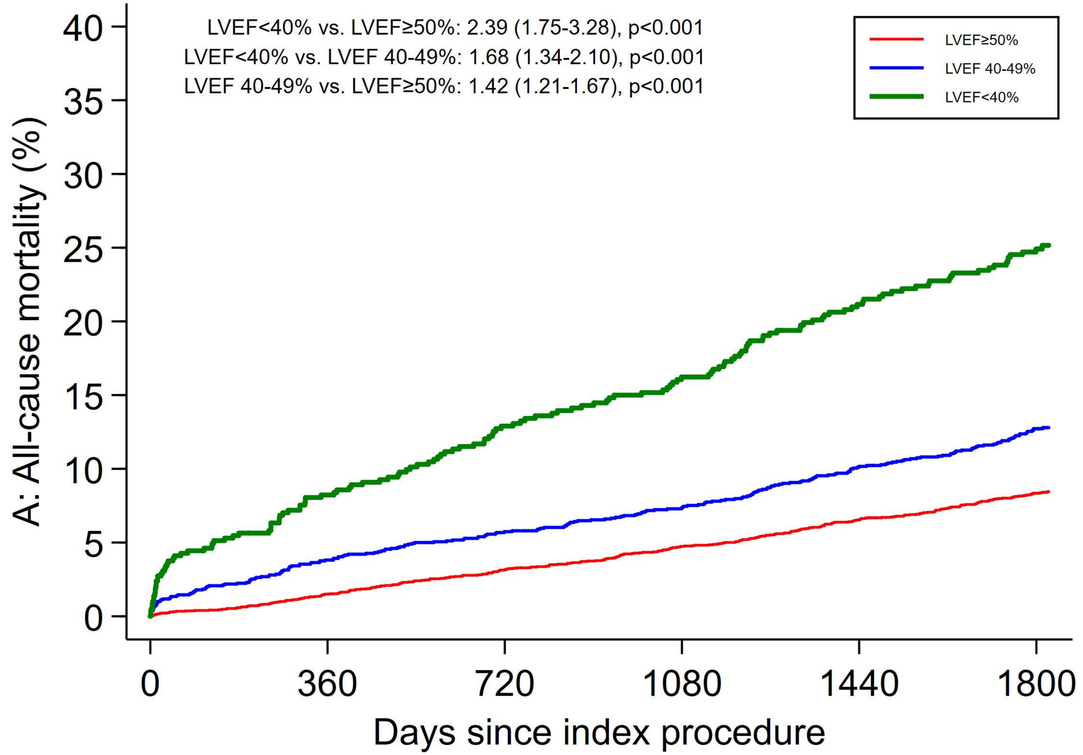
8287 patients in 5 RCTs with 5 years follow-up

SIRTAX, LEADERS, RESOLUTE, COMFORTABLE, BIOSCIENCE

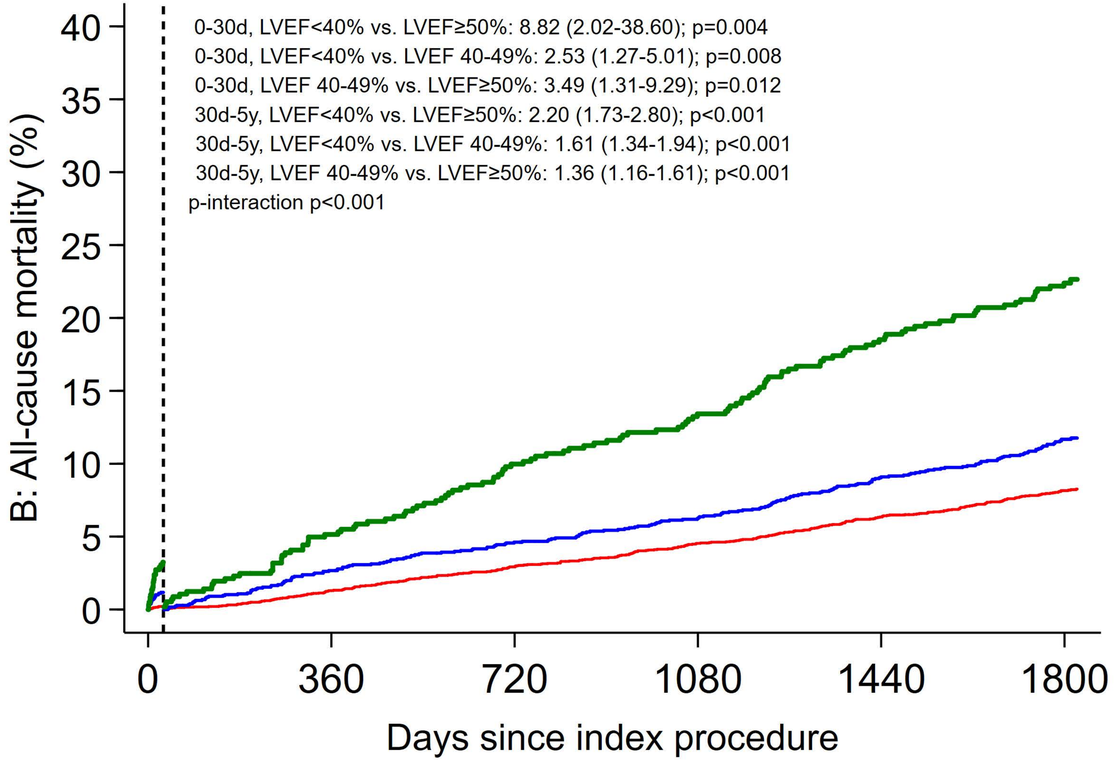
2089 patients without LVEF measurement

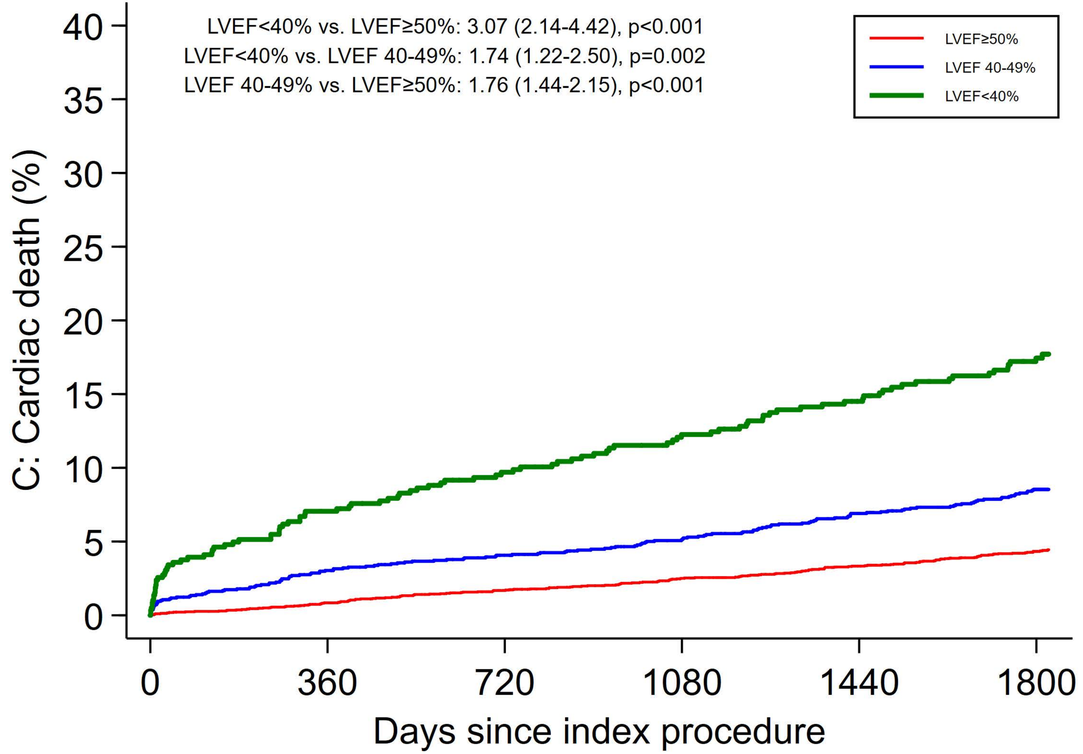
LVEF ≥50% 3816 patients	**LVEF 40-49%** 1793 patients	**LVEF <40%** 589 patients
3816 patients with clinical primary endpoint available up to 5-years 3502 alive 314 died	1793 patients with clinical primary endpoint available up to 5-years 1569 alive 224 died	589 patients with clinical primary endpoint available up to 5-years 445 alive 144 died
3816 patients analysed 3371 ≥ 1750 days follow-up 445 < 1750 days follow-up	1793 patients analysed 1515 ≥ 1750 days follow-up 278 < 1750 days follow-up	589 patients analysed 425 ≥ 1750 days follow-up 164 < 1750 days follow-up



Nr of patients

LVEF≥50%	3816	3722	3632	3541	3465	2992
LVEF 40-49%	1793	1707	1659	1611	1561	1305
LVEF<40%	589	532	502	477	446	359





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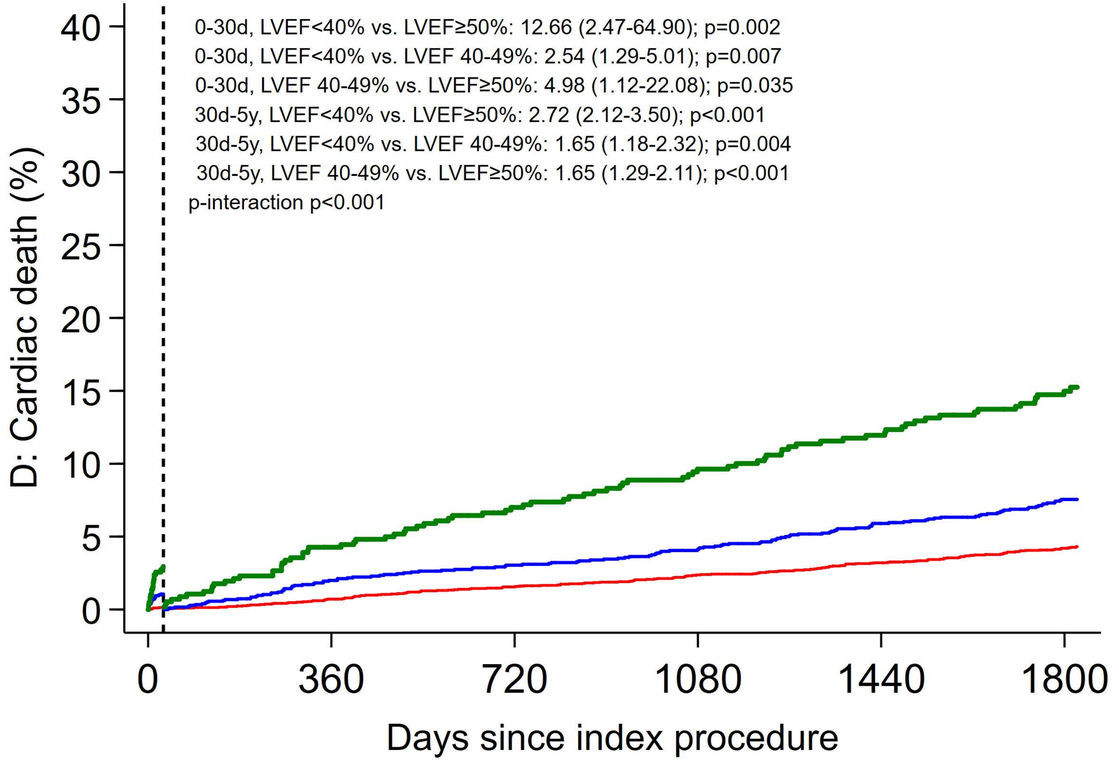
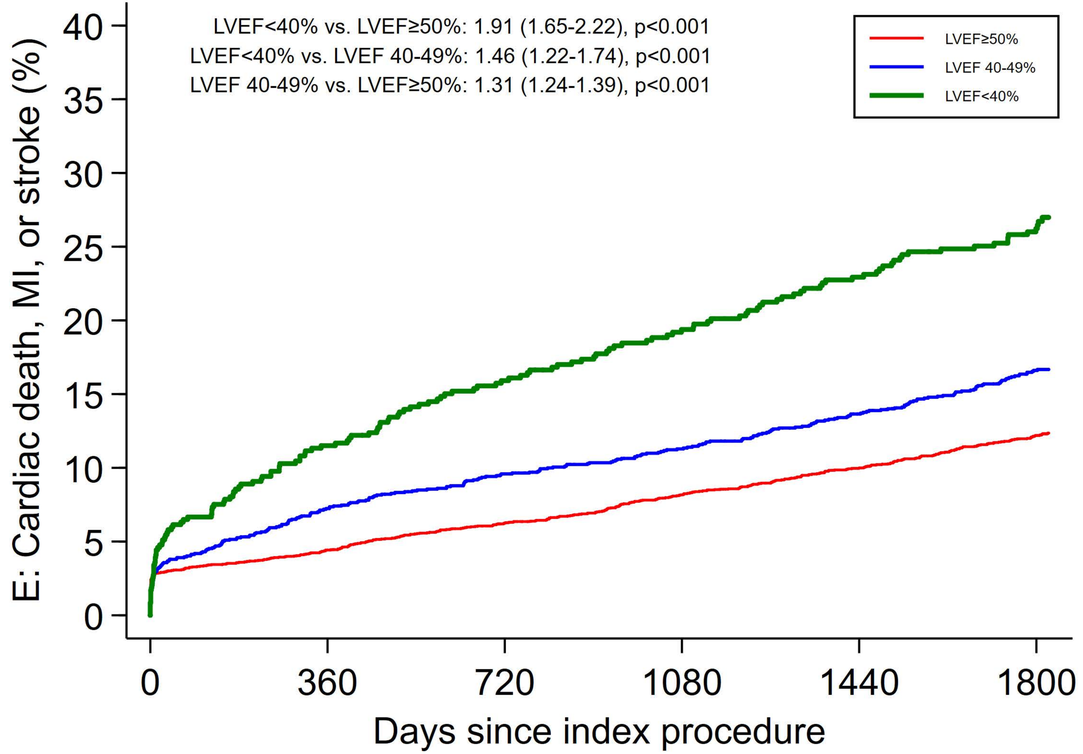
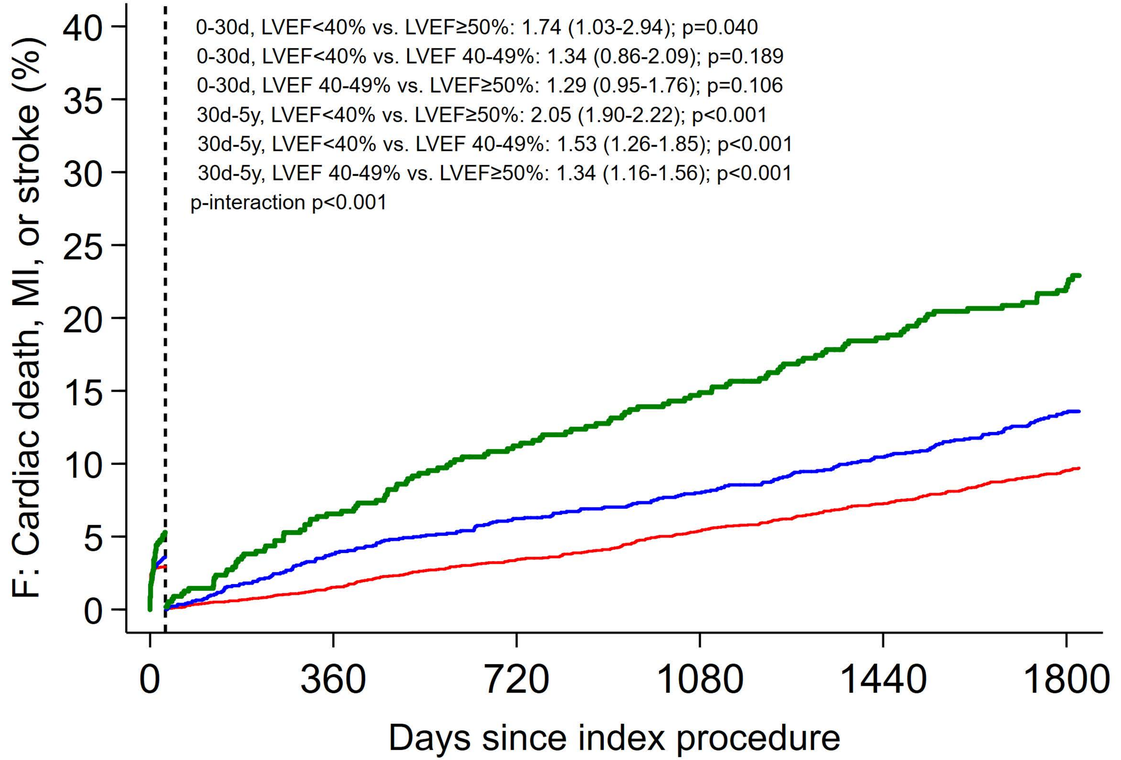
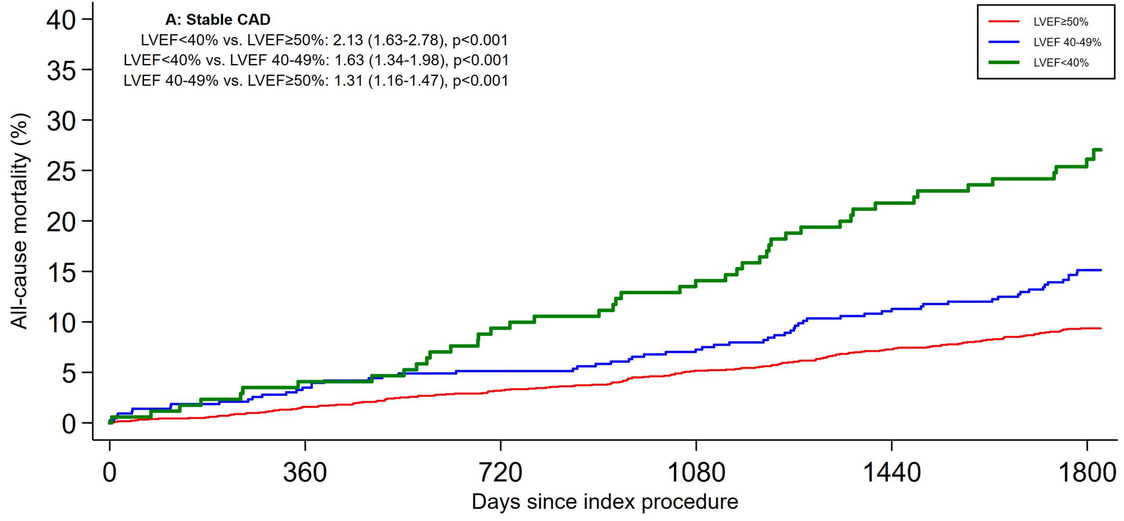




Nr of patients

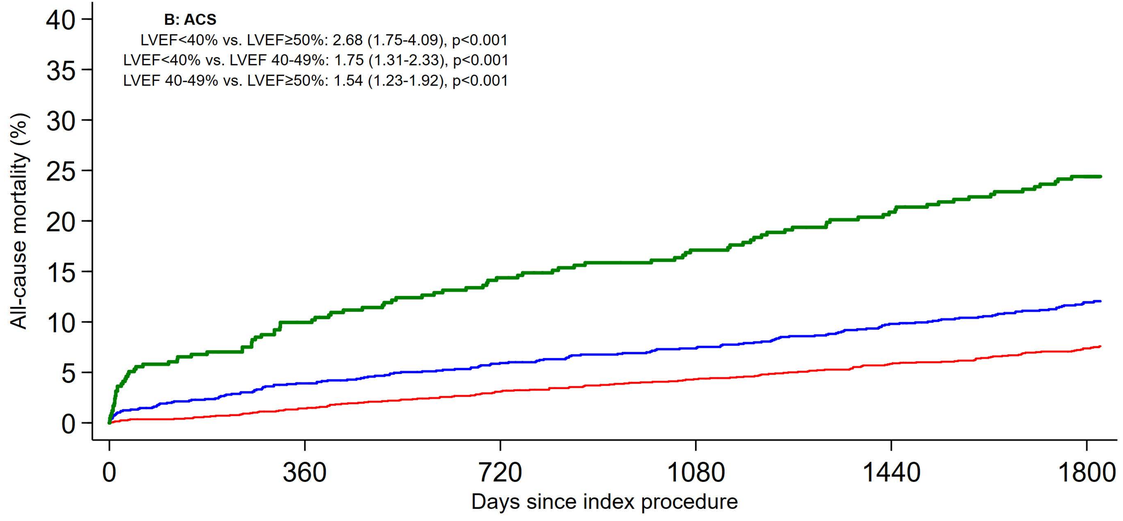
LVEF≥50%	3816	3588	3463	3334	3229	2758
LVEF 40-49%	1793	1635	1568	1510	1451	1198
LVEF<40%	589	507	467	439	404	321





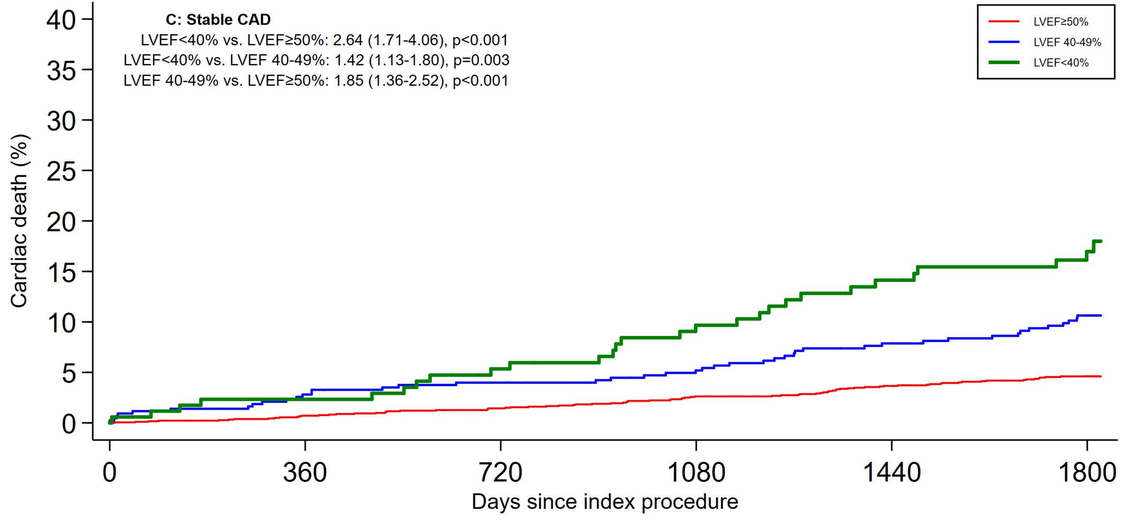
Nr of patients

LVEF≥50%	1840	1800	1756	1711	1669	1418
LVEF 40-49%	429	414	405	391	375	302
LVEF<40%	174	164	154	146	131	98



Nr of patients

LVEF≥50%	1976	1922	1876	1830	1796	1574
LVEF 40-49%	1364	1293	1254	1220	1186	1003
LVEF<40%	415	368	348	331	315	261



Nr of patients

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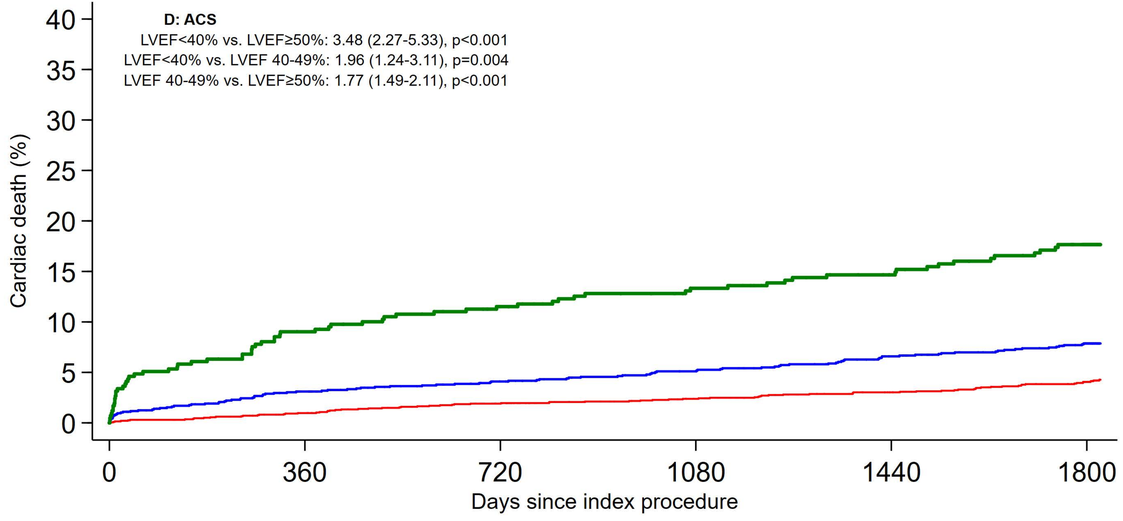
LVEF 40-49%	429	414	405	391	375	302
LVEF<40%	174	164	154	146	131	98



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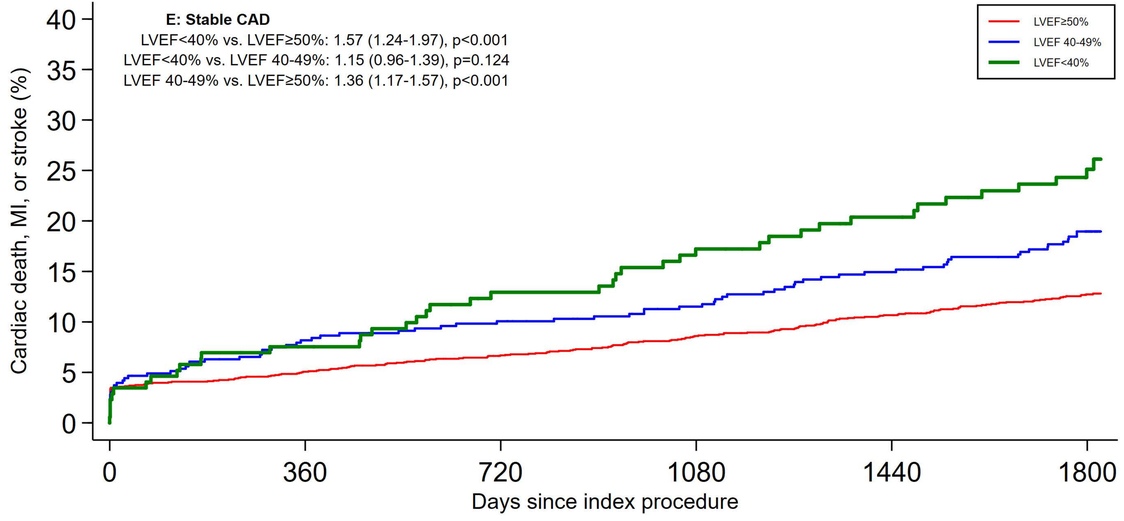
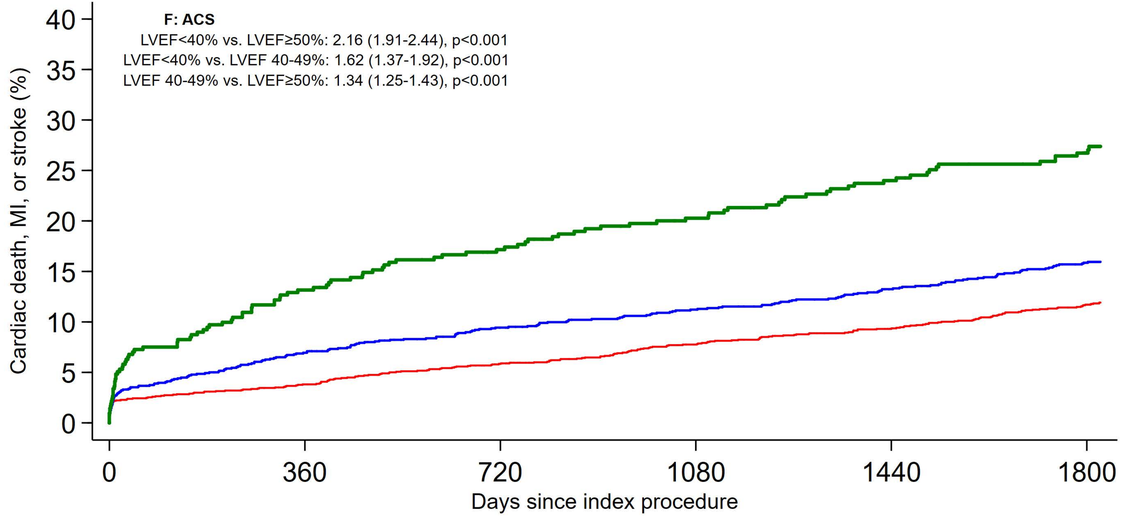


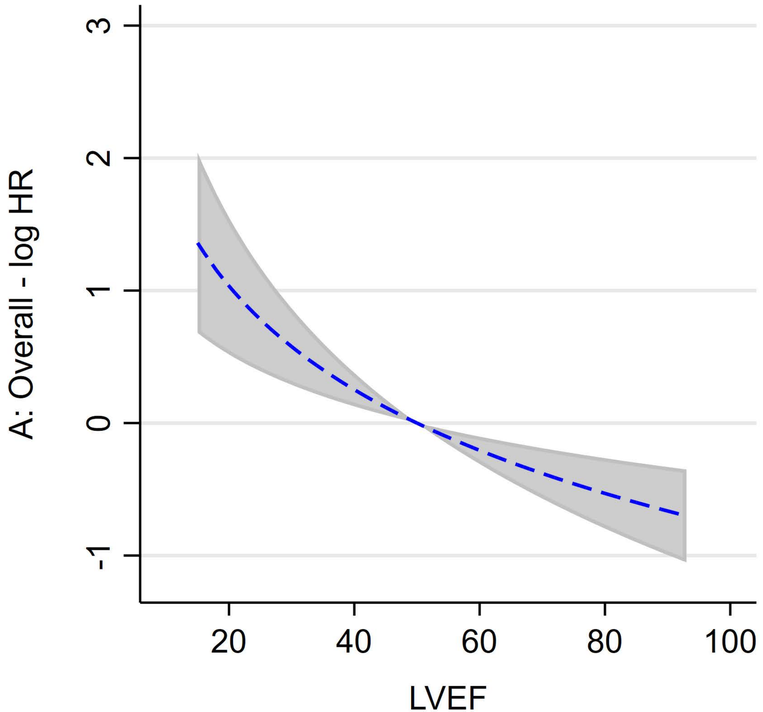
Nr of patients

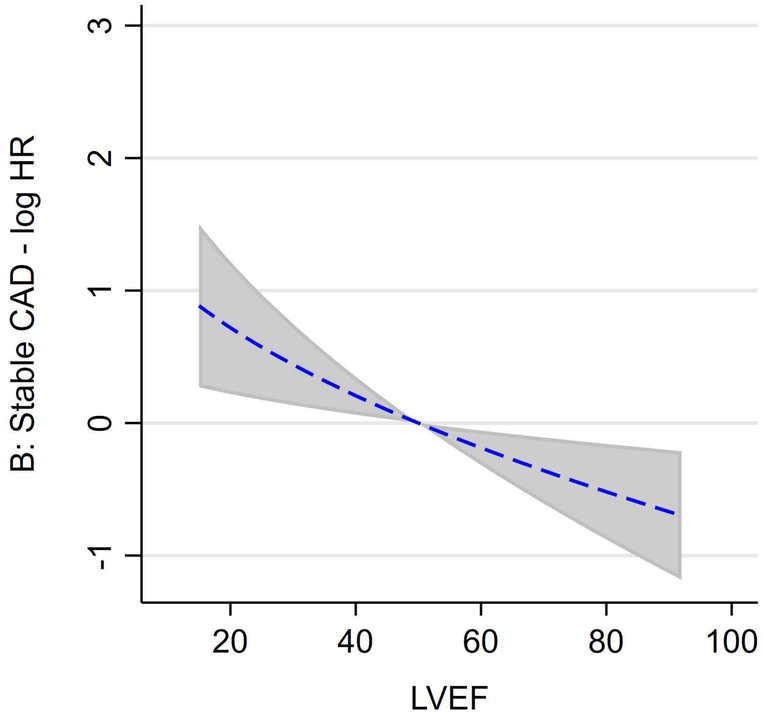
LVEF≥50%	1840	1722	1663	1606	1550	1302
LVEF 40-49%	429	391	379	364	345	275
LVEF<40%	174	156	142	135	123	91

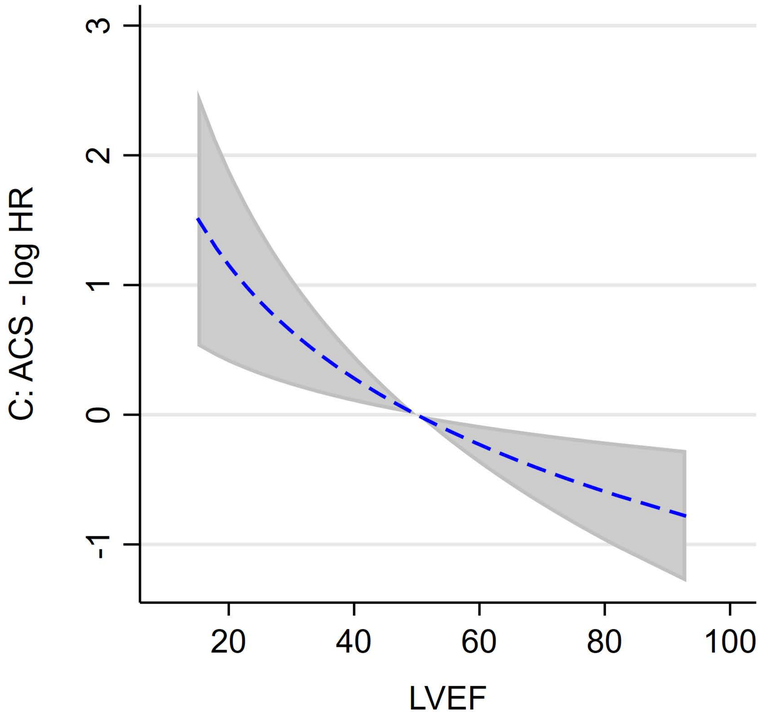


Nr of patients

LVEF≥50%	1976	1866	1800	1728	1679	1456
LVEF 40-49%	1364	1244	1189	1146	1106	923
LVEF<40%	415	351	325	304	281	230


A: Overall - log HR
3
2
1
0
-1
20
40
60
80
100
LVEF


B: Stable CAD - log HR
3
2
1
0
-1
20
40
60
80
100
LVEF


C: ACS - log HR
3
2
1
0
-1
20
40
60
80
100
LVEF