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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 cut-offs of left ventricular ejection fraction (LVEF) including an intermediate phenotype with mid-range reduced ejection fraction among patients with coronary artery disease undergoing percutaneous coronary intervention.

Methods and results: Patient-level data were summarized from five randomized clinical trials in which 6198 patients underwent clinically indicated percutaneous coronary intervention in different clinical settings. We assessed all-cause mortality as primary endpoint at five-year follow-up. According to the proposed LVEF cut-offs, 3816 patients were included in the preserved LVEF group (LVEF $\geq$ 50%), 1793 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 five years of follow-up (adjusted hazard ratio 2.39 (95% confidence interval 1.75–3.28, $p < 0.001$) and 1.68 (95% confidence interval 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 with preserved LVEF group (adjusted $p < 0.05$ for all comparisons) throughout five years. Irrespective of clinical presentation at baseline (stable coronary artery disease or acute coronary syndrome), patients with reduced or mid-range LVEF were at increased risk of all-cause mortality and cardiac death up to five years compared with 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 coronary artery disease undergoing clinically indicated percutaneous coronary intervention are at increased risk of all-cause mortality, cardiac death and the composite of cardiac death, stroke and myocardial infarction throughout five years of follow-up. The recently proposed LVEF cut-offs contribute to the differentiation and risk stratification of patients with ischaemic heart disease.

Keywords

Heart failure, left ventricular ejection fraction, heart failure reduced 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 represent a clinical challenge

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because of the complex pathophysiological substrate and comorbidity interplay.[2] Previous studies of patients with CAD and reduced left ventricular ejection fraction (LVEF < 40%) have shown favourable results of coronary revascularization (with either 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/American Heart Association (ACCF/AHA) and European Society of Cardiology (ESC) are not uniform with respect to the class and level of treatment recommendations for patients with heart failure and CAD suitable for revascularization. The ESC guidelines recommend any intervention that would achieve complete revascularization (CABG or PCI) for patients with heart failure and significant CAD in the presence of symptoms of angina and the presence of viable myocardium.[5] The ACCF/AHA guidelines recommend CABG or PCI in patients with left main or multivessel disease in the case of symptomatic patients without requiring evidence of ischaemia.[6] Recently, the ESC guidelines on acute and chronic heart failure 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 cut-off 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 cut-offs[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 Material Table 1 online).[9–16] Briefly, all studies included patients with CAD referred for clinically indicated PCI in different clinical settings (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 or drug-eluting stent) 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 LV 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 contained only 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, any target-vessel revascularization, and any revascularization up to five-years' follow-up. Follow-up in individual trials was prospectively performed at 30 days, one year and annually thereafter throughout five years. For this analysis, five-year follow-up data were available for all trials. Individual patients were censored at the valid contact in the case of lost-to-follow-up or withdrawal of the consent.

Statistical analysis

We stratified the study population according to the recently proposed LVEF cut-offs[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's *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 five years were expressed as counts with percentage for the overall population, and stratified according to clinical presentation (stable CAD or acute coronary syndrome (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 with accompanied 95% confidence intervals (CIs). We considered the different trials as random effect and we derived adjusted hazard ratios performing maximum likelihood estimation from multivariable survival parametric models for the overall population and stratified groups for all the endpoints. We obtained adjusted hazard ratios by considering baseline characteristics, excluding PCI related information and those variables with $\geq$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 CAD, previous MI, previous PCIs, previous CABG, ACS 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 hazard ratios computed separately for events up to 30 days and from 30 days to five years. Finally, we used fractional polynomials to analyse 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 centred at the value of 50. Hazard ratios are considered statistically significant at the 5% level. All statistical analyses were performed with Stata version 15.0 (StataCorp. 2017, College Station, Texas, USA).

Results

Study population and baseline clinical characteristics

A total of 8287 patients were enrolled into five trials, of whom 6198 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

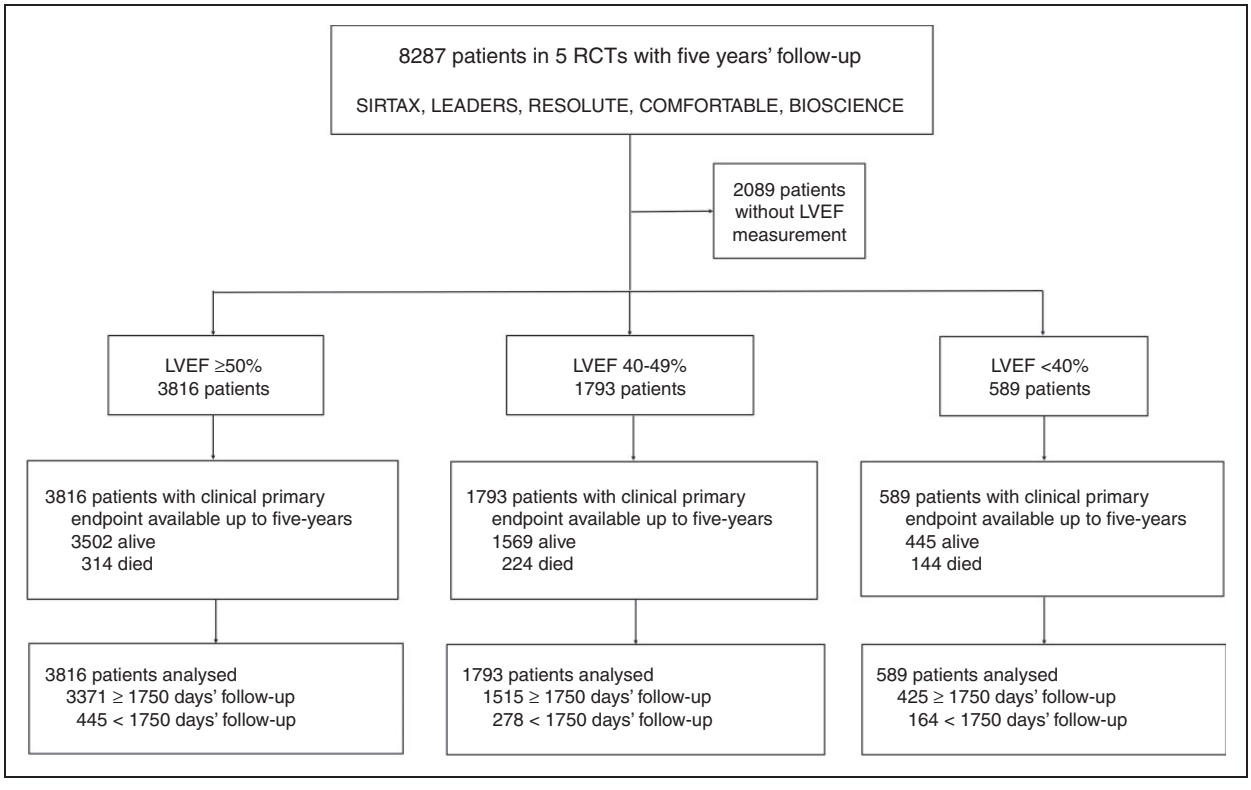

Figure 1. Flowchart of the patient selection process and group distribution according to LVEF in the study population.
RCT: randomized controlled trial; LVEF: left ventricular ejection fraction

Table 1. Baseline clinical characteristics.

	All $N = 6198$	LVEF $\geq 50\%$ $n = 3816$	LVEF 40–49% $n = 1793$	LVEF $< 40\%$ $n = 589$	p-value
Age	6198, 64 ± 11	3816, 64 ± 11	1793, 63 ± 12	589, 66 ± 12	<0.001
Gender, female	6198, 1405 (23)	3816, 888 (23)	1793, 401 (22)	589, 116 (20)	0.146
BMI, kg/m^2	6160, 28 ± 4	3792, 28 ± 4	1781, 28 ± 4	587, 27 ± 4	<0.001
Diabetes mellitus	6198, 1338 (22)	3816, 799 (21)	1793, 370 (21)	589, 169 (29)	<0.001
Insulin-requiring diabetes	6198, 416 (7)	3816, 241 (6)	1793, 123 (7)	589, 52 (9)	0.073
Diabetes diet	5635, 262 (5)	3454, 142 (4)	1659, 84 (5)	522, 36 (7)	0.012
Diabetes oral treatment	5682, 515 (9)	3488, 308 (9)	1668, 146 (9)	526, 61 (12)	0.104
Hypertension	6196, 4120 (66)	3816, 2659 (70)	1792, 1102 (61)	588, 359 (61)	<0.001
Current smoker	6144, 1993 (32)	3789, 1129 (30)	1771, 673 (38)	584, 191 (33)	<0.001
GFR, ml/min	5770, 87 ± 29	3567, 87 ± 29	1653, 88 ± 27	550, 81 ± 28	<0.001
Renal failure, < 60 eGFR	5770, 769 (13)	3567, 402 (11)	1653, 244 (15)	550, 123 (22)	<0.001
Family history of CAD	5962, 1984 (33)	3662, 1280 (35)	1734, 544 (31)	566, 160 (28)	0.001
Peripheral arterial disease	4980, 328 (7)	2990, 193 (6)	1510, 92 (6)	480, 43 (9)	0.079
Previous MI	6173, 1415 (23)	3802, 753 (20)	1789, 484 (27)	582, 178 (31)	<0.001
Previous PCI	6198, 1584 (26)	3816, 1003 (26)	1793, 436 (24)	589, 145 (25)	0.249
Previous CABG	6198, 493 (8)	3816, 291 (8)	1793, 136 (8)	589, 66 (11)	0.009
History of congestive heart failure	3958, 222 (6)	2298, 46 (2)	1257, 81 (6)	403, 95 (24)	<0.001
Cardiogenic shock	2772, 5 (1)	1530, 1 (0)	934, 5 (1)	308, 9 (3)	<0.001
Killip Class	2750	1516	930	304	<0.001
Killip I	2503 (91)	1469 (97)	825 (89)	209 (69)	<0.001
Killip II	202 (7)	41 (3)	89 (10)	72 (24)	<0.001
Killip III	30 (1)	5 (0)	11 (1)	14 (5)	<0.001
Killip IV	15 (1)	1 (0)	5 (1)	9 (3)	<0.001
Clinical presentation	6198	3816	1793	589	<0.001
Stable CAD	2443 (40)	1840 (48)	429 (24)	174 (30)	<0.001
NSTE-ACS	1811 (29)	1224 (32)	458 (25)	129 (22)	<0.001
STEMI	1944 (31)	752 (20)	906 (51)	286 (49)	<0.001
Multivessel intervention	1587 (29)	759 (30)	292 (31)	109 (33)	0.568
Medical therapy					
At hospital discharge					
Aspirin	4964, 4930 (99)	2986, 2965 (99)	1503, 1495 (99)	475, 470 (99)	0.479
Clopidogrel	4965, 3539 (71)	2987, 2229 (75)	1503, 987 (66)	475, 323 (68)	<0.001
Prasugrel	2763, 928 (34)	1529, 442 (29)	928, 378 (41)	306, 108 (35)	<0.001
Ticagrelor	1694, 459 (27)	1096, 292 (27)	434, 128 (29)	164, 39 (24)	0.318
Statin	4970, 4667 (94)	2988, 2792 (93)	1504, 1442 (96)	478, 433 (91)	<0.001
Beta-blocker	4970, 3976 (80)	2988, 2235 (75)	1504, 1330 (88)	478, 411 (86)	<0.001
ACE-inhibitor/ARB	4970, 3178 (64)	2988, 1688 (56)	1504, 1130 (75)	478, 360 (75)	<0.001
One year					
Aspirin	4714, 4487 (95)	2878, 2759 (96)	1414, 1341 (95)	422, 387 (92)	0.001
Clopidogrel	4714, 2247 (48)	2878, 1412 (49)	1414, 642 (45)	422, 193 (46)	0.056
Prasugrel	2622, 790 (30)	1469, 387 (26)	875, 320 (37)	278, 83 (30)	<0.001
Ticagrelor	1605, 347 (22)	1047, 223 (21)	405, 98 (24)	153, 26 (17)	0.167
Statin	4771, 4299 (90)	2900, 2618 (90)	1431, 1299 (91)	440, 382 (87)	0.046
Beta-blocker	4772, 3526 (74)	2900, 2017 (70)	1432, 1150 (80)	440, 359 (82)	<0.001
ACE-inhibitor/ARB	4770, 2536 (53)	2899, 1396 (48)	1432, 876 (61)	439, 264 (60)	<0.001

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

LVEF: left ventricular ejection fraction; BMI: body mass index; GFR: glomerular filtration rate; eGFR: estimated GFR; 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; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker

LVEF cut-offs[7], 3816 patients were included in the preserved LVEF (≥50%) group, 1793 in the 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 characteristics of the study population. Baseline characteristics differed considerably across the three groups with patients in the 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 ACSs (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 five 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 the mid-range reduced LVEF group (24% *vs*. 8% and 13%, respectively) with unadjusted hazard ratios of 1.56 (95% CI, 1.36 to 1.80) for mid-range versus preserved LVEF group, 3.32 (95% CI, 2.81 to 3.93) for reduced versus preserved LVEF group, and 2.13 (95% CI, 1.78 to 2.54) for reduced versus mid-range reduced LVEF group (Supplementary Table 5) at five 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 hazard ratio 2.39 (95% CI, 1.75 to 3.28), $p < 0.001$) or mid-range LVEF (40–49%) (adjusted hazard ratio 1.68 (95% CI, 1.34 to 2.10), $p < 0.001$) throughout five years of follow-up (Table 2 and Figure 2). The risk of cardiac death and the composite endpoint of cardiac death, MI or stroke remained higher for patients in the reduced LVEF group compared with either the preserved or the 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 hazard ratio 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 with the preserved LVEF group during the first 30 days and continued to be at increased risk up to five 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 hazard ratio 3.07 (95% CI, 2.14 to 4.42), $p < 0.001$) or the mid-range LVEF group (adjusted hazard ratio 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 groups, 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 with both preserved and mid-range LVEF groups throughout five 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 hazard ratio 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 with 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 cut-offs to a large group of patients with CAD undergoing clinically indicated PCI followed throughout five years of follow-up with adjudicated clinical endpoint assessment in the context of carefully conducted randomized clinical

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

	0–30 days		30 days to 5 years		0–5 years	
	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
LVEF < 40% *vs.* LVEF ≥ 50%						
All-cause mortality	8.82 (2.02 to 38.60)	0.004	2.20 (1.73 to 2.80)	<0.001	2.39 (1.75 to 3.28)	<0.001
Cardiac death	12.66 (2.47 to 64.90)	0.002	2.72 (2.12 to 3.50)	<0.001	3.07 (2.14 to 4.42)	<0.001
Cardiac death, MI or stroke	1.74 (1.03 to 2.94)	0.040	2.05 (1.90 to 2.22)	<0.001	1.91 (1.65 to 2.22)	<0.001
Myocardial infarction	0.87 (0.48 to 1.59)	0.650	1.68 (1.35 to 2.08)	<0.001	1.35 (1.17 to 1.55)	<0.001
Q-wave MI	–	–	2.67 (1.88 to 3.78)	<0.001	1.59 (1.17 to 2.16)	0.003
Non-Q-wave MI	1.12 (0.68 to 1.84)	0.664	1.50 (1.27 to 1.78)	<0.001	1.34 (1.16 to 1.54)	<0.001
Stroke	2.23 (0.72 to 6.90)	0.164	1.64 (0.90 to 3.00)	0.107	1.61 (0.94 to 2.77)	0.082
Any TLR	2.07 (1.52 to 2.81)	<0.001	0.98 (0.61 to 1.58)	0.936	1.09 (0.75 to 1.59)	0.652
Any TVR	1.90 (1.44 to 2.51)	<0.001	0.65 (0.11 to 3.65)	0.622	1.04 (0.81 to 1.33)	0.748
Any revascularization	1.77 (1.25 to 2.52)	0.001	0.95 (0.68 to 1.31)	0.749	1.04 (0.66 to 1.65)	0.868
LVEF < 40% *vs.* LVEF 40–49%						
All-cause mortality	2.53 (1.27 to 5.01)	0.008	1.61 (1.34 to 1.94)	<0.001	1.68 (1.34 to 2.10)	<0.001
Cardiac death	2.54 (1.29 to 5.01)	0.007	1.65 (1.18 to 2.32)	0.004	1.74 (1.22 to 2.50)	0.002
Cardiac death, MI or stroke	1.34 (0.86 to 2.09)	0.189	1.53 (1.26 to 1.85)	<0.001	1.46 (1.22 to 1.74)	<0.001
Myocardial infarction	0.78 (0.56 to 1.10)	0.154	1.28 (1.06 to 1.55)	0.010	1.10 (0.99 to 1.23)	0.078
Q-wave MI	–	–	1.23 (0.84 to 1.80)	0.291	0.84 (0.52 to 1.37)	0.493
Non-Q-wave MI	1.09 (0.74 to 1.60)	0.674	1.30 (0.98 to 1.72)	0.064	1.21 (0.97 to 1.52)	0.092
Stroke	1.39 (0.89 to 2.16)	0.148	1.92 (1.25 to 2.96)	0.003	1.81 (1.26 to 2.60)	0.001
Any TLR	1.05 (0.88 to 1.25)	0.582	1.04 (0.74 to 1.45)	0.826	1.03 (0.78 to 1.37)	0.818
Any TVR	1.08 (0.89 to 1.31)	0.420	0.98 (0.82 to 1.18)	0.854	0.99 (0.87 to 1.13)	0.927
Any revascularization	1.16 (0.99 to 1.37)	0.070	0.96 (0.70 to 1.32)	0.800	0.98 (0.73 to 1.31)	0.895
LVEF 40–49% *vs.* LVEF ≥ 50%						
All-cause mortality	3.49 (1.31 to 9.29)	0.012	1.36 (1.16 to 1.61)	<0.001	1.42 (1.21 to 1.67)	<0.001
Cardiac death	4.98 (1.12 to 22.08)	0.035	1.65 (1.29 to 2.11)	<0.001	1.76 (1.44 to 2.15)	<0.001
Cardiac death, MI or stroke	1.29 (0.95 to 1.76)	0.106	1.34 (1.16 to 1.56)	<0.001	1.31 (1.24 to 1.39)	<0.001
Myocardial infarction	1.11 (0.73 to 1.70)	0.630	1.31 (0.99 to 1.72)	0.058	1.22 (1.04 to 1.43)	0.013
Q-wave MI	1.52 (0.63 to 3.65)	0.347	2.17 (1.42 to 3.32)	<0.001	1.88 (1.22 to 2.90)	0.004
Non-Q-wave MI	1.03 (0.70 to 1.51)	0.887	1.16 (0.84 to 1.58)	0.366	1.10 (0.86 to 1.43)	0.446
Stroke	1.61 (0.76 to 3.41)	0.215	0.85 (0.62 to 1.18)	0.342	0.89 (0.69 to 1.16)	0.383
Any TLR	1.97 (1.30 to 2.99)	0.001	0.94 (0.76 to 1.17)	0.602	1.05 (0.94 to 1.19)	0.381
Any TVR	1.76 (1.26 to 2.45)	0.001	0.96 (0.74 to 1.26)	0.790	1.05 (0.87 to 1.26)	0.614
Any revascularization	1.53 (1.05 to 2.22)	0.027	1.02 (0.75 to 1.38)	0.900	1.06 (0.83 to 1.36)	0.640

Data shown are adjusted hazard ratios with 95% confidence intervals. 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.

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

trials (RCTs). The salient findings of our analysis can be summarized as follows:

1. 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 five years.
2. The difference in mortality emerges early (within 30 days) and continues to increase over time (throughout five years).

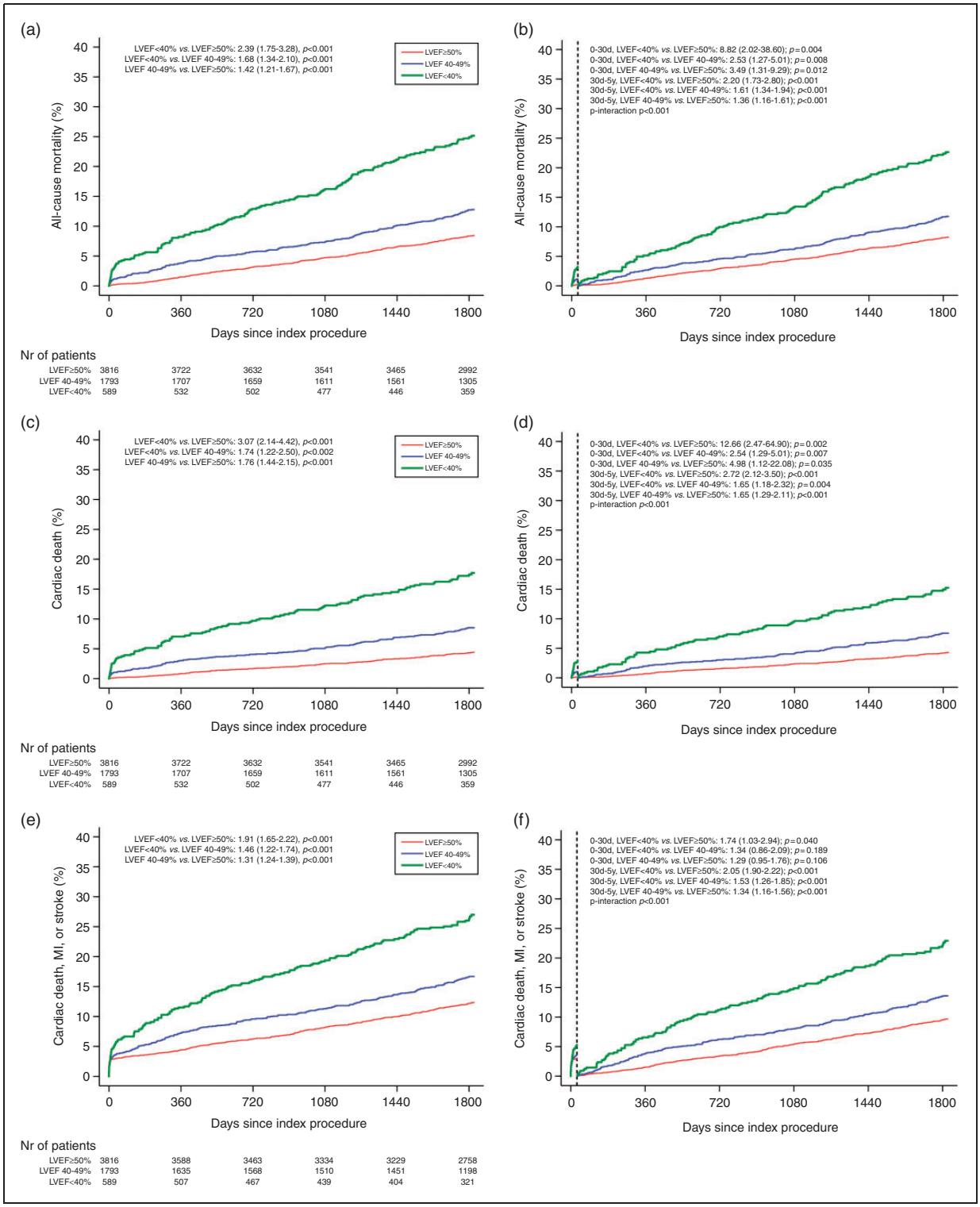

Figure 2. Time-to-first-event curves for patients across the three groups with preserved (≥50%), mid-range (40–49%) and reduced (<40%) LVEF.

(a) and (b): For the primary outcome of all-cause mortality; (c) and (d): for the outcome of cardiac death; (e) and (f): for the composite endpoint of cardiac death, myocardial infarction, or stroke. Estimates are shown as adjusted hazard ratios with accompanied 95% confidence intervals. A landmark analysis at time-point of 30 days is shown in (b), (d), and (f).

LVEF: left ventricular ejection fraction; d: day; y: year; Nr: number; MI: myocardial infarction

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

	Stable CAD		ACS	
	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
LVEF < 40% *vs.* LVEF ≥ 50%				
All-cause mortality	2.13 (1.63 to 2.78)	<0.001	2.68 (1.75 to 4.09)	<0.001
Cardiac death	2.64 (1.71 to 4.06)	<0.001	3.48 (2.27 to 5.33)	<0.001
Cardiac death, MI or stroke	1.57 (1.24 to 1.97)	<0.001	2.16 (1.91 to 2.44)	<0.001
Myocardial infarction	1.11 (0.63 to 1.93)	0.726	1.48 (1.15 to 1.90)	0.002
Q-wave MI	0.91 (0.33 to 2.48)	0.847	2.05 (1.29 to 3.27)	0.002
Non-Q-wave MI	1.12 (0.70 to 1.80)	0.627	1.46 (1.15 to 1.84)	0.002
Stroke	1.28 (0.27 to 5.98)	0.756	1.94 (1.12 to 3.36)	0.018
Any TLR	0.84 (0.49 to 1.43)	0.517	1.23 (0.88 to 1.72)	0.229
Any TVR	0.79 (0.55 to 1.13)	0.190	1.19 (0.96 to 1.47)	0.114
Any revascularization	0.70 (0.42 to 1.17)	0.176	1.27 (0.78 to 2.06)	0.335
LVEF < 40% *vs.* LVEF 40–49%				
All-cause mortality	1.63 (1.34 to 1.98)	<0.001	1.75 (1.31 to 2.33)	<0.001
Cardiac death	1.42 (1.13 to 1.80)	0.003	1.96 (1.24 to 3.11)	0.004
Cardiac death, MI or stroke	1.15 (0.96 to 1.39)	0.124	1.62 (1.37 to 1.92)	<0.001
Myocardial infarction	0.83 (0.49 to 1.41)	0.489	1.24 (1.03 to 1.48)	0.022
Q-wave MI	0.54 (0.20 to 1.45)	0.222	1.00 (0.49 to 2.01)	0.991
Non-Q-wave MI	0.92 (0.51 to 1.65)	0.771	1.34 (1.24 to 1.46)	<0.001
Stroke	1.11 (0.89 to 1.38)	0.342	2.06 (1.16 to 3.64)	0.013
Any TLR	0.79 (0.59 to 1.06)	0.120	1.17 (0.86 to 1.59)	0.306
Any TVR	0.76 (0.70 to 0.82)	<0.001	1.14 (1.00 to 1.29)	0.048
Any revascularization	0.72 (0.63 to 0.82)	<0.001	1.10 (0.82 to 1.48)	0.509
LVEF 40–49% *vs.* LVEF ≥ 50%				
All-cause mortality	1.31 (1.16 to 1.47)	<0.001	1.54 (1.23 to 1.92)	<0.001
Cardiac death	1.85 (1.36 to 2.52)	<0.001	1.77 (1.49 to 2.11)	<0.001
Cardiac death, MI or stroke	1.36 (1.17 to 1.57)	<0.001	1.34 (1.25 to 1.43)	<0.001
Myocardial infarction	1.33 (1.09 to 1.64)	0.005	1.20 (1.05 to 1.36)	0.006
Q-wave MI	1.68 (1.12 to 2.53)	0.012	2.06 (1.12 to 3.80)	0.021
Non-Q-wave MI	1.23 (0.92 to 1.64)	0.164	1.08 (0.84 to 1.40)	0.540
Stroke	1.15 (0.29 to 4.57)	0.844	0.94 (0.73 to 1.22)	0.655
Any TLR	1.06 (0.83 to 1.35)	0.657	1.05 (1.00 to 1.10)	0.069
Any TVR	1.04 (0.79 to 1.38)	0.768	1.05 (0.93 to 1.18)	0.452
Any revascularization	0.98 (0.65 to 1.47)	0.916	1.15 (0.88 to 1.49)	0.300

Data shown are adjusted hazard ratios with 95% confidence intervals. 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.

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

3. 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 five years.
4. 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 with 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 a subject of debate. In a post-hoc analysis of the CHARM trial,

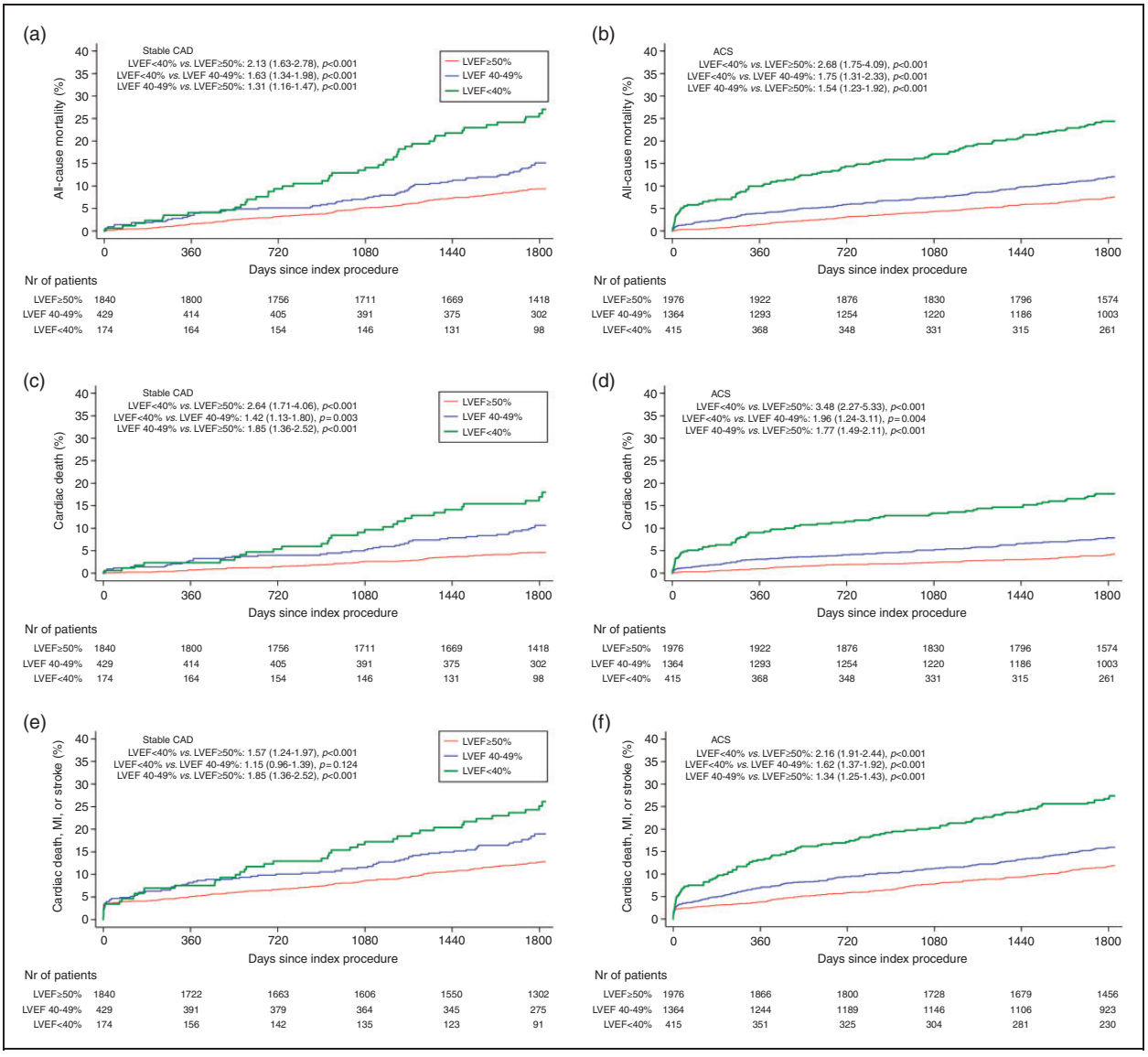

Figure 3. Time-to-first-event curves for patients across the three groups with preserved (≥50%), mid-range (40–49%) and reduced (<40%) LVEF stratified according to clinical presentation.
(a) and (b): For the primary outcome of all-cause mortality; (c) and (d): for the outcome of cardiac death; (e) and (f): for the composite endpoint of cardiac death, myocardial infarction, or stroke. Estimates are shown as adjusted hazard ratios with accompanied 95% confidence intervals.
LVEF: left ventricular ejection fraction; MI: myocardial infarction; CAD: coronary artery disease; ACS: acute coronary syndrome; Nr: number

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 indicated no significant increase in the risk of all-cause mortality or cardiovascular death in patients with either LVEF 50–59% or LVEF 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 the 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 with patients with either preserved or mid-range impaired LV function throughout five years. Most studies, of heart failure with depressed

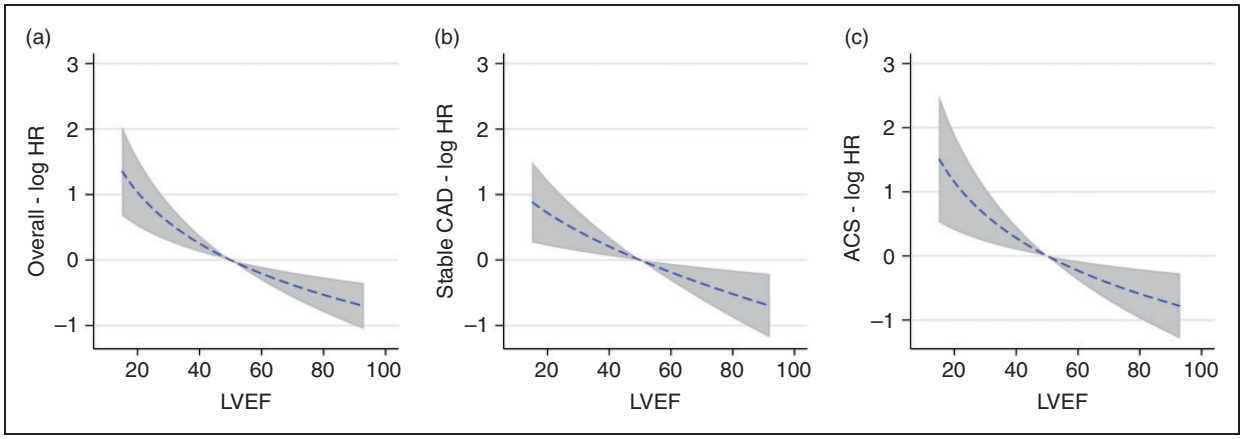

Figure 4. Fractional polynomial stratified according to clinical setting at baseline for all-cause mortality.
(a) Overall; (b): stable CAD; (c): ACS.
HR: hazard ratio; LVEF: left ventricular ejection fraction; CAD: coronary artery disease; ACS: acute coronary syndrome

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 ischaemic heart failure improved to a lesser degree compared with patients with non-ischaemic heart failure within the first year of initial assessment followed by a relative plateau thereafter. Of note, a decline in LVEF as compared with 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 three years follow-up.[24] Similarly, a retrospective analysis of the CADILLAC trial reported an increased risk of all-cause mortality at one year of follow-up among STEMI patients with baseline LVEF <40% as compared with those with baseline LVEF >40%.[25] The present study extends these findings, suggesting that baseline LV dysfunction impacts on survival up to five 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 with 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 groups 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% and 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 analysed 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 five-years' follow-up. Second, values for LVEF are continuously distributed but measurement precision is known to be imperfect and differences of 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. Fourth, we were unable to correlate clinical heart failure status with objective parameters of LV function. Finally, in any individual trial, there are always concerns about whether the study populations enrolled reflect the patients encountered in clinical practice due to selection criteria, and in this aspect this analysis is not different. However, our dataset represents the vast majority of patients enrolled in PCI RCTs.

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 MI throughout five years of follow-up. The recently proposed LVEF cut-offs contribute to the differentiation and risk stratification of patients with ischaemic heart disease.

Author contribution

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.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: 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.

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