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Increased long-term mortality in women with high left ventricular ejection fraction: data from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) long-term registry

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Aims There are significant sex-specific differences in left ventricular ejection fraction (LVEF), with a higher LVEF being observed in women. We sought to assess the clinical relevance of an increased LVEF in women and men.

Methods and results A total of 4632 patients from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry (44.8% women; mean age 58.7 ± 13.2 years in men and 59.5 ± 13.3 years in women, $P = 0.05$), in whom LVEF was measured by cardiac computed tomography, were categorized according to

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LVEF (low <55%, normal 55–65%, and high >65%). The prevalence of high LVEF was similar in both sexes (33.5% in women and 32.5% in men, $P = 0.46$). After 6 years of follow-up, no difference in mortality was observed in patients with high LVEF in the overall cohort ($P = 0.41$). When data were stratified by sex, women with high LVEF died more often from any cause as compared to women with normal LVEF (8.6% vs. 7.1%, log rank $P = 0.032$), while an opposite trend was observed in men (5.8% vs. 6.8% in normal LVEF, log rank $P = 0.89$). Accordingly, a first order interaction term of male sex and high LVEF was significant (hazard ratios 0.63, 95% confidence intervals 0.41–0.98, $P = 0.043$) in a Cox regression model of all-cause mortality adjusted for age, cardiovascular risk factors, and severity of coronary artery disease (CAD).

Conclusion Increased LVEF is highly prevalent in patients referred for evaluation of CAD and is associated with an increased risk of death in women, but not in men. Differentiating between normal and hyperdynamic left ventricles might improve risk stratification in women with CAD.

Clinical trial registration https://clinicaltrials.gov/ct2/show/NCT01443637.

Keywords women • gender • coronary computed tomography angiography • left ventricular ejection fraction • cardiovascular

Introduction

Left ventricular (LV) function and dimensions are important predictors of morbidity and mortality in various cardiovascular diseases.[1–3] Recent experimental and clinical studies indicate that there are significant sex- and age-specific differences in baseline left ventricular ejection fraction (LVEF).[4–6] Indeed, LV function is significantly higher in women than in men, and these differences further augment with age.[4–6] The latter is consistent with the observation that the risk of cardiovascular events starts at higher LVEF indices in women than in men.[7] Similarly, despite their higher mortality rates, LV function is relatively better preserved in women with coronary artery disease (CAD), even when adjusting for age and comorbidities.[8] To date, it remains unclear why LVEF differs between genders, however, the fact that women with heart failure or acute coronary syndrome show consistently poorer outcomes as compared to men emphasizes the need to better define variables that contribute to the increased cardiovascular risk in women.[9,10]

Coronary computed tomography angiography (CCTA) has proved high accuracy and reproducibility in the evaluation of LV morphology and function, and computed tomography (CT) measures of abnormal LVEF have been shown to improve risk stratification in patients with CAD.[11] While the association between impaired LVEF and increased mortality is well established, the impact of an enhanced, high LVEF on outcomes in patients with CAD is currently unknown. Thus, given (i) the discrepancies in male and female cardiovascular risk, (ii) the sex-dependent differences in LVEF, and (iii) the prognostic importance of LV function, we aimed to evaluate the impact of high LVEF as assessed by CCTA on long-term outcomes in women and men referred for evaluation of CAD in a large international multicentre cohort.

Methods

Study population

The rationale, study design, site-specific patient characteristics, and follow-up durations of the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) long-term follow-up registry have previously been described.[12] Briefly, the CONFIRM registry prospectively collects clinical, procedural, and follow-up data on patients undergoing ≥64-detector row CCTA and aims to assess the capability of CCTA findings to predict all-cause mortality. Our study screened 17 181 patients with 6-year follow-up who underwent CCTA at 17 centres in 9 countries including Austria, Canada, Germany, Israel, Italy, Portugal, South Korea, Switzerland, and USA. All patients were enrolled between 2003 and 2011 as part of the CONFIRM long-term follow-up registry. The following inclusion criteria were applied: age 18 years or older, an evaluation by CCTA scanner with 64-detector rows or greater, the presence of interpretable CCTA as well as LVEF, volume assessment by gated CCTA, and absence of structural heart disease. Given the large number of excluded patients and the associated risk of selection bias, excluded and included patient cohorts were analysed for baseline differences. The study complies with the Declaration of Helsinki, and each study site received institutional review board approval for all registry procedures. All study participants provided written informed consent.

Data collection and definition of risk factors

Prior to CCTA scanning, information regarding cardiovascular risk factors was collected at each site by standardized data collection methods.[13] Consistent definitions for cardiac symptoms, risk factors, and angiographic CAD extent and severity were applied as previously described.[12] Symptom presentation was classified into asymptomatic and symptomatic, while symptomatic individuals were further classified into typical chest pain, atypical chest pain, non-anginal pain, or dyspnoea.

Image acquisition and analysis

CCTA was uniformly acquired at all sites using standardized protocols and multi-detector row CT scanners consisting of 64-rows or greater. All CCTA images were analysed in a uniform fashion at each site by at least one highly experienced reader who was Level III equivalent with experience in interpreting several thousand CCTA scans in direct accordance with the Society of Cardiovascular Computed Tomography (SCCT) guidelines[14] and/or board certified in cardiovascular CT. Scanning parameters, dose reduction strategies, and post-processing imaging techniques used in the CONFIRM registry have been described in detail elsewhere.[11,13] LVEF was measured volumetrically (excluding papillary

muscles) with post-processing by using 10–20 phases of the cardiac cycle (temporal resolution, 83–350 ms). LVEF was automatically calculated using end-diastolic (EDV) and end-systolic (ESV) volumes. Indexed values were obtained by normalizing EDV and ESV to body surface area (BSA). Coronary segment location was defined according to the recommendations of the SCCT.[15] All segments were assessed for the presence and severity of coronary stenosis. The latter was categorized in non-obstructive stenosis (=coronary artery segments displaying plaque with a luminal diameter stenosis 1–49%) and obstructive stenosis (=coronary artery segments displaying plaque with a luminal diameter stenosis ≥50%). CAD extent was defined by ≥50% stenosis in 0, 1, 2, or 3 coronary artery vessels. In the overall cohort, LVEF was classified as follows: low (<55%), normal (55–65%), and high normal (>65%). The upper and lower cut-off values were chosen based on previously reported reference ranges.[11,16] In addition, sex-specific upper and lower limits of normal were applied according to data derived from populations free of cardiovascular disease.[6,17] Sex-specific LVEF strata were as follows: men: low LVEF <47%, normal LVEF 47–70%, high LVEF >70%; women: low LVEF <50%, normal LVEF 50–72%, high LVEF >72%. A small heart was defined as an abnormally low LVESV according to reference ranges derived from healthy female populations.[17] Cut-off values to define a small heart were LVESV <25 mL and indexed LVESV <16 mL/m^2, respectively.

Endpoints

The primary outcome measure for the present study was time to death by any causes. Secondary exploratory outcomes were late revascularization and major adverse cardiovascular events (MACE). The latter included a combination of all-cause mortality and non-fatal myocardial infarction (MI) and was assessed in a subcohort of 1359 patients. Cause of death was not obtained in the CONFIRM registry. Non-fatal MI was defined as evidence of myocardial necrosis consistent with myocardial ischaemia, as detected by changes in cardiac biomarkers together with symptoms of ischaemia, electrocardiogram changes, or imaging evidence.

Statistical analysis

Baseline characteristics of the study population were summarized according to sex, with categorical variables being presented as counts with percentages and continuous variables as mean ± standard deviation. Differences between continuous and categorical variables were analysed by the Student's *t*-test and the χ^2 test, or the Fisher's exact test, as appropriate. Kaplan–Meier curves with log-rank test were used to assess the relationship between LVEF and primary and secondary endpoints. Hazard ratios (HR) with 95% confidence intervals (CI) for the association of a high LVEF with all-cause mortality were calculated by use of unadjusted and adjusted Cox proportional hazard regression models. For Cox proportional hazards modelling the assumption of proportional hazards was assessed and verified using Schoenfeld residuals ($P = 0.253$). The Cox regression analysis was adjusted for age, cardiovascular risk factors including smoking, diabetes mellitus, hypertension, dyslipidaemia, positive family history of CAD, and severity of CAD. A first order interaction term consisting of sex and LVEF was tested in these models to assess the impact of sex on study outcomes. All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, TX, USA), and a *P*-value <0.05 was considered significant.

Results

Patient characteristics

Out of 17 181 patients, LVEF had been analysed in 4654 patients. For 22 individuals, data on age, gender, or severity of CAD were missing. Thus, the final analytic sample comprised 4632 patients [2555 (55.2%) men, *Figure 1*]. No significant difference was found between excluded and included individuals for baseline demographics (diabetes: 17.4% vs. 17.6%, $P = 0.69$; hypertension: 62.8% vs. 61.4%, $P = 0.106$; dyslipidaemia: 59.9% vs. 61.3%, $P = 0.081$), except for age: 59.3 ± 12.6 vs. 59.1 ± 13.2 years, $P = 0.04$). Mean age of our study population was 59.5 ± 13.3 years for women and 58.7 ± 13.2 years for men ($P = 0.05$ for men vs. women) with 62.9% of women and 61.6% of men ($P = 0.4$ for men vs. women) being older than 55 years. Body mass index (BMI) was slightly higher in women as compared to men (28.0 ± 6.9 vs. 27.9 ± 4.9, $P = 0.02$), while BSA was higher in men (1.8 ± 0.2 vs. 2.0 ± 0.2, $P < 0.001$). Women had less often dyslipidaemia than men (59.0% vs. 63.2%, $P = 0.004$) and more often a positive family history of CAD (45.9% vs. 39.9%, $P < 0.001$). Women were more often symptomatic (82.6% vs. 69.5%, $P < 0.001$) and suffered more often from atypical chest pain than men (39.3% vs. 30.3%, $P < 0.001$). More men than women had known CAD (13.1% vs. 6.3%, $P < 0.001$, *Table 1*). All demographic characteristics of the study population stratified by sex are listed in *Table 1*.

CCTA findings

Mean LVEF was higher in women as compared to men (61.5 ± 11.2% vs. 60.2 ± 11.8%, $P = 0.01$, *Table 2*). Also, EDV and ESV were smaller in women as compared to men (113.7 ± 30.4 vs. 142.5 ± 38.3 mL, $P < 0.001$ and 37.8 ± 20.4 vs. 52.4 ± 28.9 mL, $P < 0.001$, respectively). In addition, more women than men had smaller hearts, defined as an abnormally low LVESV according to previously published data in a healthy cohort[17] ($P < 0.001$, *Table 2*). More men than women had a reduced LVEF <55% (24.7% vs. 19.9%, $P < 0.001$, *Table 2*), while LVEF in women was more often within the normal range (≥55% to ≤65%) as compared to men (46.6% vs. 42.9%, $P = 0.012$, *Table 2*). No sex difference was observed in the prevalence of LVEF >65% (32.5% vs. 33.5%, $P = 0.5$, *Table 2*), while more women than men had a very high (>72%) LVEF (16.3% vs. 12.8%, $P = 0.001$, *Table 2*). Overall, men had more often obstructive CAD (45.2% vs. 33.0% in women, $P < 0.001$) and non-obstructive CAD (28.1% vs. 21.4% in women, $P < 0.001$) as compared to women, while more women than men were found to be free of CAD (45.6% vs. 26.6%, $P < 0.001$). Accordingly, two- and three-vessel disease was more often observed in men as compared to women ($P < 0.001$, *Table 2*). CCTA findings stratified by sex are listed in *Table 2*.

Baseline risk and extent of CAD according to LVEF strata

Table 3 shows demographic characteristics and CCTA findings of the total study population stratified by LVEF and sex. Women with high LVEF tend to be slightly older than men with high LVEF (62.2 ± 12.8 vs. 60.5 ± 12.5 years, $P = 0.008$, *Table 3*) and men with high LVEF were more often dyslipidaemic than women with high LVEF (68.0% vs. 62.1%, $P = 0.016$, *Table 3*), while no sex differences in other cardiovascular risk factors were found in patients with high LVEF (*Table 3*). Women with high LVEF had a lower prevalence of obstructive CAD than men (25.9% vs. 36.9%, $P < 0.001$) and more women than men with high LVEF had a small heart defined as an abnormally low LVESV ($P < 0.001$, *Table 3*).

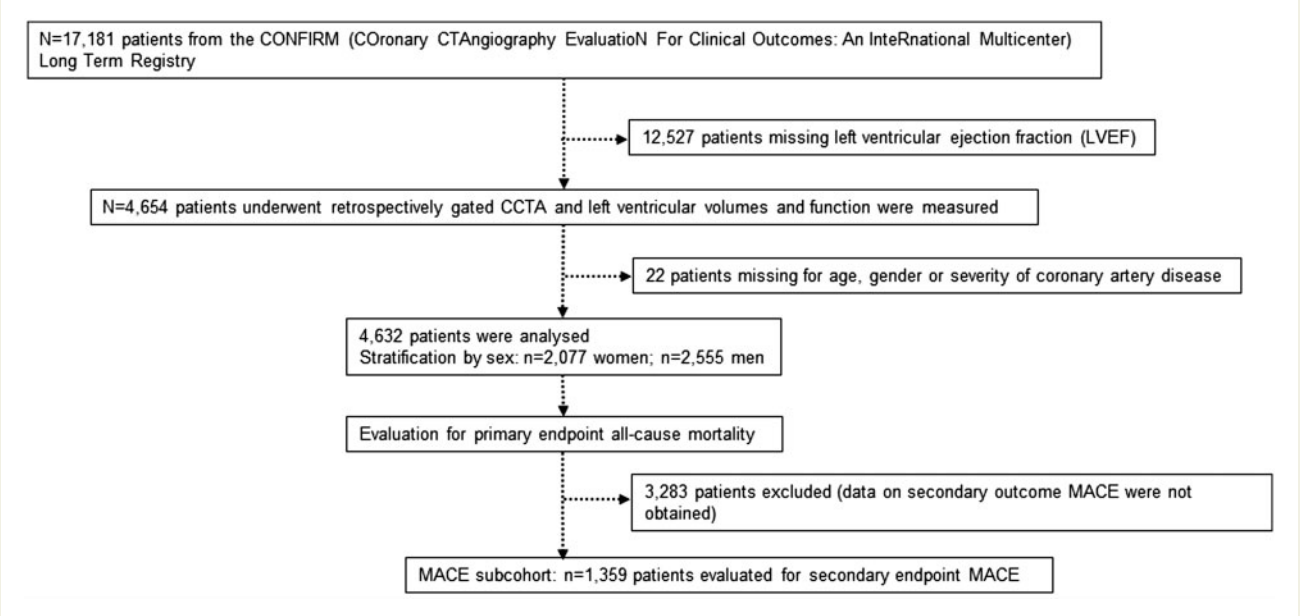

Figure 1 Stydy cohort. Flow-chart demonstrating eligible study patients selected on pre-defined criteria. The final study population comprised 4632 patients.

Table 1 Baseline characteristics of the study population stratified by sex

Baseline characteristics (total *n* = 4632)	Total (*n* = 4632)	Women (*n* = 2077)	Men (*n* = 2555)	*P*-value
Age (years), mean ± SD	59.1 ± 13.2	59.5 ± 13.3	58.7 ± 13.2	0.05
Age ≥55 years, *n* (%)	2880 (62.2)	1306 (62.9)	1574 (61.6)	0.4
BMI (kg/m^2), mean ± SD	28.0 ± 5.8	28.0 ± 6.9	27.9 ± 4.9	0.02
BSA (m^2), mean ± SD	1.9 ± 0.2	1.8 ± 0.2	2.0 ± 0.2	<0.001
Smoking, *n* (%)	897 (19.4)	376 (18.1)	521 (20.4)	0.05
Hypertension, *n* (%)	2840 (61.4)	1306 (63.0)	1534 (60.2)	0.05
Diabetes mellitus, *n* (%)	815 (17.6)	381 (18.4)	434 (17.0)	0.2
Family history of CAD, *n* (%)	1966 (42.6)	949 (45.9)	1017 (39.9)	<0.001
Dyslipidaemia, *n* (%)	2835 (61.3)	1224 (59.0)	1611 (63.2)	0.004
Symptoms, *n* (%)				<0.001
Asymptomatic	1002 (24.5)	327 (17.4)	675 (30.5)	<0.001
Non-anginal chest pain	845 (20.6)	388 (20.6)	457 (20.7)	0.9
Atypical chest pain	1411 (34.5)	741 (39.3)	670 (30.3)	<0.001
Typical chest pain	837 (20.4)	429 (22.8)	408 (18.5)	0.001
Dyspnoea	1463 (35.1)	806 (41.9)	657 (29.3)	<0.001
Prior CAD (MI/PTCA/CABG)	465 (10.0)	131 (6.3)	334 (13.1)	<0.001

BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; PTCA, percutaneous coronary intervention.

Clinical endpoints

After 6 years of follow-up, all-cause mortality was significantly higher in patients with impaired LVEF as compared to patients with normal LVEF (15.3% vs. 7.0%, $P < 0.001$), while no difference in mortality was observed in patients with high LVEF (7.1% vs. 7.0% in normal LVEF, $P = 0.41$). When data were stratified by sex, cumulative mortality over 6 years of follow-up was significantly higher in women with LVEF >65% as compared to men (8.6% vs. 5.8%, $P = 0.031$, *Figure 2A*). The increased mortality in women with high normal LVEF was particularly pronounced in patients with obstructive (≥50%) CAD (16.3% in women vs. 7.5% in men, $P = 0.003$, *Figure 2B*). In contrast, no sex differences in outcomes of patients with LVEF >65% were observed with regard to MACE ($P = 0.8$, *Figure 2C*) and late revascularization ($P = 0.1$, *Figure 2D*). When survival during 6 years of

Table 2 Cardiac CT findings of study cohort stratified by sex

Cardiac CT findings	Women (n = 2077)	Men (n = 2555)	P-value
LVEF (%), mean ± SD	61.5 ± 11.2	60.2 ± 11.8	0.01
EDV (mL), mean ± SD	113.7 ± 30.4	142.5 ± 38.3	<0.001
ESV (mL), mean ± SD	37.8 ± 20.4	52.4 ± 28.9	<0.001
EDV/BSA (mL/m^2), mean ± SD	64.9 ± 15.3	70.4 ± 18.4	<0.001
ESV/BSA (mL/m^2), mean ± SD	21.4 ± 10.7	25.9 ± 14.0	<0.001
Small heart: ESV <25 mL, n (%)	145 (22.9)	72 (7.9)	<0.001
Small heart: ESV/BSA <16 mL/m^2, n (%)	193 (31.0)	161 (18.1)	<0.001
LVEF <55%, n (%)	414 (19.9)	630 (24.7)	<0.001
LVEF ≥55 to ≤65%, n (%)	968 (46.6)	1096 (42.9)	0.01
LVEF >65%, n (%)	695 (33.5)	829 (32.5)	0.5
LVEF >70%, n (%)	429 (20.7)	438 (17.1)	0.002
LVEF >72%, n (%)	338 (16.3)	326 (12.8)	0.001
Extent and severity of CAD, n (%)			<0.001
No CAD	946 (45.6)	680 (26.6)	<0.001
Non-obstructive (<50%) CAD	445 (21.4)	719 (28.1)	<0.001
Obstructive (>50%) CAD	686 (33.0)	1156 (45.2)	<0.001
One vessel CAD	340 (16.4)	463 (18.1)	0.1
Two-vessel CAD	168 (8.1)	312 (12.2)	<0.001
Three-vessel CAD	178 (8.6)	381 (14.9)	<0.001

BSA, body surface area; CAD, coronary artery disease; EDV, end-diastolic volume; ESV, end-systolic volume; LVEF, left ventricular ejection fraction.

follow-up was compared between low, normal, and high LVEF strata, all-cause mortality rates were significantly higher in women with high LVEF as compared to women with normal LVEF (log rank $P = 0.0317$ vs. normal LVEF, *Figure 3A*), while no differences were observed in men (log rank $P = 0.9$ vs. normal LVEF, *Figure 3B*). In both, men and women, low LVEF <55% was associated with reduced survival (log rank $P < 0.001$ vs. normal LVEF, *Figure 3B* and *C*). The difference in all-cause mortality between women with high and normal LVEF was most pronounced in patients with obstructive CAD (log rank $P = 0.0297$ vs. normal LVEF, *Figure 3C* and *D*). Similar tendencies were found when patients free of obstructive CAD were analysed (*Figure 4A* and *B*), however, the difference in survival rate between women with high and normal LVEF did not reach statistical significance (log rank $P = 0.07$ vs. normal LVEF, *Figure 4A*). In contrast, in patients with non-obstructive CAD (1–49% coronary stenosis), no significant differences between high LVEF and normal LVEF strata were seen in both, women (cumulative mortality: log rank $P = 0.89$ for high vs. normal LVEF) and men (cumulative mortality: log rank $P = 0.97$ for high vs. normal LVEF). Furthermore, no differences in the occurrence of the endpoints MACE (non-fatal MI and all-cause mortality) or MACE/late revascularization or non-fatal MI (as single event) were observed in individuals with high LVEF (MACE: *Figure 4C* and *D*, MACE/late revascularization: log rank $P = 0.48$ for high normal vs. normal LVEF in women and $P = 0.61$ for high normal vs. normal LVEF in men, non-fatal MI: log rank $P = 0.15$ for high normal vs. normal LVEF in women and $P = 0.39$ for high normal vs. normal LVEF in men). When the overall higher LVEF in women was taken into account and sex-specific cut-off values for normal/abnormal LVEF were applied, similar trends and differences in outcomes were observed (*Figures 5A* and *B* and *6A–D*). Notably, in this sex-specific analysis, mortality rates in women with obstructive CAD and high LVEF were as high as mortality rates in the impaired LVEF group (*Figure 5B*).

Prognostic value of high LVEF

When the predictive value of LVEF was assessed in a multivariable Cox regression model adjusted for age, cardiovascular risk factors, and severity of CAD, high LVEF was not associated with an increased risk of 6-year mortality as a main effect variable in the overall population ($n = 4632$, *Table 4*). In contrast, a first order interaction term of male sex and high LVEF was significant (HR 0.63, 95% CI 0.41–0.98, $P = 0.043$), thereby confirming that the association of high LVEF and mortality is sex dependent. Notably, no significant interaction between the two covariates age and high LVEF was observed in both, women and men (age × LVEF > 65% in women: HR 0.99, 95% CI 0.96–1.01, $P = 0.46$ and age × LVEF > 65% in men: HR 1.00, 95% CI 0.97–1.03, $P = 0.93$) and inclusion of the interaction term did not result in a significant bias in main effect regression. This was also true when sex-specific LVEF cut-off values for LVEF were included in the interaction analysis (age × LVEF > 72% in women: $P = 0.14$ and age × LVEF > 70% in men $P = 0.661$).

Discussion

It is increasingly recognized that women manifest cardiovascular disease in ways different from men. Our study is the first to report a differential prognostic value of high LVEF in women and men. In our cohort of 4632 patients undergoing CCTA for evaluation of CAD, we observed that a high LVEF (>65%) was present in 33% of patients and was associated with an increased risk of all-cause mortality in women, but not in men. This risk increase was even more

Table 3 Demographic characteristics and cardiac CT findings stratified by LVEF

Demographic and CT parameters	LVEF <55% ($n = 1044$)			LVEF ≥55 to ≤65% ($n = 2064$)			LVEF >65% ($n = 1524$)			Comparison across LVEF strata trend *P*-value	
	Men ($n = 630$)	Women ($n = 414$)	*P*-value	Men ($n = 1096$)	Women ($n = 968$)	*P*-value	Men ($n = 829$)	Women ($n = 695$)	*P*-value	Men	Women
Age (years), mean ± SD	59.1 ± 13.8	60.4 ± 13.5	0.146	57.1 ± 13.1	57.2 ± 13.1	0.837	60.5 ± 12.5	62.2 ± 12.8	0.008	0.010	0.001
BMI (kg/m^2), mean ± SD	27.9 ± 5.1	27.7 ± 7.0	0.716	28.0 ± 4.7	28.1 ± 6.4	0.827	27.9 ± 5.0	28.1 ± 7.2	0.577	0.454	0.533
Smoking, *n* (%)	161 (25.6)	87 (21.0)	0.092	237 (21.6)	202 (20.9)	0.675	123 (14.8)	87 (12.5)	0.191	<0.001	0.0001
Hypertension, *n* (%)	420 (66.9)	270 (65.5)	0.653	598 (54.6)	576 (59.6)	0.023	516 (62.4)	460 (66.3)	0.115	0.2017	0.4341
Diabetes, *n* (%)	132 (21.0)	96 (23.3)	0.384	184 (16.8)	176 (18.2)	0.404	118 (14.3)	109 (15.7)	0.433	0.0008	0.0022
Family history of CAD, *n* (%)	239 (38.2)	201 (49.0)	0.001	461 (42.1)	467 (48.3)	0.004	317 (38.3)	281 (40.5)	0.391	0.9045	0.0020
Dyslipidaemia, *n* (%)	392 (62.4)	231 (56.1)	0.041	656 (60.0)	562 (58.1)	0.395	563 (68.0)	431 (62.1)	0.016	0.0147	0.0371
Asymptomatic, *n* (%)	147 (26.5)	68 (17.7)	0.002	256 (27.7)	121 (13.9)	<0.001	272 (37.2)	138 (21.9)	<0.001	<0.001	0.0222
Atypical chest pain, *n* (%)	157 (28.3)	133 (34.6)	0.040	297 (32.1)	345 (39.7)	0.001	216 (29.5)	263 (41.7)	<0.001	0.7586	0.0316
Typical chest pain, *n* (%)	106 (19.1)	76 (19.8)	0.802	175 (18.9)	221 (25.4)	0.001	127 (17.4)	132 (20.9)	0.094	0.3913	0.9870
Small heart: ESV <25 mL, *n* (%)	0	0		0	3 (1.7)	0.051	72 (14.7)	142 (35.6)	<0.001	<0.001	<0.001
Small heart: ESV/BSA <16 mL/m^2, *n* (%)	0	0		5 (1.7)	5 (2.9)	0.511	156 (32.6)	188 (47.7)	<0.001	<0.001	<0.001
No CAD, *n* (%)	147 (23.3)	171 (41.3)	<0.001	328 (29.9)	491 (50.7)	<0.001	205 (24.7)	284 (40.9)	<0.001	0.7642	0.3578
Non-obstructive (<50%) CAD, *n* (%)	120 (19.1)	74 (17.9)	0.634	281 (25.6)	138 (14.3)	<0.001	318 (38.4)	233 (33.5)	0.050	<0.001	<0.001
Obstructive (>50%) CAD, *n* (%)	363 (57.6)	169 (40.8)	<0.001	487 (44.4)	339 (35.0)	<0.001	306 (36.9)	178 (25.6)	<0.001	<0.001	<0.001
Prior CAD (MI/PTCA/CABG), *n* (%)	97 (15.4)	29 (7.0)	<0.001	109 (10.0)	42 (4.3)	<0.001	128 (15.4)	60 (8.6)	<0.001	0.6971	0.0951

P-values for men vs. women within each LVEF group and trend *P*-values for comparisons across LVEF strata are given.
BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass graft; CAD, coronary artery disease; CT, computed tomography; ESV, end-systolic volume; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PTCA, percutaneous coronary intervention.

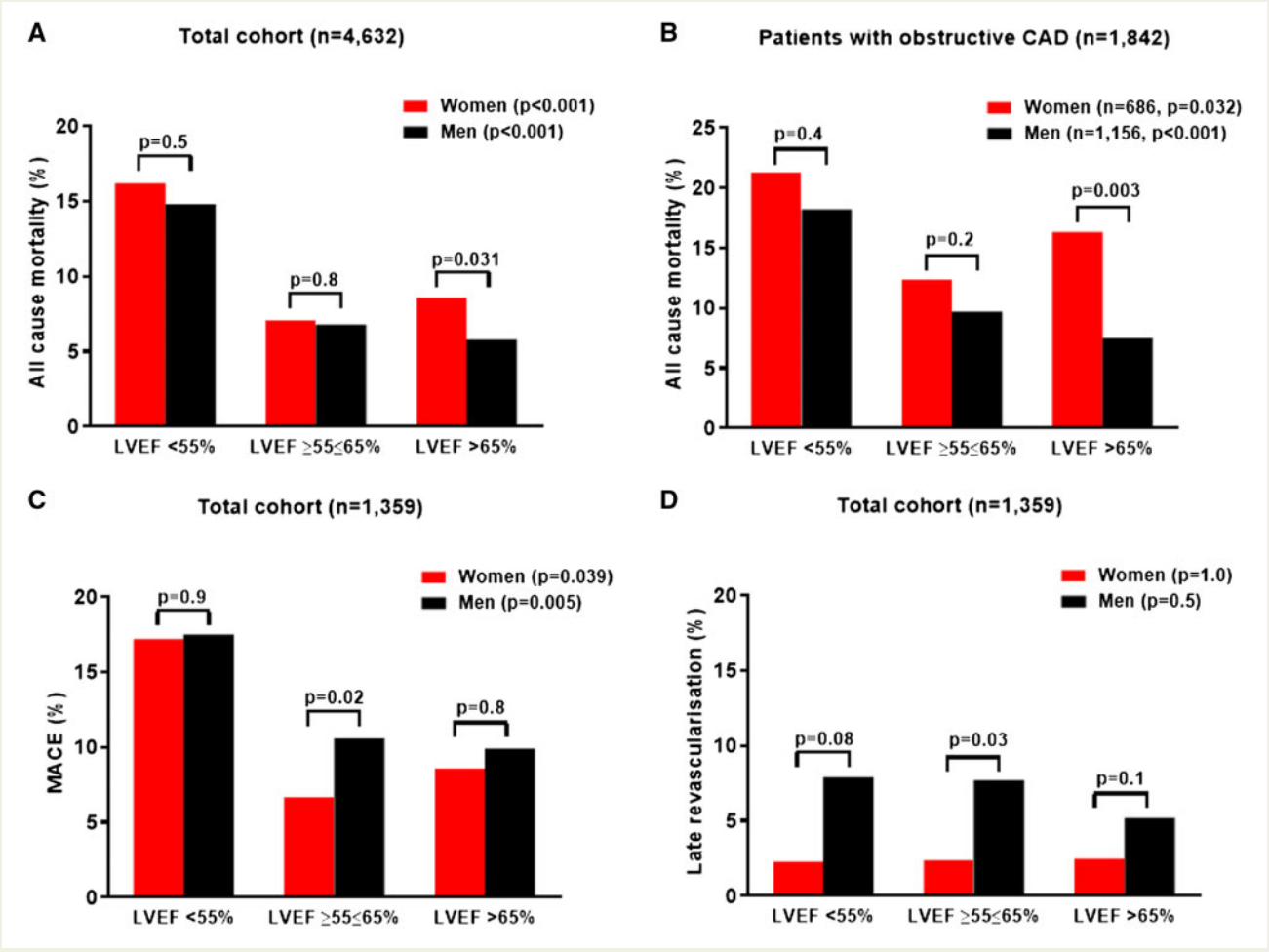

Figure 2 Cumulation clinical endpoints during 6 years of follow-up. (*A*) Six-year mortality (of any cause) rates in total study cohort. (*B*) Six-year mortality (of any cause) rates in patients with obstructive (>50%) CAD. (*C*) Six-year rate of MACE in total cohort. (*D*) Six-year rate of late revascularization in total cohort. *P*-values for men vs. women are indicated (bar graph) as well as *P*-values (ANOVA) for group comparison among different LVEF strata for each sex (right upper corner).

pronounced in women with obstructive CAD and when sex-specific cut-off values for LVEF were applied. Accordingly, a first order interaction term of female sex and high LVEF was identified as a significant predictor of mortality in a fully adjusted Cox regression model.

In accordance with published literature, we found that 6-year mortality was highest in patients with low LVEF. However, the fact that women with enhanced baseline LVEF encountered higher mortality rates than men or women with normal LVEF is a newly documented finding in patients with stable CAD. Only two previous studies have assessed the prognostic impact of high LVEF in the acute care setting. Consistent with our results, Saab *et al.*[16] reported an increase in 60-day mortality in women with LVEF >65% and acute coronary syndrome, while Paonessa *et al.*[18] observed that patients with LVEF >70% admitted to an intensive care unit experienced an increased 28-day mortality as compared to those with normal LVEF. In their study, high LVEF was associated with female sex, increased age, and the diagnoses of hypertension and cancer.[18] The mechanisms accounting for the female propensity towards worse outcomes amongst patients with enhanced LVEF are not understood.

In our study, we did not observe significant sex differences in the prevalence of cardiovascular risk factors in patients with high LVEF, except for a higher rate of dyslipidaemia in men. In addition, women in the high LVEF strata were more often symptomatic and on average 1.7 years older than men in this group, while both, women and men with high LVEF were 5 and 3.4 years older than their counterparts in the normal LVEF population. The latter is consistent with the observation of a stronger age-dependent increase in LVEF in women as compared to men.[5,6,19] However, the longer life expectancy in women, as well as the non-significant interaction of age and LVEF in our Cox regression models for all-cause mortality, suggest that increasing age is unlikely to be the major explanation of our findings.[20]

Although our observational study does not elucidate underlying mechanisms accounting for these sex differences, recent studies have

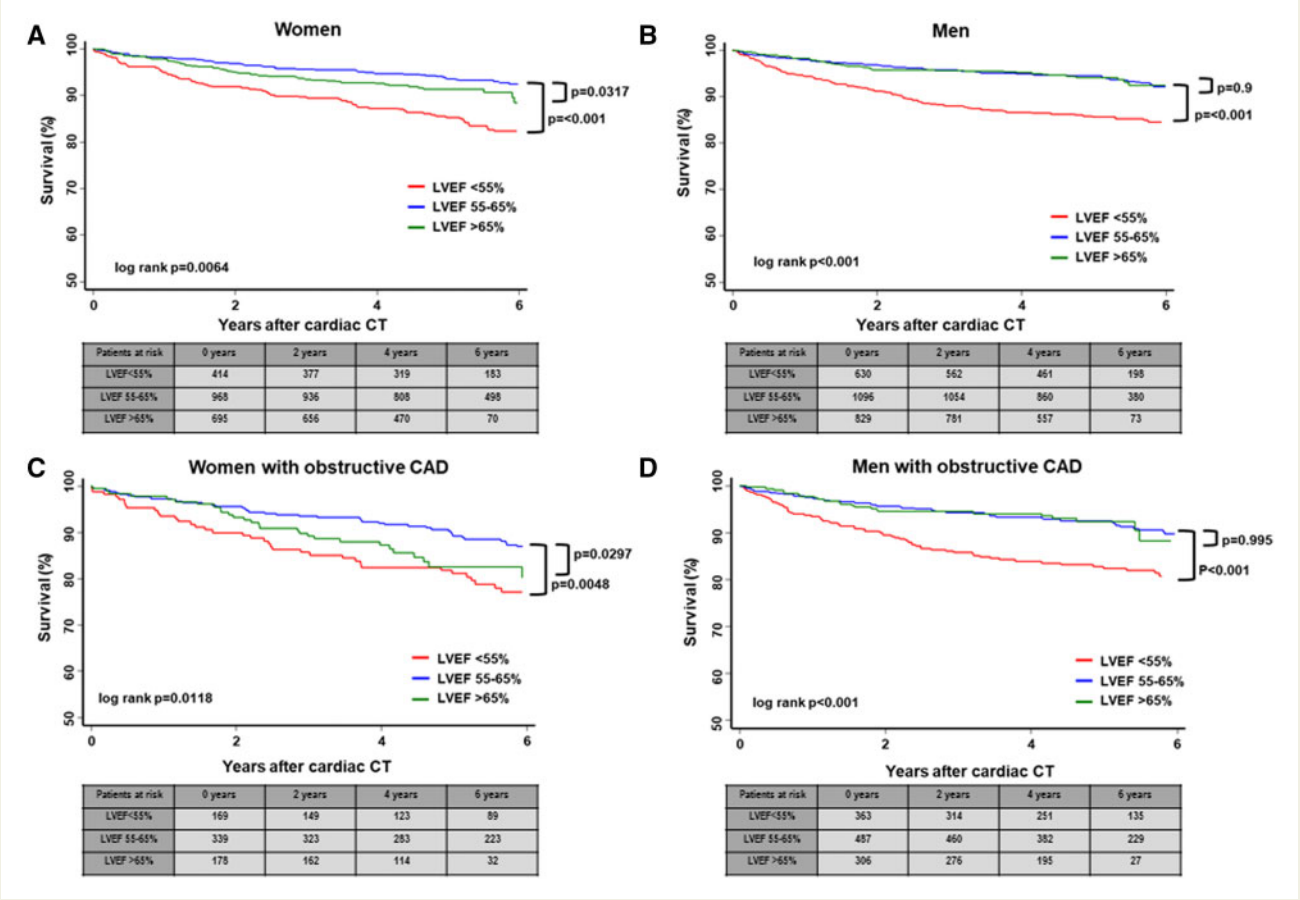

Figure 3 Survival (Kaplan–Meier curves) during 6 years of follow-up according to LVEF (low <55%, normal 55%–65%, high normal >65%) in men and women. (*A*) Survival in women ($n = 2077$). (*B*) Survival in men ($n = 2555$). (*C*) Survival in women with obstructive CAD ($n = 686$). (*D*) Survival in men with obstructive CAD ($n = 1156$). Log rank *P*-values are indicated.

suggested that myocyte hypertrophy due to an increase in aortic stiffness and enhanced afterload in older subjects may account for an age-dependent increase in LVEF.[5,21–23] Furthermore, a progressive myocyte loss in aged men, but not in women, was observed in a post-mortem analysis and may account for the sex differences in LV function.[24] Reduced testosterone levels and reduced physical activity in older men have been suggested to account for these findings.[24,25] Interestingly, in our study, the prevalence of small hearts, defined as an abnormally low LVESV was twice as high in women with high LVEF as compared to men, which confirms previous reports indicating that small hearts are more common in women.[6,19] This profound sex difference in heart size in individuals with high LVEF raises the question whether women with smaller hearts live under constant hyperdynamic conditions to compensate for the disadvantage of smaller ventricular volumes. The latter might predispose them to enhanced cardiac vulnerability in high-stress situations and might, at least in part, account for the higher mortality observed in this population. Indeed, Paonessa *et al.*[18] reported in their study that patients with LVEF >70% were more likely to suffer from cardiac arrest or ventricular fibrillation as compared to patients in the normal LVEF group. Findings consistent with this hypothesis are that women have higher baseline sympathetic activity and increased sympathetic outflow during heart failure or acute coronary syndrome as compared to men.[26–28] Furthermore, an enhanced sympathetic tone, as assessed by chronotropic responses during vasodilator stress, has been observed in patients with myocardial ischaemia, which, in turn, was associated with an increased risk of cardiac death.[29–32] Although myocardial ischaemic burden was not assessed in our CCTA study, an enhanced sympathetic response in women with high normal LVEF and ongoing ischaemia might account for the increased mortality observed in women with high LVEF and obstructive CAD in our study. Of note, however, myocardial ischaemia might also be present in individuals without significant epicardial CAD (Ischaemia and No Obstructive Coronary Artery disease, INOCA), a condition that is more common in women and referred to as coronary microvascular dysfunction.[33] Interestingly, LV hypercontractility and cardiac sympathetic hyperactivity have been observed in patients with coronary microvascular dysfunction in one previous study.[34] Given the proven benefits of sympathoinhibition on metabolic and cardiovascular functions in many disease states, the possibility of an augmented sympathetic drive to the heart and vascular bed in women with high LVEF warrants further investigation.[35–37] In addition, future studies will

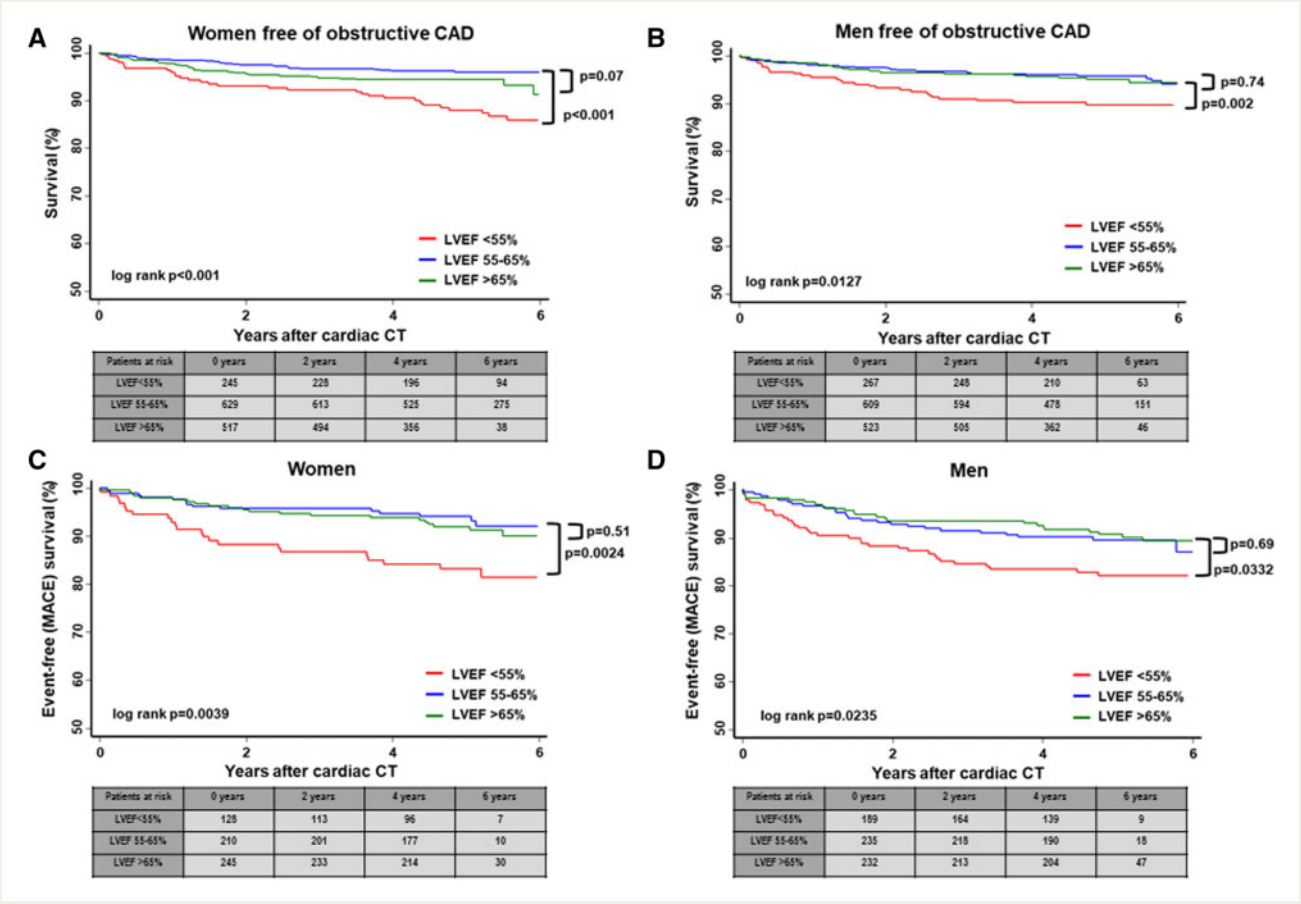

Figure 4 Event-free survival (Kaplan–Meier curves) during 6 years of follow-up according to LVEF (low <55%, normal 55%–65%, high normal >65%) in men and women. (*A*) Survival in women free of obstructive CAD ($n = 1391$). (*B*) Survival in men free of obstructive CAD ($n = 1399$). (*C*) Event-free survival from MACE (all-cause mortality and non-fatal MI) in women. (*D*) Event-free survival MACE in men. Log rank *P*-values are indicated.

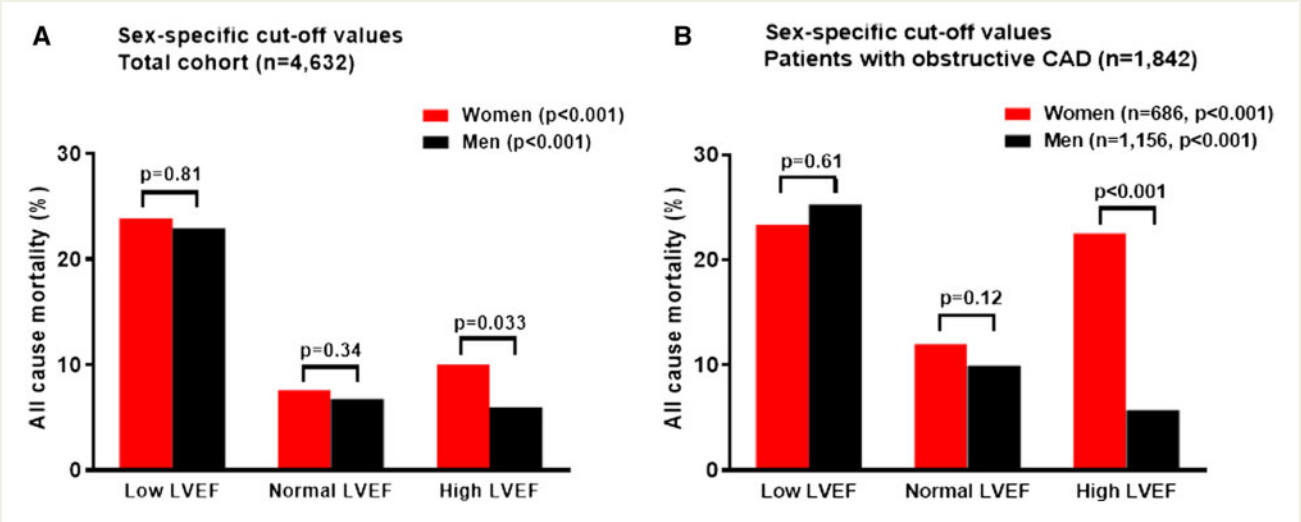

Figure 5 Sex-specific upper and lower limits of normal LVEF. All-cause mortality during 6 years of follow-up. Women: low LVEF <50%, normal LVEF ≥50% to ≤72%, high LVEF >72%. Men: low LVEF <47%, normal LVEF ≥47% to ≤70%, high LVEF >70%. (*A*) Six-year mortality (of any cause) rates in total study cohort. (*B*) Six-year mortality (of any cause) rates in patients with obstructive (>50%) CAD. *P*-values for men vs. women are indicated (bar graph) as well as *P*-values (ANOVA) for group comparison among different LVEF strata for each sex (right upper corner).

have to explore whether the combination of INOCA and a high LVEF might result in a survival detriment in patients affected by this condition.

Interestingly, increasing evidence suggests that coronary microvascular dysfunction shares common pathophysiological pathways with the development and progression of heart failure with preserved ejection fraction,[38–42] a disease that is characterized by impaired LV relaxation, elevated LV filling pressures, and a hypertrophied, non-dilated LV.[43] Post-menopausal women are more prone to develop the disease.[43] Similarly, diastolic filling abnormalities are a common finding in elderly women and are associated with increased mortality.[44] Although we found no sex difference in the prevalence of hypertension in patients with high LVEF, we cannot exclude an influence of loading conditions, LV mass, or afterload on our study endpoints as these parameters were not quantified in our cohort. In fact, as elderly women with hypertrophic hearts might be particularly susceptible to oxygen supply-mediated ischaemia and worse outcomes,[45] a higher prevalence of LV hypertrophy in elderly women might have accounted for the particularly pronounced survival detriment observed in women with high LVEF and obstructive CAD in our study. Of note, however, an increasing body of evidence supports the notion that ESV is commonly increased in these patients, thus, yielding a lower—and not a high—LVEF.[46–49] A recent cardiovascular magnetic resonance study even described a significantly reduced myocardial contraction in LV hypertrophy, independent of aetiology.[50] Interestingly, a primary increase in cardiac output has only been seen in patients with borderline hypertension, and an

Table 4 Cox regression analysis for all-cause mortality adjusted by age, cardiovascular risk factors, and severity of coronary artery disease

Risk estimates for all-cause mortality Total population ($n = 4632$)			
Predictor	**HR**	**95% CI**	***P*-value**
LVEF >65%	1.02	0.75–1.39	0.89
Male sex	1.05	0.84–1.32	0.645
Interaction term: male sex × LVEF >65%	0.63	0.41–0.98	0.043

LVEF, left ventricular ejection fraction.

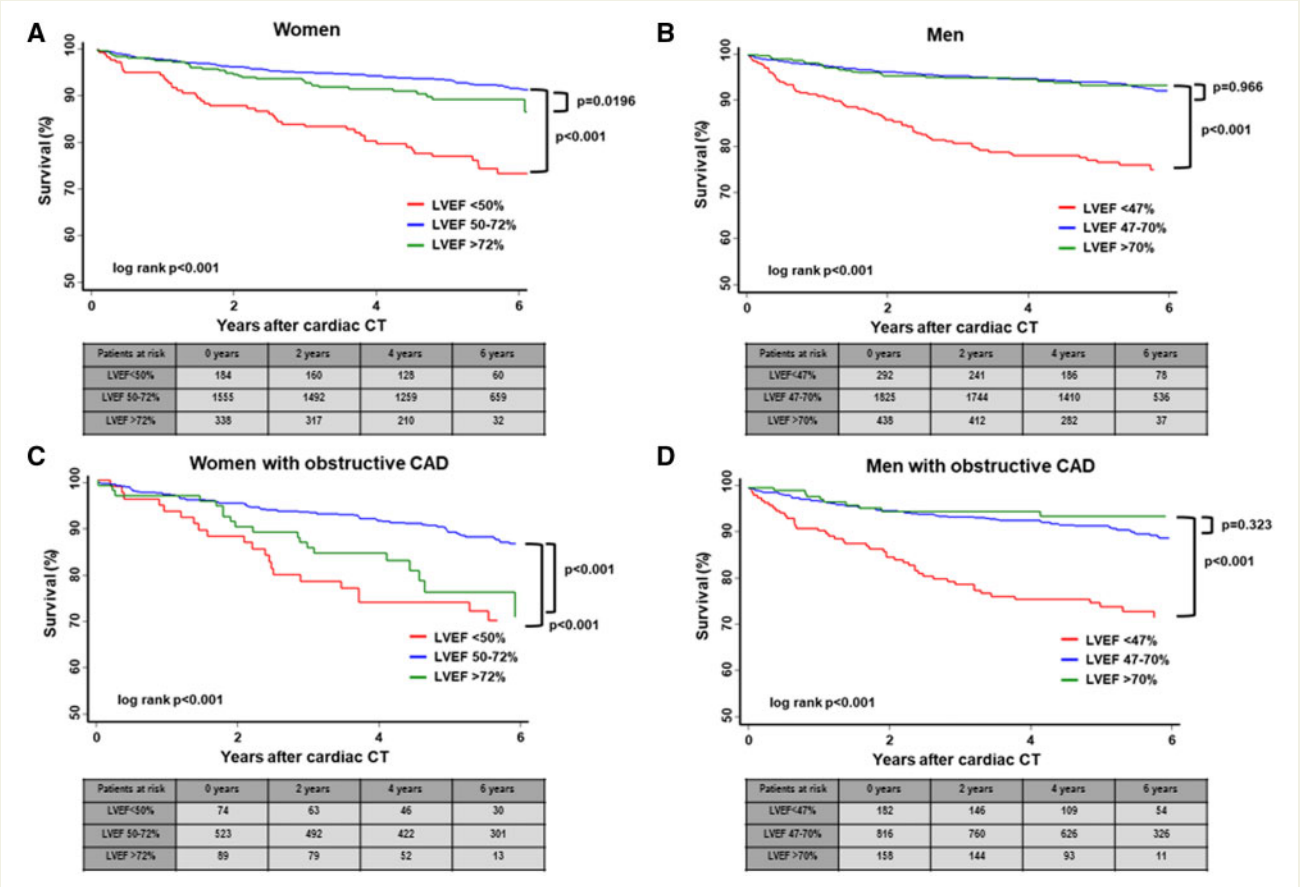

Figure 6 Sex-specific upper and lower limits of normal LVEF. Survival (Kaplan–Meier curves) during 6 years of follow-up according to LVEF. Men: low LVEF <50%, normal LVEF ≥50% to ≤72%, high LVEF >72%. Women: low LVEF <47%, normal LVEF ≥47% to ≤70%, high LVEF >70%. (*A*) Survival in women ($n = 2077$). (*B*) Survival in men ($n = 2555$). (*C*) Survival in women with obstructive CAD ($n = 686$). (*D*) Survival in men with obstructive CAD ($n = 1156$). Log rank *P*-values are indicated.

augmented sympathetic outflow has been suggested to account for the elevation of both cardiac output and vascular resistance in these patients.[51,52] Similar to apparent hypertension, borderline hypertension has been associated with an elevated risk of death.[53]

There are limitations to this study that should be pointed out. First, our study is observational. We report the frequency of high LVEF and its association with adverse long-term outcomes in patients referred for evaluation for CAD. Our study does not provide information on the underling mechanism. Second, our study has the inherent limitations of an open-label registry, including intersite variability in image acquisition and analysis, inclusion of a relatively heterogeneous group of patients, and residual confounding. In fact, we cannot completely rule out the potential impact of variables not accounted for in our regression model (e.g. comorbidities such as cancer or infectious disease or the presence of myocardial ischaemia) on our study endpoints. Third, as currently no definition of a 'small heart' exists, cut-off values for abnormally low ESVs were taken from a healthy female reference population.[17] Accordingly, discrepancies exist regarding comorbidities and morphometric characteristics between this reference population and our cohort resulting in a higher prevalence of 'small hearts' in our study when indexed cut-off values for low ESV were applied as compared to non-indexed ESV. Finally, LVEF is pre- and afterload dependent and is not an intrinsic measure of contractility. As measures of contractility and afterload (e.g. blood pressure, pulse wave velocity) were not available in our CT registry, it remains unknown whether the higher LVEF in women vs. men is due to differences in contractile state or loading conditions. However, LVEF is widely used in clinical decision-making, thus, we believe that the observed sex differences demonstrated in our study have clinical relevance irrespective of their underlying cause.

In summary, in this large international multicentre cohort, we observed a significant increase in long-term mortality in women with high LVEF; this survival detriment was particularly pronounced in a subgroup of women with obstructive CAD. Our findings indicate that a high LVEF might exert detrimental effects in women. Our study emphasizes the need for sex-specific criteria in clinical decision-making and suggests that an upper cut-off value for normal LVEF may provide additional prognostic information in women with CAD. Given the high prevalence of high LVEF in patients referred for evaluation of CAD, further research is warranted to decipher the pathophysiologic process(es) related to the survival detriment in women with increased LVEF and to determine the role of the sympathetic nervous system in the development and clinical course of an increased LVEF.

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