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Sex-specific relationships between patterns of ventricular remodelling and clinical outcomes

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Aims Left ventricular hypertrophy (LVH) is the most common form of myocardial remodelling and predicts adverse outcomes in patients with coronary artery disease (CAD). However, sex-specific prevalence and prognostic significance of LVH patterns are poorly understood. We investigated the sex-specific influence of LVH pattern on clinical outcomes in patients undergoing cardiovascular magnetic resonance (CMR) and coronary angiography following adjustment for co-morbidities including CAD burden.

Methods and results Patients undergoing CMR and coronary angiography between 2005 and 2013 were included. Volumetric measurements of left ventricular (LV) mass with classification of concentric vs. eccentric remodelling patterns were determined from CMR cine images. Multivariable Cox analysis was performed to assess independent associations with the primary outcome of all-cause mortality. In total, 3754 patients were studied (mean age 59.3 ± 13.1 years), including 1039 (27.7%) women. Women were more likely to have concentric remodelling (8.1% vs. 2.1%, $P < 0.001$), less likely to have eccentric hypertrophy (15.1% vs. 26.8%, $P < 0.001$) and had a similar prevalence of concentric hypertrophy (6.1 vs. 5.2%, $P = 0.296$) compared to men. At a median follow-up of 3.7 years, 315 (8.4%) patients died. Following adjustment including CAD burden, concentric hypertrophy was associated with increased all-cause mortality in women [adjusted hazard ratio (HR) 3.48, $P < 0.001$] and men (adjusted HR 2.57, $P < 0.001$). Eccentric hypertrophy was associated with all-cause mortality only in women (adjusted HR 1.78, $P = 0.047$).

Conclusion Patterns of LV remodelling differ by sex and LVH and provides prognostic information in both men and women. Our findings support the presence of sex-specific factors influencing LV remodelling.

Keywords Coronary disease • Magnetic resonance imaging • Left ventricular geometry • Left ventricular hypertrophy

Introduction

Left ventricular (LV) mass and pre-defined definitions of left ventricular hypertrophy (LVH) are well-recognized markers of cardiovascular risk in patients with known or suspected coronary artery disease (CAD).[1] In the Framingham heart study, left ventricular mass index (LVMI), indexed for height, was independently associated with cardiovascular events and all-cause mortality.[2] Objectively defined thresholds of LVH based on LVMI were also independently associated with sudden cardiac death following adjustment for relevant co-morbidities,[3] a finding that has been confirmed among patients with stable CAD.[4] The presence of LVH determined by cardiovascular magnetic resonance (CMR) imaging, which provides reproducible

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and precise measures of LV mass and LVH pattern,[5] has also been demonstrated to increase risk for all-cause mortality.[6]

Beyond LVMI, phenotypic patterns of LVH have been reported to yield incremental prognostic information. Velagaleti *et al.*[7] illustrated that eccentric hypertrophy was associated with incident heart failure with reduced ejection fraction while concentric hypertrophy was associated with incident heart failure with preserved ejection fraction. Conversely, an analysis from the Multi-ethnic Study of Atherosclerosis cohort found that LVMI had a stronger association with clinical outcomes than did the pattern of LVH.[8] However, a key factor that may influence the prognostic value of LVH pattern and LVMI is sex. In a large echocardiography-based study of hypertensive patients, women were more likely than men to develop LVH.[9] Petrov *et al.*[10] observed a higher prevalence of concentric remodelling and hypertrophy in women as well as greater prognostic relevance of eccentric hypertrophy.

Overall, existing studies suggest a need to clarify sex-related differences in both LVH extent and pattern. To accomplish this, we studied a large cohort of patients undergoing both CMR imaging and diagnostic coronary angiography to assess sex-related differences in patterns of LVH and their prognostic significance, adjusting for important co-morbidities including extent of CAD at baseline.

Materials and methods

Study population

The patient population was identified from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) registry, a prospective registry of patients undergoing diagnostic coronary angiography. Database and data collection methods have been described previously.[11] Additional details regarding the patient population, data elements, and assessment of CAD severity are available in the Supplementary data online.

CMR imaging and analysis

Details of image acquisition and quantification are available in the Supplementary data online. Categories of LVH were defined using previously published CMR reference values which are referenced for gender and age.[12] LV mass patterns were classified as normal, concentric remodelling, eccentric hypertrophy, or concentric hypertrophy using a two-tiered classification system.[13] Concentric remodelling was defined as a normal LVMI with an increase in concentricity [LVM/left ventricular end-diastolic volume (LVEDV) ratio]; eccentric LVH as increased LVMI without an increase in concentricity; and concentric LVH as an increase in both values. Increased concentricity was defined as >95th percentile for concentricity (>0.95 g/mL for women and >1.15 g/mL for men).[14,15] All measurements were performed at the time of clinical image reporting. Examples of the LVH patterns are shown in Supplementary data online, *Figure S1*. Since there are multiple reference values used in the literature, we repeated our analysis using reference values from Maceira *et al.* and identified no significant differences in LVH classification.[16]

We also assessed the four-tiered system for LV geometry classification proposed by Khouri *et al.*[17] and validated using data from the Dallas Heart Study. In this analysis, similarly performed by CMR, the aim was to sub-classify LVH on the basis of concurrent chamber dilation, concentric thickening, or both. In this classification system, LVH was defined as LV mass/height$^{2.7}$> 39 g/m2.7 in women and >48 g/m2.7 in men.[18] Increased LV dilation was defined as LVEDV/Body surface area ≥68 mL/m^2 in women and ≥74 mL/m^2 in men.[17,18] We used the same calculation for concentricity$^{0.67}$ (LV mass/LVEDV0.67) with increased concentricity$^{0.67}$ defined ≥8.1 g/mL$^{0.67}$ in women and ≥9.1 g/mL$^{0.67}$ in men. Using these definitions, four classes of hypertrophy are established: 'thick hypertrophy' in patients with increased concentricity$^{0.67}$ without dilation, 'dilated hypertrophy' in patients with increased dilation without increased concentricity$^{0.67}$, 'thick and dilated hypertrophy' in patients with increased dilation and concentricity$^{0.67}$, and 'indeterminate hypertrophy' in patients with neither increased dilation nor increased concentricity$^{0.67}$.[17]

Clinical outcomes

The primary outcome was all-cause mortality, determined by linkage with Alberta Vital Statistics.[11] The secondary outcome was a combination of all-cause mortality or symptom-driven late percutaneous or surgical coronary revascularization, ascertained from APPROACH. Early revascularization, defined as within 30 days of coronary angiography, was excluded to minimize influence of revascularization related to baseline angiographic findings or procedural complications.

Statistical analysis

Baseline features of men versus women in the study population were compared. Categorical variables were summarized as number (proportion) and compared with a χ^2 or Fisher exact test. Continuous variables were summarized as mean [standard deviation (SD)] and compared with a Student's *t*-test if normally distributed, and otherwise summarized as median [interquartile range (IQR)] and compared with a Wilcoxon rank sum test.

Associations between LVMI categories and the primary and secondary outcomes were performed using univariable and multivariable Cox-proportional hazards models, adjusting for variables from *Tables 1* and *2*. This included baseline clinical characteristics, co-morbidities, presence of LGE, and severity of angiographic CAD as determined by the Duke Jeopardy score. We used a stepwise backwards elimination method to refine the multivariable models, excluding variables with non-significant association until only variables significantly associated with the outcome remained ($P < 0.05$).[19] We assessed for interactions between LV remodelling patterns and all other variables in the final models. There was a significant interaction between sex and eccentric hypertrophy for association with death or late revascularization $P = 0.029$. Therefore, the primary and secondary analyses were stratified by sex. The proportional hazards assumption was assessed using Schoenfeld residuals and found to be valid in all analyses. Collinearity was assessed using covariance matrix estimates, with no substantial collinearity identified in the final models.

The additive prognostic utility with the addition of LVH pattern to the multivariable model was assessed using the continuous net reclassification index (NRI) for 1-year outcomes and models with and without LVH pattern were compared using the likelihood-ratio test. Model calibration was assessed with the Hosmer–Lemeshow goodness of fit test using deciles of risk and all models were found to be well calibrated ($P > 0.05$).

Sensitivity analyses

Given the presence of significant differences between male and female patients, propensity-matching analysis was performed. We used 1:1 nearest neighbour matching to identify a matched group of men with similar age, LVEF, Duke Jeopardy score, and indication for CMR as women included in the study. The prevalence of LVH pattern was compared in the matched cohort. Additionally, multivariable Cox analysis of association with the primary and secondary outcome were performed in the matched

Table 1 Baseline clinical and cardiovascular magnetic resonance (CMR) patient characteristics

	Women ($n = 1039$)	Men ($n = 2715$)	*P*-value
Clinical characteristics			
Age, mean ± SD	60.0 ± 13.1	59.0 ± 13.1	0.031
BMI, median (IQR)	26.5 (22.8–31.2)	27.6 (24.5–31.1)	<0.001
Past medical history, *n* (%)			
Hypertension	562 (55.9)	1572 (59.3)	0.071
Diabetes mellitus	214 (20.6)	704 (25.9)	0.001
Hyperlipidaemia	667 (64.2)	1911 (70.4)	0.001
Current smoker	187 (18.0)	638 (23.5)	<0.001
CAD	181(17.4)	789 (29.1)	<0.001
CHF	200 (19.3)	594 (21.9)	0.082
PVD	69 (6.9)	294 (11.2)	<0.001
CVD	110 (11.1)	308 (11.8)	0.641
CKD[a]	46 (4.4)	184 (6.8)	0.008
Malignancy	91 (8.8)	278 (10.2)	0.178
Coronary angiography			
Systolic BP (mmHg), median (IQR)	119 (104–135)	114 (100–129)	<0.001
Diastolic BP (mmHg), median (IQR)	68 (60–75)	70 (62–78)	<0.001
Heart rate, median (IQR)	71 (63–82)	71 (61–83)	0.682
Angiographic CAD (≥70%), *n* (%)	368 (36.5)	1609 (60.0)	<0.001
Duke jeopardy, median (IQR)	0 (0–2)	0 (0–6)	<0.001
Medications			
Statin, *n* (%)	669 (64.4)	1844 (67.9)	0.044
ACE-inhibitor or ARB, *n* (%)	572 (58.5)	1506 (58.1)	0.849
Beta-blocker, *n* (%)	670 (67.4)	1769 (67.3)	1.000
Calcium-channel blocker, *n* (%)	145 (14.7)	365 (14.0)	0.592
No. of anti-hypertensives, median (IQR)	1 (1–2)	1 (1–2)	0.817

Angiographic CAD defined as any lesion ≥50% visually.
[a]Chronic kidney disease defined as an eGFR <45 mL/min/1.76 m^2.
BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cerebrovascular disease; IQR, interquartile range; PVD, peripheral vascular disease.

population. Additionally, the primary analysis was repeated in patients in whom gadolinium was administered.

All analyses were performed using Stata version 13 (StataCorp, College Station, TX, USA). This study complies with the Declaration of Helsinki and was approved by the institutional review board at the University of Calgary. Data will be made available upon receipt of written request.

Results

Baseline clinical characteristics

Baseline characteristics of the study population are shown in *Table 1*. The mean age of the cohort was 59.3 ± 13.1 years (IQR 51.0–68.9 years) with 1039 (27.7%) women included. Women demonstrated a higher median BMI (27.6 vs. 26.5 kg/m^2, $P < 0.001$) and were less likely to have diabetes (20.6% vs. 25.9%, $P = 0.001$) or prior CAD (17.4% vs. 29.1%, $P < 0.001$). However, the prevalence of obesity was similar in women and men (31.6% vs. 31.7%, $P = 0.969$). Diagnostic angiography and CMR imaging were performed with a median interval of 19 days (IQR 3–93). The prevalence of any coronary stenosis ≥70% was lower in women (35.5 vs. 60.0%, $P < 0.001$) and the 75th percentile of the Duke Jeopardy score was also lower (2 vs. 6, $P < 0.001$).

Early revascularization (within 30 days of coronary angiography) occurred in 854 (22.8%) patients. During this period, women were less likely to undergo revascularization (13.0% vs. 26.5%, $P < 0.001$), including those women with angiographic CAD [130/368 (35.3%) vs. 710/1609 (44.1%), $P = 0.002$].

CMR-based imaging findings

CMR imaging characteristics are shown in *Table 2*. Abnormal LGE was present in 38.0% of women compared to 48.1% of men ($P < 0.001$). Median LVMI was also significantly lower in women than men when indexed by body surface area (54.5 vs. 69.1 g/m^2, $P < 0.001$) and by height (62.0 vs. 81.0 g/m^2, $P < 0.001$).

Overall, 28.9% of patients demonstrated LV myocardial mass that was above pre-defined limits of normal (21.2% of women and 32.0% of men). However, women were more likely to have LVH using the criteria established by Khouri *et al.* (21.2% vs. 14.6%, $P < 0.001$). Women were more likely to have concentric remodelling (8.1% vs. 2.1%, $P < 0.001$) and less likely to have eccentric hypertrophy (15.1% vs. 26.8%, $P < 0.001$). Comparisons of LVH pattern using the four-

Table 2 Population imaging characteristics

	Women ($n = 1039$)	Men ($n = 2715$)	*P*-value
CMR indication, *n* (%)			
Ischaemic CM	137 (13.2)	598 (22.0)	<0.001
Non-ischaemic CM	207 (19.9)	464 (17.1)	0.046
Undifferentiated CM	234 (22.5)	697 (25.7)	0.047
Stress perfusion	57 (5.5)	121 (4.5)	0.198
Myocarditis	232 (22.3)	395 (14.6)	<0.001
Other	172 (16.6)	440 (16.2)	0.805
CMR characteristics			
LVMI, median (IQR)	54.5 (45.6–67.9)	69.1 (57.7–84.4)	<0.001
Cardiac index, median (IQR)	2.6 (2.2–3)	2.6 (2.1–3)	0.997
LVEDVI, median (IQR)	84 (68–109)	106 (86–139)	<0.001
LVESVI, median (IQR)	34 (24–55)	47 (32–78)	<0.001
LVEF, median (IQR)	54 (38–63)	46 (31–57)	<0.001
Low LVEF, *n* (%)	266 (25.6)	1016 (37.4)	<0.001
Any visual fibrosis by LGE, *n* (%)	395 (38.0)	1306 (48.1)	<0.001
LV geometry (two-tier), *n* (%)			
Normal	735 (70.7)	1790 (65.9)	0.005
Concentric remodelling	84 (8.1)	57 (2.1)	<0.001
Eccentric hypertrophy	157 (15.1)	727 (26.8)	<0.001
Concentric hypertrophy	63 (6.1)	141 (5.2)	0.296
LV geometry (four-tier), *n* (%)			
Normal	819 (78.8)	2318 (85.4)	<0.001
Thick hypertrophy	47 (4.5)	81 (3.0)	0.026
Dilated hypertrophy	124 (11.9)	199 (7.3)	<0.001
Thick and dilated hypertrophy	37 (3.6)	110 (4.1)	0.512
Indeterminate hypertrophy	7 (0.3)	12 (1.2)	0.001

Angiographic CAD defined as any lesion ≥50% visually.
CM, cardiomyopathy; IQR, interquartile range; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LGE, late gadolinium enhancement; LVMI, left ventricular mass indexed to body surface area.

tiered classification are shown in *Table 2*. In patients undergoing contrast examinations, women were more likely to have no LGE (54.5% vs. 35.9%, $P < 0.001$) and less likely to have sub-endocardial (13.7% vs. 24.8%, $P < 0.001$) or transmural LGE patterns (12.5% vs. 18.6%, $P < 0.001$).

Primary outcome: all-cause mortality

The median follow-up was 3.7 years (IQR 1.7–6.0 years). During follow-up a total of 315 (8.4%) patients died with similar cumulative mortality observed in women and men (7.3% vs. 8.8%, $P = 0.148$). The Kaplan–Meier survival curves for all-cause mortality stratified by LVH pattern using the two-tiered classification are shown in Supplementary data online, *Figure S2* and for the four-tiered classification in Supplementary data online, *Figure S3*.

Unadjusted associations with the primary and secondary outcomes are shown in Supplementary data online, *Table S1*. In unadjusted analyses, women demonstrated strong associations between LVH pattern and all-cause mortality for both eccentric hypertrophy [unadjusted hazard ratio (HR) 2.61, $P = 0.001$] and concentric hypertrophy (unadjusted HR 3.89, $P < 0.001$) patterns, with a non-significant increase observed for concentric remodelling (unadjusted HR 2.19, 95% CI 0.98–4.89; $P = 0.056$). Similar results were observed in men.

Multivariable analyses for all-cause mortality in all patients (men and women combined) are shown in Supplementary data online, *Table S2*.

Multivariable analyses of the association with all-cause mortality stratified by sex are shown in *Table 3*, and corresponding associations with the two-tier LVH pattern are visualized in *Figure 1*. Eccentric hypertrophy was independently associated with increased all-cause mortality in women (adjusted HR 1.78, 95% CI 1.01–3.15; $P = 0.047$) with a similar trend in men (adjusted HR 1.20, 95% CI 0.89–1.61; $P = 0.239$; interaction *P*-value 0.103). Concentric hypertrophy was associated with increased all-cause mortality in both women (adjusted HR 3.48, 95% CI 1.73–6.99; $P < 0.001$) and men (adjusted HR 2.57, 95% CI 1.61–4.13; $P < 0.001$; interaction *P*-value 0.261). LVMI as a continuous variable was not significantly associated with all-cause mortality in women (adjusted HR 1.06 per 10 g/m^2, $P = 0.427$) or men (adjusted HR 0.94 per 10 g/m^2, $P = 0.191$). Using the four-tier classification, dilated hypertrophy (adjusted HR 2.53, $P = 0.001$) and indeterminate hypertrophy (adjusted HR 5.38, $P = 0.005$) were associated with all-cause mortality in women but not

Table 3 Multivariable analyses of association between LV geometry and all-cause mortality

	Women N = 1039, 76 (7.3%) deathsMedian follow-up 3.7 years		MenN = 2715, 239 (8.8%) deathsMedian follow-up 3.6 years	
Variables	Adjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
LV geometry (two-tier) normal as reference				
Concentric remodelling	1.65 (0.73–3.70)	0.228	1.28 (0.40–4.06)	0.677
Eccentric hypertrophy	1.78 (1.01–3.15)	0.047	1.20 (0.89–1.61)	0.239
Concentric hypertrophy	3.48 (1.73–6.99)	<0.001	2.57 (1.61–4.13)	<0.001
Age (per 10 years)	1.44 (1.17–1.76)	0.001	1.88 (1.66–2.13)	<0.001
Diabetes	2.07 (1.28–3.37)	0.003	1.41 (1.08–1.85)	0.006
Duke Jeopardy score	1.10 (1.04–1.17)	0.001	1.05 (1.02–1.08)	0.002
BMI	–	–	0.97 (0.95–0.99)	0.006
Low LVEF	–	–	2.15 (1.63–2.85)	<0.001
LV geometry (four-tier) normal as reference[a]				
Thick hypertrophy	2.16 (0.77–6.06)	0.142	0.90 (0.36–2.22)	0.819
Dilated hypertrophy	2.53 (1.48–4.32)	0.001	1.21 (0.77–1.89)	0.410
Thick and dilated hypertrophy	[b]	[b]	0.73 (0.30–1.80)	0.494
Indeterminate hypertrophy	5.38 (1.66–17.5)	0.005	3.11 (0.73–13.2)	0.125

–indicates that the variable was not included in the final model due to lack of statistical significance.
HR, hazard ratio; LV, left ventricular; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction.
[a]The two-tier and four-tier classification were assessed in separate models.
[b]Unable to obtain HR estimates due to small number of events.

men (adjusted HR 1.21, $P = 0.410$ and adjusted HR 3.11, $P = 0.125$, respectively). There was no interaction between the presence of LVH and sex (interaction $P = 0.077$). There was no interaction between age and LVH pattern when modelled as a categorical variable (age > 60) or a continuous variable ($P > 0.05$ for all patterns). Results were similar in the full multivariable model (Supplementary data online, *Table S3*) in the subgroup of patients administered gadolinium contrast (Supplementary data online, *Table S4*).

The continuous NRI was 0.484 ($P = 0.002$) in women and 0.379 ($P = 0.027$) in men when added to the remaining variables in the multivariable analysis, suggesting that inclusion of the two-tier LVH classification significant improved prediction for both men and women. Conversely, the addition of LVMI did not significantly improve performance when added to the remaining clinical variables in the multivariable models (continuous NRI in women 0.331, $P = 0.052$; in men 0.030, $P = 0.199$) Use of the four-tier classification did not improve risk prediction in women (NRI 0.281, $P = 0.092$) or men (NRI 0.051, $P = 0.630$).

Secondary outcome: all-cause mortality or late revascularization

During follow-up, 168 patients (4.5%) experienced late revascularization (occurring beyond 30 days; 54 by percutaneous coronary intervention and 114 by coronary artery bypass grafting). Women experienced similar rates of late revascularization compared to men (3.7% vs. 4.8%, $P = 0.158$), but they were less likely to experience the secondary composite outcome of all-cause mortality or late revascularization (10.4% vs. 13.1%, $P = 0.023$). The Kaplan–Meier survival curves for all-cause mortality or late revascularization stratified by LVH pattern using the two-tiered classification are shown in Supplementary data online, *Figure S4* and for the four-tiered classification in Supplementary data online, *Figure S5*.

Results of multivariable analyses for the secondary composite outcome of all-cause mortality or revascularization are shown in Supplementary data online, *Table S5* and associations with LVH pattern are shown in *Figure 2*. There was a significant interaction between sex and eccentric hypertrophy (interaction *P*-value 0.029) and well as sex and dilated hypertrophy (interaction *P*-value 0.049). There was no interaction between the presence of LVH and sex (interaction $P = 0.264$). In women, eccentric hypertrophy (adjusted HR 2.05, 95% CI 1.28–3.27; $P = 0.003$) was independently associated with the composite outcome but not in men (adjusted HR 1.21, 95% CI 0.94–2.22; $P = 0.132$). LVMI was not associated with the composite outcome in women (adjusted HR 1.09 per 10 g/m^2, $P = 0.190$) or men (adjusted HR 1.00, $P = 0.994$). There was no interaction between age and LVH pattern when modelled as a categorical variable (age > 60) or a continuous variable ($P > 0.05$ for all LVH patterns).

Prediction of 1-year survival free of revascularization was improved with the addition of the two-tier LVH classification in women (NRI 0.407, $P = 0.007$), but not in men (NRI 0.247, $P = 0.178$) when added to the remaining variables in the multivariable analysis. Use of the four-tier classification did not improve risk prediction in women (NRI 0.292, $P = 0.142$) or men (NRI 0.032, $P = 0.710$).

Propensity-matched cohort

In the matched cohort of men and women with similar age, left ventricular ejection fraction (LVEF), Duke Jeopardy score, and indication for CMR, concentric remodelling remained more common in women than men (8.1% vs. 3.3%, $P < 0.001$), while eccentric hypertrophy was less common in women than men (15.1% vs. 19.9%, $P = 0.005$).

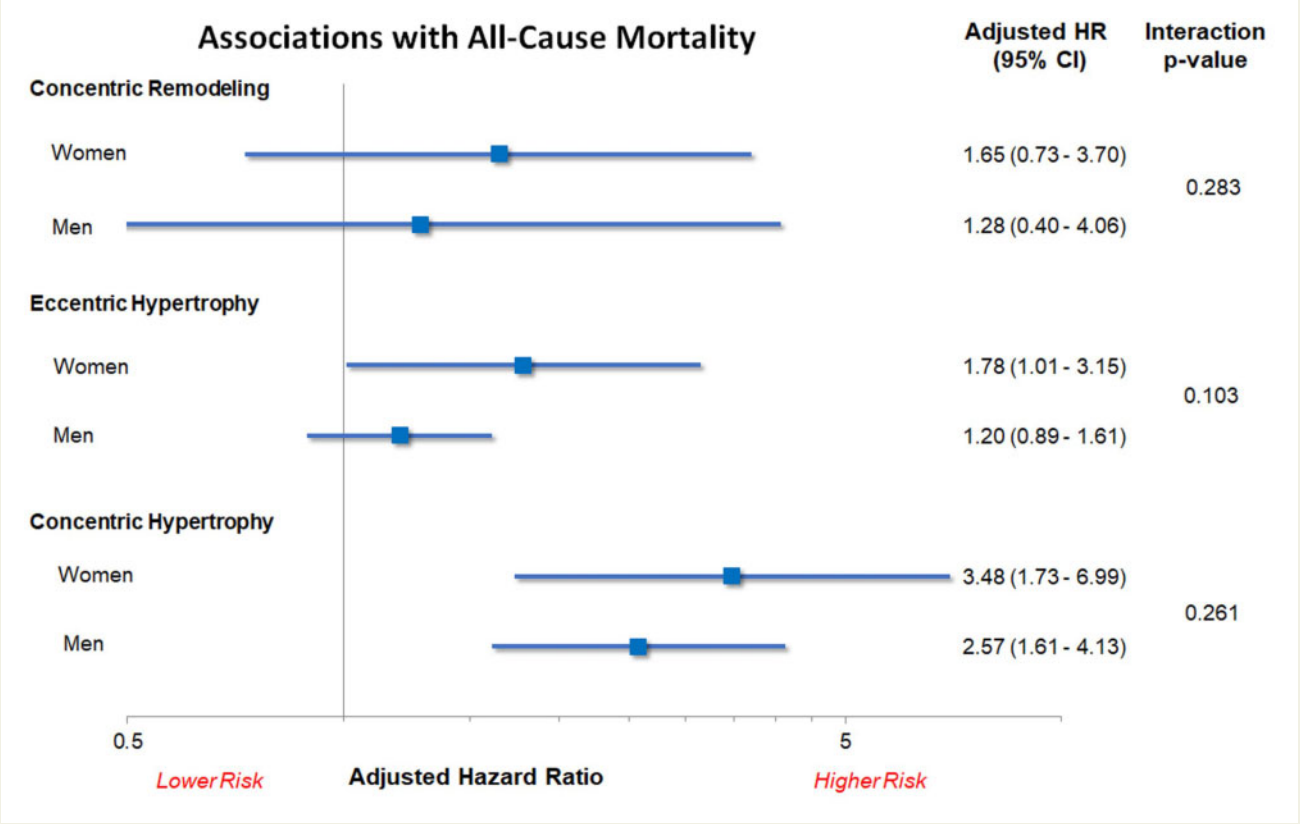

Figure 1 Associations between LVH pattern and all-cause mortality. Eccentric hypertrophy was associated with increased all-cause mortality in women (adjusted HR 1.78, $P = 0.047$), but not men (adjusted HR 1.20, $P = 0.239$). CI, confidence interval; HR, hazard ratio.

Details of the matched group are shown in Supplementary data online, *Table S6*. Adjusted associations with all-cause mortality and all-cause mortality or late revascularization are outlined in Supplementary data online, *Table S7*.

Discussion

In this large, retrospective study of patients with known or suspected CAD we identified that women had a lower prevalence of eccentric hypertrophy, higher prevalence of concentric remodelling, and similar prevalence of concentric hypertrophy compared to men. Following adjustment for underlying CAD burden and other relevant confounders, concentric hypertrophy was associated with the greatest risk of both all-cause mortality and death or revascularization in men and women. Additionally, pattern of LVH had greater prognostic utility compared to LVMI alone. Overall, our findings support the presence of sex-specific factors influencing patterns of LV remodelling and that LVH pattern is associated future cardiovascular outcomes in both men and women with known or suspected CAD.

Our findings support the conclusion that the myocardial remodelling response to disease may be unique in women vs. men. We found that women were more likely to show elevation in myocardial mass relative to LV end-diastolic volume (i.e. concentric remodelling) and less likely to develop balanced elevations in LV mass and LV end-diastolic volume (i.e. eccentric hypertrophy). This observed predisposition for concentric remodelling has been described previously among women with aortic valve disease.[10,20] Treibel *et al.*[20] also demonstrated that eccentric hypertrophy was more prevalent in men with aortic stenosis. Differential patterns of remodelling have also been observed following myocardial infarction (MI), with women being more likely to develop eccentric or concentric patterns of hypertrophy.[21] Collectively, these findings provide compelling evidence that sex-dependent influences exist in myocardial remodelling pathways. Further studies are required to elucidate the pathophysiologic mechanisms.

Importantly, our study examined the incremental prognostic relevance of LVH patterns separately in women and men. Among patients referred for known or suspected CAD, the identification of any LVH pattern, using in the two-tier classification (eccentric hypertrophy or concentric hypertrophy), in women was associated with greater impact on outcomes than that observed in men. Dilated hypertrophy, using the four-tier classification, was also associated with increased risk in women. However, it should be noted that formal interaction testing was only significant with respect to the combined outcome of death or revascularization. Our findings may suggest that the cut-offs for hypertrophy and concentricity in women should be different. However, the results reflect the performance of commonly utilized criteria. Importantly, we identified sex-specific differences with respect to both the prevalence and prognostic significance of LVH pattern using both classification systems.

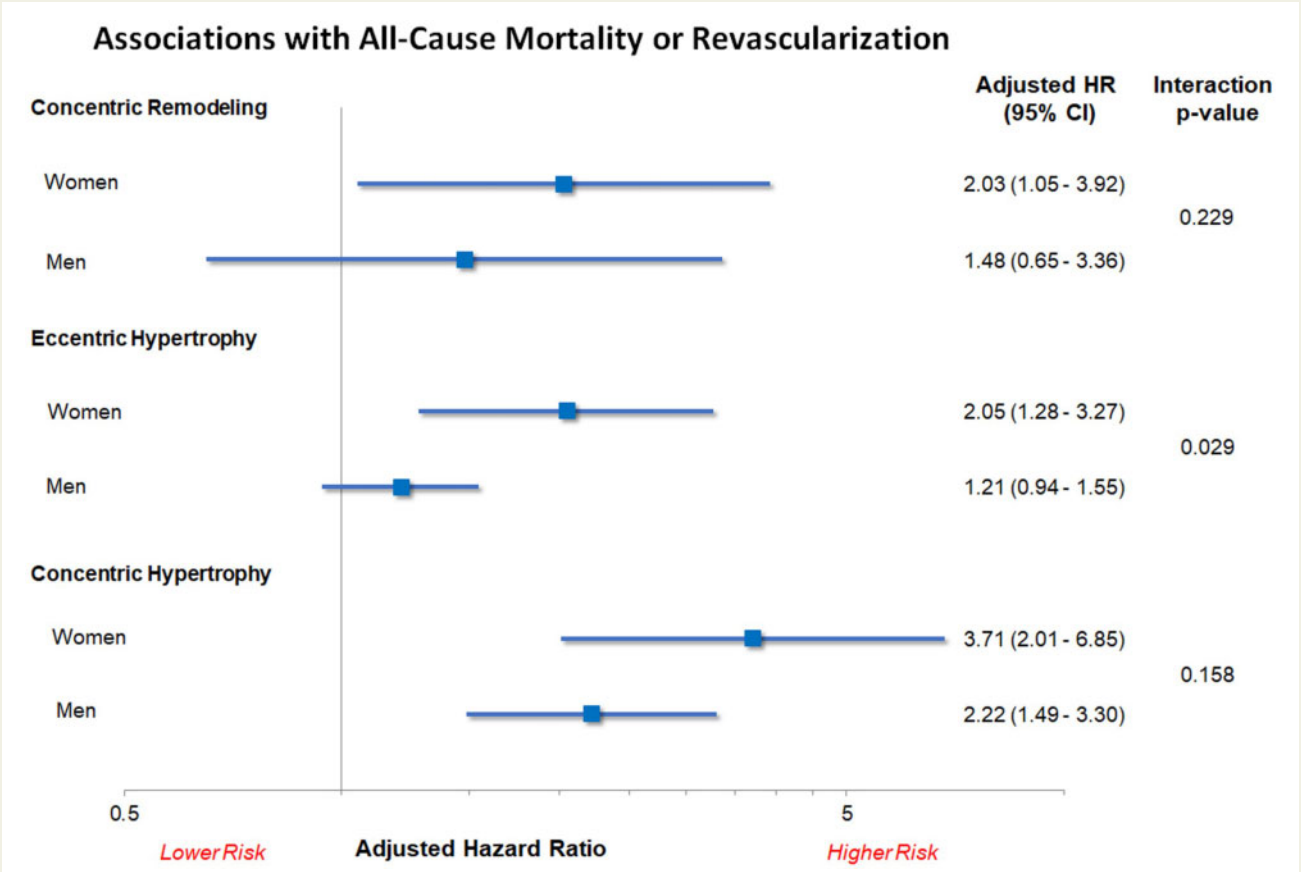

Figure 2 Associations between LVH pattern and all-cause mortality or late revascularization. Eccentric hypertrophy was associated with increased all-cause mortality or late revascularization in women (adjusted HR 2.05), but not men (adjusted HR 1.21). CI, confidence interval; HR, hazard ratio.

Few studies have not assessed for sex-specific differences in the influence of LVH on clinical outcomes. Petrov *et al.*[10] reported that concentric hypertrophy was associated with increased all-cause mortality in women, but not men undergoing aortic valve replacement for severe aortic stenosis. Other studies have provided compelling data linking LVH to adverse clinical outcomes in mixed-sex cohorts. From the same referral population, our group identified that moderate to severe LVH was associated with a 1.7-fold increase in the risk of death in patients with known or suspected CAD.[6] Verma *et al.*[21] also demonstrated that concentric hypertrophy was associated with an increase in death and non-fatal cardiovascular events in patients following acute MI, independent of LVMI. Finally, in patients with hypertension, the presence of dilation in patients with LVH (i.e. progression to eccentric hypertrophy) is associated with an increase in major adverse cardiovascular events.[22]

Pathophysiologic studies of sex-based differences in relevant referral populations are limited. However, women have been shown to experience less myocyte loss or cellular hypertrophy with age compared to men.[23] Women are also less likely to experience myocyte apoptosis in response to ischaemia.[24] Further, women with aortic stenosis develop greater LVMI and relative wall thickness compared to men with similar aortic valve gradients.[25] Overall, these differences suggest altered compensatory pathways in women which predispose to concentric remodelling instead of eccentric hypertrophy in response to myocardial stress.[25] Whether such differences exist due to known paracrine influences of circulating oestrogen on the myocardium or sex-related differences in gene expression remain unknown.[26]

Study limitations

Our study has several important limitations. First, the requirement of patients to have undergone CMR imaging introduces an inherent referral bias to this cohort. Additionally, we studied only those patients also undergoing coronary angiography which adds to the referral bias. However, this was intentional to allow adjustment for extent of underlying CAD, a major confounder of the future need for revascularization. We observed that women were more likely to have been referred to CMR for the evaluation of non-ischaemic cardiomyopathy compared to men, thus explaining the lower prevalence of CAD in the female population. Second, we employed a provincial vital statistics database to identify death, which did not allow us to identify cause of death. Third, as a large, retrospective cohort study we did not employ core laboratory-based quantification of LV mass or volumes. Rather we used measurements performed in clinical practice, representing a conservative, 'real world' estimate of the value provided by LVH pattern description. The CMR Centre maintained

standard operating procedures for all contouring throughout the course of patient enrolment. Additionally, tissue characterization, with myocardial T1 or T2 values, was not routinely performed during the study period but may have important interactions with LVH pattern and associations with cardiovascular outcomes.[27] While our results demonstrate the importance of LVH pattern defined using CMR, it is not clear if these findings can be extrapolated to LVH patterns defined with other modalities such as echocardiography. Finally, due to the registry-based methodology of this study we are unable to determine the duration or severity of hypertension, which may be an important driver of LVH-related outcomes.

Conclusions

In patients with known or suspected CAD, patterns of LVH differ in women compared to men. Following adjustment for relevant confounders, inclusive of age, LVEF, extent of CAD, and LVMI, the presence of concentric hypertrophy in both women and men was associated with the highest risk of death. Overall, our findings support the presence of sex-specific factors influencing patterns of LV remodelling and that LVH pattern is associated with future cardiovascular outcomes in both men and women with known or suspected CAD.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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