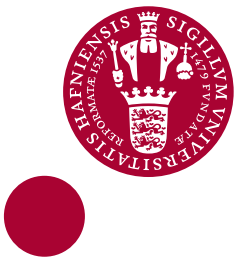

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Left Ventricular Hypertrophy Is Associated With Increased Infarct Size and Decreased Myocardial Salvage in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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***Background*—**Approximately one third of patients with ST-segment elevation myocardial infarction (STEMI) have left ventricular hypertrophy (LVH), which is associated with impaired outcome. However, the causal association between LVH and outcome in STEMI is unknown. We evaluated the association between LVH and: myocardial infarct size, area at risk, myocardial salvage, microvascular obstruction, left ventricular (LV) function (all determined by cardiac magnetic resonance [CMR]), and all-cause mortality and readmission for heart failure in STEMI patients treated with primary percutaneous coronary intervention.

***Methods and Results*—**In this substudy of the DANAMI-3 trial, 764 patients underwent CMR. LVH was defined by CMR and considered present if LV mass exceeded 77 (men) and 67 g/m^2 (women). One hundred seventy-eight patients (24%) had LVH. LVH was associated with a larger final infarct size (15% [interquartile range {IQR}, 10–21] vs 9% [IQR, 3–17]; P<0.001) and smaller final myocardial salvage index (0.6 [IQR, 0.5–0.7] vs 0.7 [IQR, 0.5–0.9]; P<0.001). The LVH group had a higher incidence of microvascular obstruction (66% vs 45%; P<0.001) and lower final LV ejection fraction (LVEF; 53% [IQR, 47–60] vs 61% [IQR, 55–65]; P<0.001). In a Cox regression analysis, LVH was associated with a higher risk of all-cause mortality and readmission for heart failure (hazard ratio 2.59 [95% CI, 1.38–4.90], P=0.003). The results remained statistically significant in multivariable models.

***Conclusions*—**LVH is independently associated with larger infarct size, less myocardial salvage, higher incidence of microvascular obstruction, lower LVEF, and a higher risk of all-cause mortality and incidence of heart failure in STEMI patients treated with primary percutaneous coronary intervention.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01435408. **(*J Am Heart Assoc*. 2017;6: e004823. DOI: 10.1161/JAHA.116.004823.)**

Key Words: cardiac magnetic resonance imaging • left ventricular hypertrophy • myocardial infarction • primary percutaneous coronary intervention • ST-segment elevation myocardial infarction

Several studies have shown that increased left ventricular (LV) mass, known as LV hypertrophy (LVH), is an independent predictor of cardiovascular events and death.[1–3]

LVH increases the risk of myocardial infarction (MI) and it is prognostic post-MI.[4,5] Despite the presence of LVH in approximately one third of patients with MI,[6] the causal association between LVH and impaired outcome in patients with ST-segment elevation myocardial infarction (STEMI) remains unknown. Experimental studies have demonstrated that animals with LVH have less myocardial salvage and larger

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Accompanying Tables S1 and S2 and Figure S1 are available at http://jaha.ahajournals.org/content/6/1/e004823/DC1/embed/inline-supplementary-material-1.pdf

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infarct size following ischemia-reperfusion.[7–10] However, the impact of LVH on myocardial infarct size has only sparsely been studied in STEMI patients,[11] and data regarding the relationship between LVH and microvascular obstruction (MVO), area at risk or myocardial salvage are to the best of our knowledge non-existent.

LVH is defined as increased LV mass indexed by body surface area (BSA)[12] and is divided into eccentric and concentric hypertrophy.[13] The utility of this subclassification has previously been demonstrated by significant differences in outcomes between patients with eccentric and concentric LVH.[1,5,6] However, there are no data regarding the relationship between these subgroups and the extent of post-MI myocardial damage.

Cardiovascular magnetic resonance (CMR) provides an accurate method for in vivo assessment of infarct size,[14,15] area at risk,[16–19] myocardial salvage index,[20,21] MVO,[22] LV mass, and LV ejection fraction (LVEF).[23]

Thus, in the present study we evaluated the association between LVH and myocardial infarct size, area at risk, myocardial salvage, MVO, and LV function in STEMI patients. Moreover, we investigated the association between LVH and all-cause mortality and hospitalization for heart failure.

Methods

Study Population

The present study is a substudy of the DANAMI-3 trial (www.clinicaltrials.gov; identifier: NCT01435408) that has been previously described.[24] In brief, DANAMI-3 comprises 3 randomized, multicenter trials evaluating ischemic postconditioning (DANAMI3-iPOST), deferred stenting (DANAMI3-DEFER), and complete fractional flow reserve guided revascularization (DANAMI3-PRIMULTI) in STEMI patients. Only patients included at 1 center, Rigshospitalet, Copenhagen University Hospital, were considered for inclusion in the CMR substudy. Patients were eligible if they were aged ≥18 years and had acute onset of chest pain of <12 hours' duration and ST-segment elevation ≥0.1 mV in ≥2 contiguous leads, or documented newly developed left bundle branch block. Patients were excluded from the CMR substudy if they had contraindications for CMR, such as claustrophobia, severely reduced kidney function, metal implants, arrhythmia, previous infarction in the current infarct-related artery, or were clinically unstable. The clinical endpoint of all-cause mortality and hospitalization for heart failure was chosen a priori.[25] All-cause mortality and hospitalization for heart failure were identified from the National Danish Heart Registry and validated using hospital records; all events were validated by an independent events committee.

The study protocol was approved by a central ethics committee in Copenhagen, and the trial program was undertaken in accord with the Declaration of Helsinki. Ethical approval was received, according to local regulations, and data were gathered electronically and stored at the Clinical Trial Unit of Rigshospitalet. All patients provided written informed consent.

CMR and Image Analysis

All patients without contraindications for CMR were offered an initial scan during the index admission (median of 1 day [interquartile range {IQR}, 1–1] following primary percutaneous coronary intervention [primary PCI]) to assess mass, area at risk, acute infarct size, cardiac function, and MVO. A second scan was performed 3 months later (median of 91 days [IQR, 88–96]) to assess final infarct size and cardiac function. CMR was performed using a 1.5 Tesla scanner (Avanto [admission] and Espree [follow-up] scanner; Siemens, Erlangen, Germany) using a 6-channel body array coil.

Scout images and electrocardiographic (ECG) gated breath-hold steady-state free-precession images in 2-, 4-, and 3-chamber views were performed to set up short-axis plane imaging. Area at risk was assessed as edema on the initial scan using a T_2-weighted short tau inversion-recovery sequence.[21,26] LV volume, function, and mass were measured on both CMR examinations using a standard ECG-triggered balanced steady-state free-precession cine sequence. Acute and final infarct sizes were evaluated on the initial and second CMR examination, respectively, using delayed contrast-enhancement CMR.[21] Infarct images were obtained 10 minutes after intravenous injection of 0.1 mmol/kg body weight of gadolinium-based contrast (Gadovist; Bayer Schering, Berlin, Germany) using an ECG-triggered inversion-recovery sequence. The inversion time was adjusted to null the signal from the normal myocardium. All short-axis images were obtained from the atrioventricular plane to the apex with 8-mm-thick slices and no interslice gap to cover the entire LV.

All images were analyzed by an independent observer blinded to all clinical data, using CVI[42] (Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). All analyses were reviewed and finalized by a second observer. The epicardial and endocardial contours were manually traced on all images, incorporating the papillary muscles as part of the LV cavity. LV volumes, LVEF, and mass were calculated on the short-axis cine images. End-diastole and end-systole were identified as the largest and smallest volume, respectively, according to blood pool area. Area at risk was defined as the hyperintense area on T_2-weighted images. A myocardial area was reported as hyperintense when the signal intensity was >2 SDs of the mean signal intensity of normal reference myocardium. Using CVI[42] (Circle Cardiovascular Imaging Inc.), an area of at least

10 pixels in the remote normal myocardium was used as a reference value for the normal signal intensity. This area was visually identified in each short-axis slice. All areas with signal intensity >2 SDs of the normal value were automatically measured. Hyperintensive areas scattered throughout the remote myocardium were manually excluded from the area at risk, just as hypointensive areas within the area at risk were manually included as part of the area at risk. The area at risk was expressed in percentages of LV. The infarction was defined as the hyperenhanced myocardium on the delayed gadolinium-enhanced short-axis images. A myocardial area was regarded as hyperenhanced when the signal intensity was >5 SDs of the mean intensity of normal reference myocardium.[27] Using CVI[42] (Circle Cardiovascular Imaging Inc.), an area of at least 10 pixels in the remote normal myocardium was used as a reference value for the normal signal intensity. This area was visually identified in each short-axis slice. All areas with signal intensity >5 SDs of the normal value were automatically measured. Hyperenhanced areas scattered throughout the remote myocardium were manually excluded from the infarct size, just as nonculprit infarct areas were excluded. The infarct size was expressed in grams and percentage of LV mass. Hypointense core areas in the enhanced myocardium were defined as MVO and manually included in the total infarct size. MVO was manually measured in each short-axis image slice. The salvage index was calculated as (area at risk−infarct size)/area at risk.[20]

Interobserver reproducibility was assessed in 20 randomly chosen patients and expressed as mean difference±limits of agreement: 0.2±6 g for acute LV mass; 0.5±4% for acute LVEF; 0.1±2% LV for acute infarct size; and 1±2% LV for area at risk.

Left Ventricular Hypertrophy

Previous studies have reported different values for the upper limit of normal LV mass.[13,28,29] To address these differences, CMR data on LV mass and concentricity were obtained from 44 healthy subjects (22 men and 22 women). None of the healthy subjects had hypertension, diabetes mellitus, or known previous heart diseases, and there was no statistically significant difference in age between the healthy subjects and the patients in the substudy group (60±9 vs 59±11 years; P=0.596). End-diastolic LV mass on the acute CMR was indexed by BSA and LVH was defined as LV mass exceeding the upper 95th percentile among healthy subjects. BSA was calculated using the Du Bois formula.[29] In order to stratify patients with LVH into eccentric and concentric LVH, data from the healthy subjects were used to calculate sex-specific values for LV concentricity$^{0.67}$ (mass/LV end-diastolic volume$^{0.67}$).[13] Increased concentricity was defined as concentricity$^{0.67}$ exceeding the upper 95th percentile. The presence of LVH and increased concentricity was classified as concentric LVH. The presence of LVH in absence of increased concentricity was classified as eccentric LVH. To minimize the risk of the CMR readers being aware of the presence or absence of LVH they were blinded to BSA. Additionally, the images from the 44 healty subjects were analyzed after CMR data from the study population were obtained.

Statistical Analysis

Normality of continuous variables was evaluated by histograms. Student t test was performed if the data were considered normally distributed, and the Mann–Whitney U test was used otherwise. Categorical variables were compared with the chi-square test or Fisher's exact test. Regression analyses were performed to compare the relationship between area at risk and infarct size, and ANCOVAs were used to test equality of the regression lines for the hypertrophic and the normotrophic groups. The effect of LVH was adjusted for potential confounders in multivariable linear and logistic regression analyses using any baseline variable with $P\leq0.20$ for the difference between the groups. Interaction between LVH and any baseline variable used in the multivariable models were evaluated in an ANCOVA. The assumptions for general linear models were checked and deemed valid. The Kaplan–Meier method was used for visual assessment of time-to-event endpoints. Hazard ratios (HRs) were calculated using Cox regression analyses. The effect of LVH was adjusted for potential confounders in a multivariable Cox regression analysis using any baseline variable with $P\leq0.20$ for the difference between the groups. The assumptions of the proportional hazard were checked and deemed valid. A 2-sided probability value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (version 23.0; SPSS, Inc., Chicago, IL).

Results

Left Ventricular Hypertrophy

Based on the 44 healthy subjects, LVH was considered present if LV mass exceeded 77 g/m^2 for men and 67 g/m^2 for woman. The values for concentricity were ≥5 (men) and ≥4 g/mL$^{0.67}$ (women).

Study Population

A flow chart of patient inclusion is shown in Figure 1. A total of 178 patients (24%) had LVH and 579 (76%) had normotrophic left ventricles. Baseline demographics as well as angiographic and procedural characteristics of all patients, stratified by the presence of LVH, are depicted in Table 1.

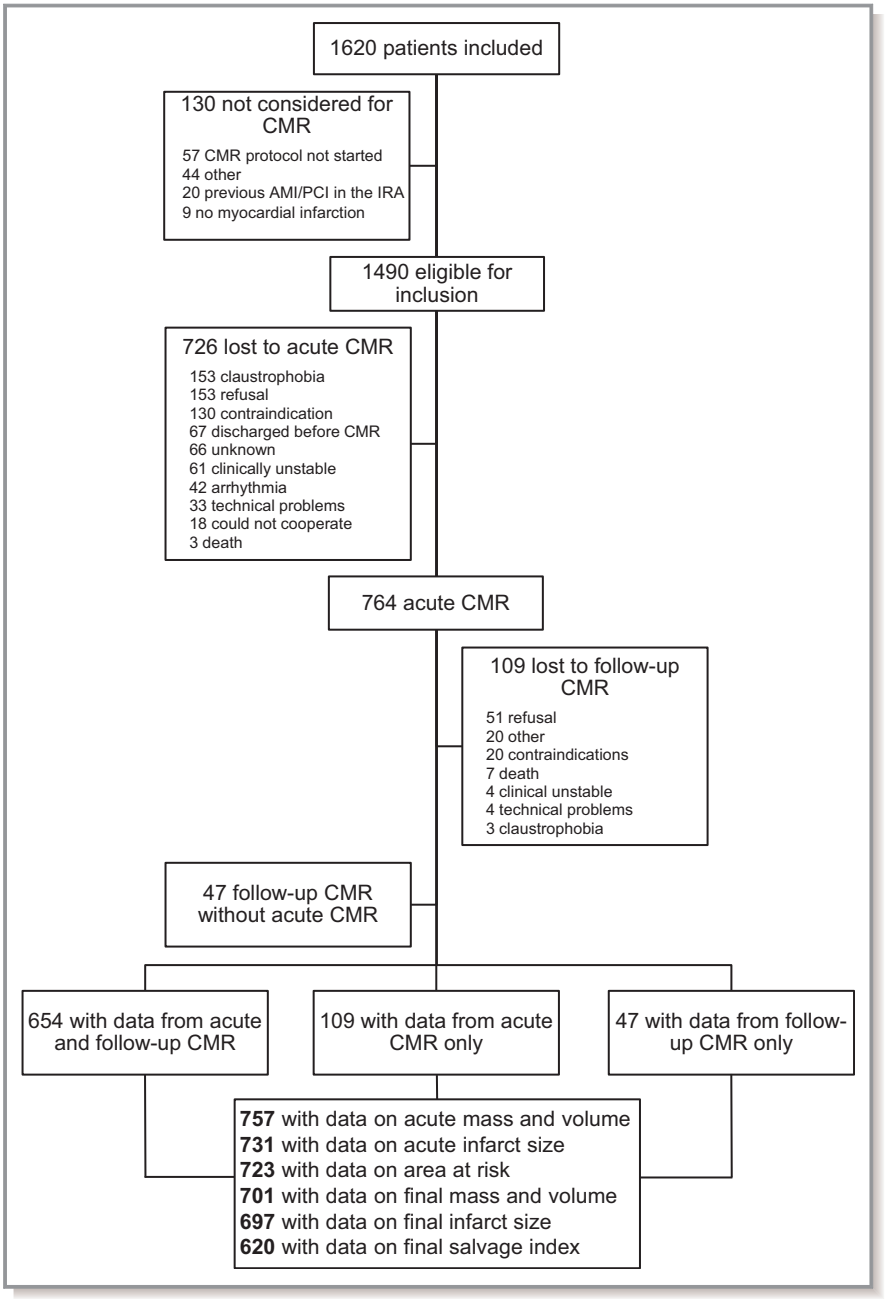

Figure 1. Flow chart of patient inclusion. AMI indicates acute myocardial infarction; CMR, cardiac magnetic resonance; IRA, infarct related artery PCI, percutaneous coronary intervention.

Patients with LVH were more likely to be men, have a higher body mass index (BMI), higher blood pressures at admission, higher levels of peak troponins, pre-PCI thrombolysis in myocardial infarction (TIMI) flow 0/1, ECG-verified anterior infarct location, and thus also a higher incidence of infarcts located to the left anterior descending artery (Table 1). Additionally, there was a trend towards a higher incidence of previous MI and longer delays from symptom onset to wire in patients with LVH. All patients included, with the exception of 4, were followed for 37 months (IQR, 30–47).

Infarct Size and Salvage Index

Patients with LVH had larger area at risk and developed larger acute and final infarct size compared with normotrophic patients (Table 2). After adjusting for area at risk, a linear regression analysis showed that the group with LVH had significantly larger acute and final infarcts than the normotrophic group (Figures 2 and 3), which indicates that patients with LVH developed significantly larger infarcts for an equivalent area at risk. There was no interaction between

Table 1. Baseline Demographics and Angiographic and Procedural Characteristics

	Normal (n=579)	Hypertrophic (n=178)	*P* Value
Age, y	59±11	58±10	0.457*
Male (%)	450 (78)	153 (86)	0.019
BMI	27±4	28±4	0.032*
Diabetes mellitus (%)	43 (7)	13 (7)	>0.999
Family history of CAD (%)	281 (49)	89 (50)	0.863
Current smoking (%)	312 (54)	98 (55)	0.863
Hypertension (%)	190 (33)	70 (39)	0.125
Hyperlipidemia (%)	208 (36)	57 (32)	0.369
Previous MI (%)	18 (3)	11 (6)	0.074
Previous PCI (%)	22 (4)	11 (6)	0.206
Heart rate at admission	72±18	73±19	0.748*
Systolic BT at admission	133 (118–147)	137 (124–157)	0.001†
Diastolic BT at admission	83 (72–94)	90 (75–104)	<0.001†
Symptoms to wire, minutes	214 (125–262)	232 (130–290)	0.075†
Peak troponins, ng/L	2390 (893–4930)	4595 (2185–9028)	<0.001†
Anterior infarct, verified by ECG (%)	217 (38)	92 (52)	0.001
TIMI flow pre-PCI 0/1 (%)	332 (57)	126 (71)	0.002
TIMI flow post-PCI 3 (%)	562 (97)	167 (94)	0.104
Multiple vessel disease (%)	227 (39)	80 (46)	0.162
Thrombectomy (%)	343 (59)	100 (56)	0.487
Left main (%)	1 (0.2)	0 (0)	>0.999
LAD (%)	217 (38)	89 (50)	0.003
LCx (%)	85 (15)	22 (12)	0.464
RCA (%)	274 (47)	66 (37)	0.020
Medication at discharge (%)			
ACE inhibitors	178 (31)	90 (51)	<0.001
ARB	34 (6)	15 (9)	0.224
β-blockers	536 (93)	161 (91)	0.519
ARA	7 (1)	8 (5)	0.010

Data are presented as mean±SD, median (interquartile range) or n (%). ACE indicates angiotensin-converting enzyme; ARA, aldosteron receptor antagonist; ARB, angiotensin II-receptor blocker; BMI, body mass index; BT, blood pressure; CAD, coronary artery disease; LAD, left anterior descending artery; LCx, left circumflex artery; MI, myocardial infarction; PCI, primary percutaneous intervention; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.
Chi-square test was performed unless stated otherwise. *Student *t* test. †Mann–Whitney *U* test.

area at risk and LVH (*P*=0.120). Furthermore, patients with LVH had smaller myocardial salvage indices and a higher incidence of MVO compared with normotrophic patients (Table 2). Patients with LVH also had lower LVEF both in the acute phase and at follow-up (Table 2). Adjusting for sex, BMI, hypertension, systolic and diastolic blood pressure (BT), previous MI, symptom to wire, anterior infarct location, pre-PCI TIMI flow 0/1, post-PCI TIMI-flow 3, and multivessel disease in multivariable linear regression analyses, the difference in infarct size, myocardial salvage index, and LVEF between the LVH group and the normotrophic group remained statistically significant (Table 3). Adjusting for the same variables in a logistic regression analysis, the association between MVO and LVH also remained statistically significant (Table 3).

A combined endpoint of all-cause mortality and readmission for heart failure occurred in 16 (9%) of the patients with LVH and in 24 (4%) of the normotrophic patients (HR, 2.59 [95% CI, 1.38–4.90]; *P*=0.003; Figure 4). This association remained statistically significant in a multivariable Cox regression analysis, adjusting for sex, BMI, hypertension,

Table 2. Outcomes Evaluated by CMR

	n	Normal	n	Hypertrophic	*P* Value
Acute CMR					
Acute infarct size (% LV)	558	13 (6–22)	171	22 (15–32)	<0.001
Area at risk (% LV)	547	32 (24–38)	170	36 (28–45)	<0.001
Acute salvage index	531	0.5 (0.4–0.7)	165	0.4 (0.2–0.5)	<0.001
Presence of MVO	558	251 (45%)	172	113 (66%)	<0.001*
Acute LVEF	579	53 (46–59)	178	45 (39–52)	<0.001
Acute ESV index	579	37 (30–45)	178	51 (42–62)	<0.001
Acute EDV index	579	80 (70–89)	178	95 (85–104)	<0.001
Eccentric LVH			81	46%	
Concentric LVH			97	54%	
Final CMR					
Final infarct size (% LV)	490	9% (3–17)	157	15% (10–21)	<0.001
Final salvage index	466	0.7 (0.5–0.9)	150	0.6 (0.5–0.7)	<0.001
Final LVEF	492	61 (55–65)	157	53 (47–60)	<0.001
Final ESV index	492	32 (26–39)	157	45 (35–58)	<0.001
Final EDV index	492	80 (72–91)	157	97 (86–109)	<0.001
Final LV mass index	492	57 (50–63)	157	74 (68–82)	<0.001

Data are presented as median (interquartile range) or n (%). CMR indicates cardiac magnetic resonance; EDV, end-diastolic volume; ESV, end-systolic volume; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MVO, microvascular obstruction.
Mann–Whitney *U* test was performed unless stated otherwise. *Chi-square test.

systolic and diastolic BT, previous MI, symptoms to wire, anterior infarct location, pre-PCI TIMI flow 0/1, post-PCI TIMI-flow 3, and multivessel disease (HR, 2.52 [95% CI, 1.27–5.02; *P*=0.008). However, adjusting for acute infarct size in the multivariable Cox regression analysis, the association between LVH and the combined endpoint of all-cause mortality and readmission for heart failure was no longer significant (HR, 1.96 [95% CI, 0.95–4.10; *P*=0.070).

LV mass indexed by BSA as a continuous variable was highly significant associated with infarct size (*r*=0.3;

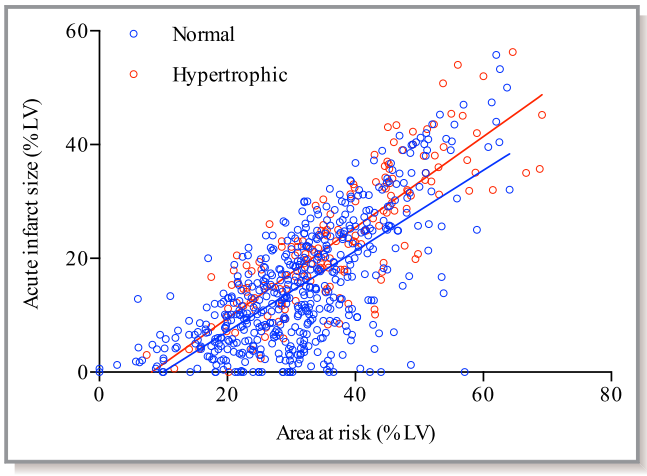

Figure 2. Acute infarct size (% of left ventricular mass) plotted against myocardial area at risk (% of left ventricular mass). The line for the LVH group lies significantly above the line for the normotrophic group (*P*<0.001). In both groups, the infarct size correlates with the area at risk *r*=0.68 and 0.49, *P*<0.001. LV indicates left ventricle; LVH, left ventricular hypertrophy.

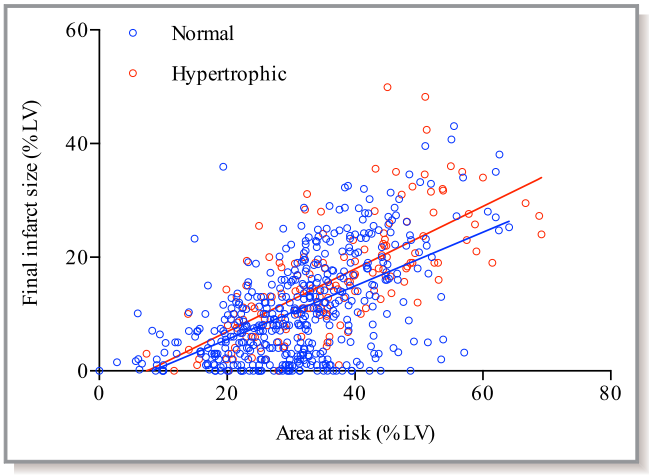

Figure 3. Final infarct size (% of left ventricular mass) plotted against myocardial area at risk (% of left ventricular mass). The line for the LVH group lies significantly above the line for the normotrophic group (*P*<0.001). In both groups, the infarct size correlates with the area at risk *r*=0.47 and 0.31, *P*<0.001. LV indicates left ventricle; LVH, left ventricular hypertrophy.

Table 3. Adjusted Association of Left Ventricular Hypertrophy

	Correlation Coefficient	*P* Value
Acute infarct size	0.2	<0.001
Acute salvage index	−0.2	<0.001
Acute LVEF	−0.2	<0.001
Final infarct size	0.2	<0.001
Final salvage index	−0.1	0.006
Final LVEF	−0.3	<0.001
Presence of MVO (odds ratio)	1.9 (1.3; 2.8)	0.002*

Left ventricular hypertrophy adjusted for sex, body mass index, hypertension, blood pressure at admission, previous MI, symptoms to wire, anterior infarct location, pre-PCI TIMI flow 0/1, post-PCI TIMI-flow 3, and multivessel disease. LVEF indicates left ventricular ejection fraction; MI, myocardial infarction; MVO, microvascular obstruction; PCI, primary percutaneous intervention; TIMI, thrombolysis in myocardial infarction. Multivariable linear regression analysis was performed unless stated otherwise.
*Multivariable logistic regression analysis.

P<0.001), LVEF (*r*=0.4; *P*<0.001), myocardial salvage index (*r*=0.3; *P*<0.001), and the combined endpoint of all-cause mortality and readmission for heart failure (HR, 1.03 [95% CI, 1.01–10.5]; *P*=0.005).

Stratifying the LVH group according to the calculated sex-specific types of hypertrophy, 81 (46%) patients had eccentric LVH and 97 (54%) concentric LVH. Patients with eccentric LVH had significantly lower acute LVEF, whereas no other endpoints were significantly different between the two groups (Table 4).

There was no interaction between LVH and treatment (ischemic postconditioning [*P*=0.381] and deferred stenting [*P*=0.253]) on the effect on infarct size.

Attributed to the difference in previous MI between the LVH group and the normotrophic group, sensitivity analyses

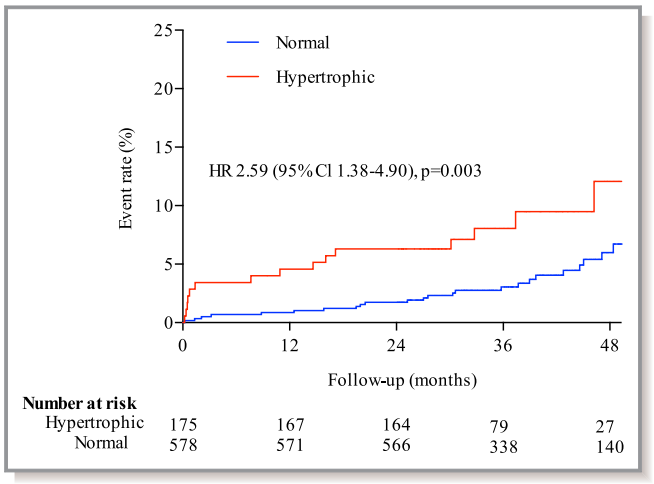

Figure 4. Event rate of the combined endpoint (all-cause mortality and readmission for heart failure). HR indicates hazard ratio.

Table 4. Comparison of Eccentric and Concentric Left Ventricular Hypertrophy Evaluated by CMR

	n	Eccentric	n	Concentric	*P* Value
Acute CMR					
Acute infarct size (% LV)	77	22 (13–32)	94	22 (16–32)	0.429
Area at risk (% LV)	78	35 (27–44)	92	36 (29–47)	0.306
Acute salvage index	75	0.4 (0.3–0.5)	90	0.4 (0.3–0.5)	0.796
Presence of MVO	77	50 (65%)	95	63 (66%)	0.873*
Acute LVEF	81	43 (37–49)	97	48 (41–54)	0.002
Final CMR					
Final infarct size (% LV)	72	15 (10–25)	85	16 (9–20)	0.413
Final salvage index	69	0.6 (0.4–0.7)	81	0.6 (0.5–0.7)	0.096
Final LVEF	72	52 (46–59)	85	55 (48–62)	0.090

Data are presented as median (interquartile range) or n (%). CMR indicates cardiac magnetic resonance; LV, left ventricle; LVEF, left ventricular ejection fraction; MVO, microvascular obstruction.
Mann–Whitney *U* test was performed unless stated otherwise. *Chi-square test.

for patients without previous MI were performed. The analyses did not change the association between LVH and CMR parameters, nor did they change the trend between LVH and the combined endpoint (Tables S1 and S2; Figure S1).

Discussion

In the present study, we observed LVH in ≈25% of a consecutive STEMI cohort. These patients had significantly larger infarct size and area at risk, smaller myocardial salvage index, higher incidence of MVO, and reduced LVEF compared with normotrophic patients.

The results remained significant when adjusting for potential confounding factors in multivariable models, indicating that LVH is independently associated with increased infarct size, MVO, and impaired LVEF. Moreover, we showed an increased risk of all-cause mortality and heart failure in the presence of LVH, but not when adjusting for infarct size. These findings, for the first time, demonstrate a causal relationship between LVH and increased myocardial damage and that LVH in STEMI patients is related to adverse prognosis, partly through the mechanism of larger myocardial damage.

Our findings are consistent with a previous study in STEMI patients using CMR to measure LV mass and infarct size.[11] However, the findings by Małek et al were limited by a small number of patients (n=52), the lack of multivariable analyses

despite important differences in baseline variables between LVH and normotrophic patients, and missing measurements of MVO, area at risk, and salvage index. In contrast to our and previous observations,[6] Małek et al did not report any difference in LVEF. The importance of measuring area at risk in addition to infarct size has previously been emphasized given that area at risk has an impact on infarct size.[30] Given that infarct size, myocardial salvage index, LVEF, LVH, and MVO are associated with adverse outcome in STEMI patients,[20,22,31–33] findings in the present study indicate that the impaired prognosis in patients with acute MI and LVH may directly be attributed to more-extensive myocardial damage and smaller salvage.

The differences between the eccentric and concentric LVH groups regarding LVEF are consistent with a previous study by Verma et al, who found a significantly reduced LVEF in patients with eccentric LVH.[6] They also showed that concentric LVH was associated with a higher risk of adverse cardiovascular events following a STEMI, even after adjusting for LVEF, suggesting that the character of LVH carries a great prognostic value. However, based on our results, a possible prognostic difference between eccentric and concentric LVH cannot be attributed by differences in infarct size or myocardial salvage.

Previous studies have reported very different values for the upper limit of normal LV mass, with ranges of 89 to 112 (men) and 67 to 89 g/m^2 (women). To overcome these differences, we chose to obtain CMR data from 44 healthy subjects that match our study cohort. Taken into account that the papillary muscles were incorporated as part of the LV cavity, the limits used in the present study are very close to previously published values.[34]

The mechanisms for the association between LVH and larger infarct size are still incompletely understood and may be numerous. Cardiac hypertrophy decreases capillary density with as much as 30%,[35] resulting in an increased diffusion distance from capillaries to cardiomyocytes.[9,36,37] This exchange may be further hampered by deterioration of the coronary reserve in hypertrophic hearts[1] and an increase in the extracellular collagen matrix leading to increased oxygen consumption.[5] LVH leads to a shift in metabolism, which may lead to increased vulnerability to ischemia.[35,38] Finally, ischemia results in interstitial edema,[39] with thickening of the myocardium.[40] Thus, a large area at risk (with subsequent large infarct size) causes thickening of the myocardial wall, resulting in a greater LV mass. However, this cannot alone explain the difference in infarct size between LVH and normotrophic patients, given that the difference in infarct size remained statistically significant when adjusting for area at risk. Also, the data in the present study show that the presence of LVH in STEMI is related to larger infarct size, more-extensive myocardial damage and poor outcome whatever the cause for the presence of LVH.

Limitations

First, CMR data on LV mass were obtained after the STEMI diagnosis. Ischemia results in interstitial edema,[39] causing thickening of the myocardial wall.[40] This may pose a risk of overestimating the number of STEMI patients with LVH in the present study. However, this is a general challenge regarding evaluation of LVH in imaging studies on STEMI patients, regardless of choice of imaging modality. Second, of the 1490 patients considered for CMR in the DANAMI-3 trial at Rigshospitalet, only 764 underwent CMR. Although reasons are well described and patients were recruited on a consecutive basis, these dropouts may represent a risk of selection bias, given that the clinical condition is likely to correlate with infarct size and/or LVEF. Third, area at risk was evaluated using a T_2-weighted CMR technique, which has been validated against histopathologically defined area at risk.[19] Myocardial salvage assessed by CMR has also been shown to be a reproducible tool with excellent agreement with single-photon emission computed tomography and angiography.[18,41] However, T_2-weighted images can be technically challenging, with a sufficient diagnostic quality obtainable in only 88% to 95% of patients with STEMI.[16] Fourth, given the nature of the study, we did not have continuous data on heart rate and blood pressure. Furthermore, we did not have information regarding the duration and severity of hypertension, which would have been interesting in relation to LVH. Finally, data on medication at admission were not available.

Conclusions

LVH is independently associated with larger infarct size, smaller myocardial salvage, a higher incidence of MVO, lower LVEF, and a significantly increased risk of all-cause mortality and readmission for heart failure in patients with STEMI treated with primary PCI.

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Supplemental Material

Table S1. Sensitivity analysis for patients without previous myocardial infarction.

	n	Normal	n	Hypertrophic	*p* value
Acute CMR					
Acute infarct size (%LV)	541	13 (6-22)	162	22 (15-32)	<0.001
Area at risk (%LV)	533	32 (24-38)	160	36 (29-45)	<0.001
Acute salvage index	517	0.5 (0.4-0.7)	156	0.4 (0.3-0.5)	<0.001
Presence of MVO	541	243 (45%)	163	108 (66%)	<0.001*
Acute LVEF	561	53 (46-59)	167	45 (39-52)	<0.001
Acute ESV index	561	37 (30-45)	167	50 (41-61)	<0.001
Acute EDV index	561	80 (70-89)	167	95 (85-104)	<0.001
Final CMR					
Final infarct size (%LV)	476	9 (3-17)	148	15 (9-20)	<0.001
Final salvage index	456	0.7 (0.5-0.9)	142	0.6 (0.5-0.7)	<0.001
Final LVEF	479	61 (55-65)	148	53 (47-60)	<0.001
Final ESV index	479	32 (26-38)	148	45 (36-57)	<0.001
Final EDV index	479	80 (72-91)	148	100 (87-109)	<0.001
Final LV mass index	479	57 (50-63)	148	74 (68-82)	<0.001

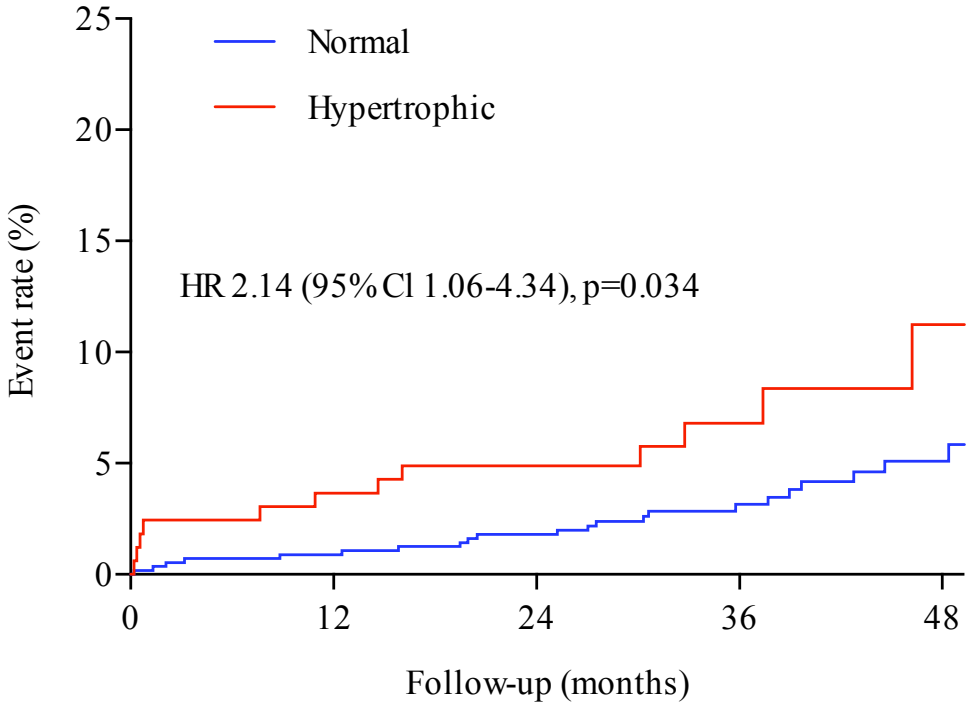
Outcomes evaluated by CMR.
LV indicates left ventricle; MVO microvascular obstruction; LVEF left ventricular ejection fraction; ESV end-systolic volume; EDV end-diastolic volume; LVH left ventricular hypertrophy.
Data are presented as median (interquartile range) or n (%).
Mann Whitney U test was performed unless stated otherwise. *Chi-square test.

Table S2. Temporal changes evaluated by CMR.

	n	Normal	n	Hypertrophic	*p* value
Mass, grams	492	-8 (-14;0.0)	157	-11 (-17;-5)	<0.001
LVEDV	492	2 (-7;14)	157	4 (-5;15)	0.305
LVESV	492	-11 (-26;3)	157	-8 (21;5)	0.215
LVEF	492	13 (3;24)	157	15 (3;26)	0.307
Infarct size	451	-33 (-54;-14)	150	-40 (-51;-23)	0.191

EDV indicates end-diastolic volume; ESV end-systolic volume; LVEF left ventricular ejection fraction; LVH left ventricular hypertrophy.
Data are shown as relative changes (%) form the first to the second CMR, presented as median (interquartile range).
Mann Whitney U test was performed unless stated otherwise.

Figure S1. Cox regression of the combined endpoint of all-cause mortality and readmission for heart failure for patients without previous myocardial infarction:



Number at risk

Hypertrophic	164	158	156	75	26
Normal	560	553	548	328	136

Event rate of the combined endpoint (all-cause mortality and readmission for heart failure) for patients without previous myocardial infarction. HR indicates hazard ratio.

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