HEART FAILURE AND CARDIOMYOPATHY

Prevalence and prognostic implications of electrocardiographic left ventricular hypertrophy in heart failure: evidence from the CHARM programme

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Background: Electrocardiographic left ventricular hypertrophy (ECG LVH) is a powerful independent predictor of cardiovascular morbidity and mortality in hypertension.
Objective: To determine the contemporary prevalence and prognostic implications of ECG LVH in a broad spectrum of patients with heart failure with and without reduced left ventricular ejection fraction (LVEF).
Methods and outcome: The Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme randomised 7599 patients with symptomatic heart failure to receive candesartan or placebo. The primary outcome comprised cardiovascular death or hospital admission for worsening heart failure. The relative risk (RR) conveyed by ECG LVH compared with a normal ECG was examined in a Cox model, adjusting for as many as 31 covariates of prognostic importance.
Results: The prevalence of ECG LVH was similar in all three CHARM trials (Alternative, 15.4%; Added, 17.1%; Preserved, 14.7%; Overall, 15.7%) despite a more frequent history of hypertension in CHARM-Preserved. ECG LVH was an independent predictor of worse prognosis in CHARM-Overall. RR for the primary outcome was 1.27 (95% confidence interval (CI) 1.04 to 1.55, p = 0.018). The risk of secondary end points was also increased: cardiovascular death, 1.50 (95% CI 1.13 to 1.99, p = 0.005); hospitalisation due to heart failure, 1.19 (95% CI 0.94 to 1.50, p = 0.148); and composite major cardiovascular events, 1.35 (95% CI 1.12 to 1.62, p = 0.002).
Conclusion: ECG LVH is similarly prevalent in patients with symptomatic heart failure regardless of LVEF. The simple clinical finding of ECG LVH was an independent predictor of a worse clinical outcome in a broad spectrum of patients with heart failure receiving extensive contemporary treatment. Candesartan had similar benefits in patients with and without ECG LVH.

Left ventricular hypertrophy (LVH) is a powerful independent predictor of cardiovascular morbidity and mortality irrespective of aetiology.[1] It is also a major risk factor for the development of heart failure.[2–5] However, conflicting data exist regarding the prevalence of electrocardiographic (ECG) LVH in patients with heart failure, at least partly as a result of limited sample size.[6–11] In addition, the prognostic implications of ECG LVH in these patients are unknown. In the recent Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme, candesartan significantly reduced cardiovascular deaths and hospital admissions for heart failure.[12] The CHARM programme provides a unique opportunity to examine ECG LVH in a large cohort of patients with heart failure. The aim of our study was to provide detailed information on the contemporary prevalence and prognostic implications of ECG LVH in both the CHARM population as a whole and in the groups with and without reduced left ventricular ejection fraction (LVEF).

PATIENTS AND METHODS

Patients with symptomatic heart failure (New York Heart Association class II–IV) receiving standard treatment were enrolled into one of three parallel clinical trials according to LVEF and treatment with angiotensin-converting enzyme inhibitor (ACEI): LVEF ⩽40% and not receiving an ACEI due to previous intolerance (CHARM-Alternative); LVEF ⩽40% receiving ACEI (CHARM-Added); and LVEF >40% (CHARM-Preserved). In all, 7599 patients were randomised (with data), 3803 received candesartan and 3796 placebo: 2028 patients in CHARM-Alternative (candesartan, n = 1013; placebo, n = 1015), 2548 in CHARM-Added (candesartan, n = 1276; placebo, n = 1272) and 3023 in CHARM-Preserved (candesartan, n = 1514; placebo, n = 1509). Details of the rationale, methods, exclusion criteria and main outcomes have been published previously.[12–14] The study was approved by the local ethics committees of all participating centres, and all patients provided written informed consent.

Investigators at each participating centre interpreted a baseline 12-lead ECG recorded in all patients and completed a structured report documenting ECG findings. Investigators categorised ECGs as normal or abnormal. Abnormal ECGs were further subdivided into one or more of the following categories (check ''all that apply''): (a) atrial fibrillation or flutter, (b) bundle branch block, (c) paced rhythm, (d) pathological Q waves, (e) LVH and (f) other, investigator-specified abnormalities. According to the ''Instructions for the Investigator'' in completing the case report forms, the ECG diagnosis of LVH stated: ''This might include: voltage criteria e.g. the sum of the deepest R wave in V4–6 and the tallest S wave in V1–3 exceeds 35 mm (3.5 mV)[15] strain pattern, left axis deviation, and left atrial enlargement.'' The overall responsibility for diagnosing

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; CHARM, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; ECG LVH, electrocardiographic left ventricular hypertrophy; HF-PSF, heart failure with preserved systolic function; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy

Table 1 Baseline characteristics of patients with electrocardiographic left ventricular hypertrophy

	Preserved, n = 3023			Reduced, n = 4576			Overall, n = 7599		
Characteristics mean (SD) or n (%)	**ECG LVH n = 444 (14.7%)**	**Other ECG abnormal n = 2045 (67.6%)**	**Normal n = 534 (17.7%)**	**ECG LVH n = 748 (16.3%)**	**Other ECG abnormal n = 3614 (79.0%)**	**Normal n = 214 (4.7%)**	**ECG LVH n = 1192 (15.7%)**	**Other ECG abnormal n = 5659 (74.5%)**	**Normal n = 748 (9.8%)**
Demographics									
Age (years)	66.6 (11.3)	67.3 (11.0)	64.3 (11.0)	63.4 (11.2)	65.1 (10.8)	62.7 (12.3)	64.6 (11.4)	65.9 (10.9)	63.8 (11.4)
Women	186 (41.9)	769 (37.6)	257 (48.1)	192 (25.7)	922 (25.5)	74 (34.6)	378 (31.7)	1691 (29.9)	331 (44.3)
Black ethnicity	36 (8.1)	79 (3.9)	11 (2.1)	54 (7.2)	136 (3.8)	10 (4.7)	90 (7.6)	215 (3.8)	21 (2.8)
Weight (kg)	79.1 (17.9)	83.0 (18.9)	84.3 (19.7)	78.0 (17.7)	81.2 (17.5)	84.0 (18.6)	78.4 (17.7)	81.9 (18.0)	84.2 (19.4)
Medical history									
Hypertension	360 (81.1)	1257 (61.5)	326 (61.0)	461 (61.6)	1677 (46.4)	105 (49.1)	821 (68.9)	2934 (51.8)	431 (57.6)
Treated hypertension	334 (75.2)	1114 (54.5)	291 (54.5)	410 (54.8)	1433 (39.7)	92 (43.0)	744 (62.4)	2547 (45.0)	383 (51.2)
Stroke	37 (8.3)	194 (9.5)	37 (6.9)	65 (8.7)	307 (8.5)	23 (10.7)	102 (8.6)	501 (8.9)	60 (8.0)
Atrial fibrillation	143 (32.2)	665 (32.5)	73 (13.7)	180 (24.1)	992 (27.4)	30 (14.0)	323 (27.1)	1657 (29.3)	103 (13.8)
Diabetes mellitus	118 (26.6)	606 (29.6)	133 (24.9)	212 (28.3)	1031 (28.5)	63 (29.4)	330 (27.7)	1637 (28.9)	196 (26.2)
Myocardial infarction	166 (37.4)	1016 (49.7)	158 (29.6)	329 (44.0)	2251 (62.3)	84 (39.3)	495 (41.5)	3267 (57.7)	242 (32.4)
Aortic regurgitation	28 (6.3)	84 (4.1)	15 (2.8)	47 (6.3)	106 (2.9)	3 (1.4)	75 (6.3)	190 (3.4)	18 (2.4)
Mitral regurgitation	84 (18.9)	334 (16.3)	36 (6.7)	192 (25.7)	671 (18.6)	25 (11.7)	276 (23.2)	1005 (17.8)	61 (8.2)
Previous HF admission	344 (77.5)	1383 (67.6)	349 (65.4)	574 (76.7)	2613 (72.3)	163 (76.2)	918 (77.0)	3996 (70.6)	512 (68.4)
Severity markers									
Ejection fraction	54 (9.6)	53 (9.2)	56 (9.5)	28 (7.6)	29 (7.5)	32 (6.8)	38 (15.1)	38 (14.4)	49 (14.2)
Cardiomegaly	106 (23.9)	329 (16.1)	59 (11.0)	242 (32.4)	893 (24.7)	38 (17.8)	348 (29.2)	1222 (21.6)	97 (13.0)
NYHA class									
II	266 (59.9)	1199 (58.6)	371 (69.5)	272 (36.4)	1227 (34.0)	81 (37.9)	538 (45.1)	2426 (42.9)	452 (60.4)
III	170 (38.3)	810 (39.6)	160 (30.0)	456 (61.0)	2259 (62.5)	130 (60.7)	626 (52.5)	3069 (54.2)	290 (38.8)
IV	8 (1.8)	36 (1.8)	3 (0.6)	20 (2.7)	128 (3.5)	3 (1.4)	28 (2.3)	164 (2.9)	6 (0.8)
Systolic BP (mm Hg)	141.9 (18.7)	134.4 (18.1)	137.9 (18.5)	130.8 (19.2)	126.3 (18.5)	134.0 (20.5)	135.0 (19.7)	129.2 (18.8)	136.8 (19.2)
Diastolic BP (mm Hg)	80.2 (10.9)	77.0 (10.6)	78.9 (10.5)	77.5 (10.8)	75.3 (10.7)	78.6 (10.7)	78.5 (10.9)	76.0 (10.7)	78.8 (10.5)
Dependent oedema	134 (30.2)	605 (29.6)	96 (18.0)	160 (21.4)	817 (22.6)	42 (19.6)	294 (24.7)	1422 (25.1)	138 (18.4)
Venous congestion	166 (37.4)	750 (36.7)	150 (28.1)	270 (36.1)	1203 (33.3)	69 (32.2)	436 (36.6)	1953 (34.5)	219 (29.3)
S3 gallop	25 (5.6)	117 (5.7)	20 (3.7)	155 (20.7)	597 (16.5)	20 (9.3)	180 (15.1)	714 (12.6)	40 (5.3)
Pulmonary crepitations	65 (14.6)	358 (17.5)	67 (12.5)	116 (15.5)	596 (16.5)	30 (14.0)	181 (15.2)	954 (16.9)	97 (13.0)
Concomitant treatment									
β-Blockers	266 (59.9)	1117 (54.6)	301 (56.4)	416 (55.6)	1978 (54.7)	125 (58.4)	682 (57.2)	3095 (54.7)	426 (57.0)
Digoxin	159 (35.8)	622 (30.4)	61 (11.4)	395 (52.8)	1937 (53.6)	80 (37.4)	554 (46.5)	2559 (45.2)	141 (18.9)
Spironolactone	45 (10.1)	261 (12.8)	46 (8.6)	159 (21.3)	732 (20.3)	29 (13.6)	204 (17.1)	993 (17.5)	75 (10.0)
Other vasodilators	209 (47.1)	771 (37.7)	180 (33.7)	308 (41.2)	1428 (39.5)	68 (31.8)	517 (43.4)	2199 (38.9)	248 (33.2)
Loop diuretics	314 (70.7)	1301 (63.6)	292 (54.7)	514 (68.7)	2446 (67.7)	147 (68.7)	828 (69.5)	3747 (66.2)	439 (58.7)

BP, blood pressure; ECG LVH, electrocardiographic left ventricular hypertrophy; HF, heart failure; NYHA, New York Heart Association.

LVH rested with individual site investigators. The specific ECG abnormalities suggesting LVH, either single or multiple, were not documented.

The primary outcome was a composite of cardiovascular death or unplanned hospital admission for management of worsening heart failure. Secondary prespecified end points and components included cardiovascular death; hospital admission for heart failure; and composite of cardiovascular death, hospital admission for heart failure, non-fatal myocardial infarction or non-fatal stroke. The relationship between baseline characteristics, particularly history of hypertension and blood pressure levels, and prevalence of ECG LVH, was examined. The present study focused on the associations between ECG LVH and cardiovascular events in cohorts with reduced (combined CHARM-Alternative/Added) and preserved (CHARM-Preserved) left ventricular systolic function. In secondary analyses, we evaluated the influence of ECG LVH on the effect of treatment benefit in these two populations with heart failure.

All data analyses were performed independently by the Medical Statistics Unit at the London School of Hygiene and Tropical Medicine, London, UK. Baseline characteristics of patients with ECG LVH, other ECG abnormalities and a normal ECG were summarised as mean (standard deviation (SD)) for continuous variables and by frequency (%) for categorical variables. Means were compared using the Student t test and proportions using the χ^2 test. All analyses were carried out by intention-to-treat analyses. The prognostic significance of ECG LVH was evaluated for predefined clinically relevant outcomes, including the primary outcome and other major cardiovascular events. In Cox regression analyses, the main results on ECG effects modelled the ECG as three categories: ECG LVH, other ECG abnormality and ECG normal. In a supplemental analysis, ECG was coded as two categories: ECG LVH presence and ECG LVH absence. The relative risks (RRs) and 95% confidence intervals (CIs) associated with ECG LVH compared with the normal ECG and the absence of ECG LVH are therefore estimated.

Table 2 CHARM-Overall: independent predictors of electrocardiographic left ventricular hypertrophy

Predictor	Odds ratio (95% CI)	p Value
Previous percutaneous coronary intervention	1.77 (1.43 to 2.20)	<0.001
Previous myocardial infarction	1.56 (1.36 to 1.79)	<0.001
European origin	1.54 (1.27 to 1.86)	<0.001
Previous smoker	1.19 (1.04 to 1.36)	0.011
Female	1.19 (1.02 to 1.38)	0.023
Ejection fraction (per 10% decrease)	1.12 (1.07 to 1.18)	<0.001
Body mass index	1.07 (1.06 to 1.09)	<0.001
Age (per year)	1.01 (1.01 to 1.02)	<0.001

The estimated hazard (risk) ratios (HRs) were adjusted for all important predictors of mortality and morbidity identified in the CHARM programme, including age, sex, diabetes mellitus, New York Heart Association class, rest dyspnoea, current cigarette smoking, previous hospitalisation for heart failure (none, within 6 months, after 6 months), first diagnosis of heart failure over 2 years ago, previous myocardial infarction, atrial fibrillation, heart rate, diastolic blood pressure, dependent oedema, pulmonary crackles, cardiomegaly, bundle branch block, pulmonary oedema, mitral regurgitation and candesartan treatment, using a multivariate Cox proportional hazards model. A two-tailed $p<0.05$ was considered significant. Data from the two studies of patients with reduced ejection fraction were combined, as this group was prespecified as clinically important. For combined analysis of the three trials, statistical heterogeneity tests were performed for each end point. To identify the independent predictors of ECG LVH, a logistic regression model was used, with demographic and disease-related characteristics as potential predictors.

RESULTS

Baseline characteristics

The findings from 7599 patients were analysed. The median duration of follow-up was 37.7 months. A detailed review of patients' baseline characteristics has been published previously.[14] Table 1 shows the baseline characteristics of patients with ECG LVH (n = 1192), other ECG abnormalities (n = 5659) and a normal ECG (n = 748).

Overall, and in the groups with reduced and preserved systolic function, patients with ECG LVH had a more frequent history of hypertension (68.9% *v* 57.6%), cardiomegaly (29.2% *v* 13.0%), aortic regurgitation (6.3% *v* 2.4%) and mitral regurgitation (23.2% *v* 8.2%), all $p<0.001$ compared with those with a normal ECG. The comparison with other ECG abnormalities was similar. After adjusting for baseline characteristics, multivariate analysis for the presence of ECG LVH revealed several independent predictors (table 2). Interestingly, neither history of hypertension nor baseline blood pressure was a predictor of ECG LVH.

Table 3 Risk associated with electrocardiographic left ventricular hypertrophy relative to the normal electrocardiogram

Outcome, systolic function	ECG LVH present, n (%)	ECG normal, n (%)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	p Value interaction*
CV death or HF hospitalisation							
Overall	418 (35.1)	139 (18.6)	1.78 (1.46 to 2.16)	<0.001	1.27 (1.04 to 1.55)	0.018	
Reduced LVEF	307 (41.0)	49 (22.9)	2.03 (1.50 to 2.75)	<0.001	1.44 (1.06 to 1.96)	0.019	0.219
Preserved LVEF	111 (25.0)	90 (16.9)	1.61 (1.22 to 2.12)	<0.001	1.14 (0.85 to 1.52)	0.379	
CV death							
Overall	255 (21.4)	62 (8.3)	2.17 (1.64 to 2.87)	<0.001	1.50 (1.13 to 1.99)	0.006	
Reduced LVEF	183 (24.5)	24 (11.2)	2.38 (1.56 to 3.64)	<0.001	1.68 (1.09 to 2.58)	0.019	0.908
Preserved LVEF	72 (16.2)	38 (7.1)	2.43 (1.64 to 3.59)	<0.001	1.58 (1.05 to 2.37)	0.029	
Sudden death							
Overall	121 (10.2)	23 (3.1)	2.63 (1.68 to 4.12)	0.002	1.96 (1.24 to 3.08)	0.004	
Reduced LVEF	91 (12.2)	9 (4.2)	3.11 (1.57 to 6.17)	0.001	2.28 (1.14 to 4.55)	0.019	0.848
Preserved LVEF	30 (3.8)	14 (2.6)	2.73 (1.45 to 5.14)	0.002	1.93 (1.00 to 3.71)	0.049	
Death due to HF progression							
Overall	72 (6.0)	15 (2.0)	2.47 (1.41 to 4.33)	<0.001	1.47 (0.84 to 2.60)	0.180	
Reduced LVEF	58 (7.8)	4 (1.9)	4.54(1.65 to 12.50)	0.003	2.89 (1.04 to 8.02)	0.042	0.068
Preserved LVEF	14 (3.2)	11 (2.1)	1.62 (0.74 to 3.58)	0.228	0.90 (0.39 to 2.04)	0.793	
HF hospitalisation							
Overall	279 (23.4)	103 (13.8)	1.65 (1.31 to 2.08)	<0.001	1.19 (0.94 to 1.50)	0.148	
Reduced LVEF	203 (27.1)	35 (16.4)	1.87 (1.31 to 2.68)	<0.001	1.35 (0.94 to 1.95)	0.105	0.221
Preserved LVEF	76 (17.1)	68 (12.7)	1.45 (1.04 to 2.01)	0.027	1.03 (0.73 to 1.44)	0.884	
CV death, HF hospitalisation, non-fatal MI, non-fatal stroke							
Overall	469 (39.3)	157 (21.0)	1.84 (1.53 to 2.21)	<0.001	1.35 (1.12 to 1.62)	0.002	
Reduced LVEF	332 (44.4)	53 (24.8)	2.05 (1.53 to 2.74)	<0.001	1.49 (1.11 to 2.00)	0.008	0.377
Preserved LVEF	137 (30.9)	104 (19.5)	1.74 (1.35 to 2.25)	<0.001	1.28 (0.99 to 1.67)	0.063	

CV, cardiovascular; ECG, electrocardiogram; ECG LVH, electrocardiographic left ventricular hypertrophy; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction.
*Interaction between presence of ECG LVH (*v* ECG normal) and reduced LVEF (*v* preserved LVEF).

Table 4 Risk associated with electrocardiographic left ventricular hypertrophy, presence relative to absence

Outcome, systolic function	ECG LVH present, n (%)	ECG LVH absent, n (%)	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p value	p Value interaction*
CV death or HF hospitalisation							
Overall	418 (35.1)	2042 (31.9)	1.10 (0.99 to 1.23)	0.064	1.07 (0.96 to 1.19)	0.230	0.572
Reduced LVEF	307 (41.0)	1454 (38.0)	1.10 (0.97 to 1.24)	0.144	1.06 (0.94 to 1.21)	0.348	
Preserved LVEF	111 (25.0)	588 (22.8)	1.13 (0.92 to 1.38)	0.247	1.12 (0.91 to 1.38)	0.286	
CV death							
Overall	255 (21.4)	1205 (18.8)	1.11 (0.97 to 1.28)	0.116	1.09 (0.95 to 1.26)	0.208	0.621
Reduced LVEF	183 (24.5)	937 (24.5)	0.99 (0.85 to 1.16)	0.925	0.98 (0.83 to 1.16)	0.828	
Preserved LVEF	72 (16.2)	268 (10.4)	1.60 (1.24 to 2.08)	<0.001	1.60 (1.22 to 2.09)	<0.001	
HF hospitalisation							
Overall	279 (23.4)	1396 (21.8)	1.08 (0.95 to 1.23)	0.233	1.04 (0.91 to 1.19)	0.534	0.136
Reduced LVEF	203 (27.1)	955 (24.9)	1.10 (0.95 to 1.28)	0.202	1.07 (0.92 to 1.25)	0.373	
Preserved LVEF	76 (17.1)	441 (17.1)	1.03 (0.81 to 1.31)	0.827	1.01 (0.78 to 1.29)	0.950	
CV death, HF hospitalisation, non-fatal MI, non-fatal stroke							
Overall	469 (39.3)	2220 (34.6)	1.15 (1.04 to 1.27)	0.007	1.12 (1.02 to 1.25)	0.024	0.490
Reduced LVEF	332 (44.4)	1540 (40.2)	1.12 (0.99 to 1.26)	0.061	1.10 (0.98 to 1.25)	0.111	
Preserved LVEF	137 (30.9)	680 (26.4)	1.22 (1.01 to 1.46)	0.036	1.21 (1.00 to 1.46)	0.052	

CV, cardiovascular; ECG, electrocardiogram; ECG LVH, electrocardiographic left ventricular hypertrophy; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction.
*Interaction between presence of ECG LVH (*v* absence of ECG LVH) and reduced LVEF (*v* preserved LVEF).

Prevalence

There was a significant difference in the prevalence of history of hypertension in each of the three CHARM trials between patients with ECG LVH (Alternative 63.5%, Added 60.3%, Preserved 81.1% and Overall 68.9%) and those with a normal ECG (Alternative 48.2%, Added 50.0%, Preserved 61.0% and Overall 57.6%). However, the prevalence of ECG LVH was less varied between the three CHARM trials despite the differences in the history of hypertension (Alternative 15.4%, Added 17.1%, Preserved 14.7% and Overall 15.7%). In particular, the Preserved group exhibited the least ECG LVH (14.7%) compared with the combined Alternative/Added group (16.3%, $p = 0.052$), while having the highest prevalence of history of hypertension.

Prognosis: overall

ECG LVH significantly increased occurrence of the primary outcome by 78% (unadjusted HR 1.78 (95% CI 1.46 to 2.16), $p<0.001$) compared with the normal ECG. Overall, 418 of 1192 (35.1%) patients with ECG LVH died of cardiovascular causes or were admitted to hospital for management of worsening heart failure compared with 139 of 748 (18.6%) patients with a normal ECG (table 3). This increased RR remained significant after correcting for additional cardiovascular risks in multivariate analysis (covariate adjusted 1.27 (95% CI 1.04 to 1.55), $p = 0.018$).

Overall, all prespecified secondary outcomes were increased by the presence of ECG LVH. Cardiovascular death was significantly increased by 50% (1.50 (95% CI 1.13 to 1.99), $p = 0.005$) and major cardiovascular events (defined as cardiovascular death, heart failure hospitalisation, non-fatal myocardial infarction or non-fatal stroke) were increased by 35% (1.35 (95% CI 1.12 to 1.62), $p = 0.002$). However, the risk of hospitalisation for heart failure failed to achieve significance after multivariate adjustment (1.19 (95% CI 0.94 to 1.50), $p = 0.148$). Increases in the risk of both sudden death (1.96 (95% CI 1.24 to 3.08), $p = 0.004$) and death due to progression of heart failure (1.47 (95% CI 0.84 to 2.60), $p = 0.180$) contributed to the increased risk of cardiovascular death. Overall, risk of the primary outcome associated with ECG LVH compared with the normal ECG was similarly increased in patients receiving candesartan (1.30 (95% CI 0.98 to 1.72)) and placebo (1.25 (95% CI 0.95 to 1.64)), with formal statistical testing yielding no significant interaction between presence of ECG LVH and effect of candesartan treatment ($p = 0.899$).

Prognosis: reduced versus preserved systolic function

Adjusted risk of the primary outcome was significantly raised by 44% (1.44 (95% CI 1.06 to 1.96), $p = 0.019$) in patients with reduced systolic function. This reflected an increase of 68% in cardiovascular death (1.68 (95% CI 1.09 to 2.58), $p = 0.019$) and 35% in hospitalisation due to heart failure (1.35 (95% CI 0.94 to 1.95), $p = 0.105$). The risk was further amplified with the addition of non-fatal myocardial infarction and non-fatal stroke to the composite outcome (1.49 (95% CI 1.11 to 2.00), $p = 0.008$).

In the CHARM-Preserved population, the presence of ECG LVH was associated with a significantly increased risk of cardiovascular death (1.58 (95% CI 1.05 to 2.37), $p = 0.033$) in Cox model analysis. The RR of the composite primary outcome was lower (1.14 (95% CI 0.85 to 1.52), $p = 0.379$), reflecting the minimal effect on hospitalisation due to heart failure (1.03 (95% CI 0.73 to 1.44), $p = 0.884$). The increased risk of major cardiovascular events associated with ECG LVH was of borderline significance (1.28 (95% CI 0.99 to 1.67), $p = 0.063$) in patients with preserved systolic function. No significant difference was observed between patients with reduced and preserved systolic function when testing each outcome for an interaction between presence of ECG LVH and reduced LVEF (*v* preserved LVEF; table 3). Similarly, the hazard associated with ECG LVH was not modified by LVEF in an analysis using LVEF as a continuous variable.

Prognosis: ECG LVH presence versus absence

ECG LVH was compared with the normal ECG because of the disparate nature and varying prognostic significance of the other ECG abnormalities, which included arrhythmias, pathological Q waves, paced rhythm and bundle branch block. When comparing patients with and without ECG LVH, the associated risk was more modest (table 4). Overall, presence of ECG LVH significantly increased risk of major cardiovascular events by 12% (1.12 (95% CI 1.02 to 1.25), $p = 0.024$). However, risk of the primary outcome was not significantly increased.

DISCUSSION

The main causes of heart failure are coronary artery disease and hypertension, alone or in combination. Hypertension is considerably more frequent, reflecting disease aetiology, in heart failure with preserved systolic function (HF-PSF) compared with left ventricular systolic dysfunction (the EuroHeart Failure Survey (59% *v* 50%, p<0.001)[16]; the US National Heart Failure Project (69% *v* 61%, p<0.001)[17]; the CHARM programme (64% *v* 49%, p<0.001)[14]). Our results additionally show that a history of hypertension is significantly higher in patients with ECG LVH, regardless of left ventricular systolic function.

Conflicting data exist regarding the prevalence of ECG LVH in patients with heart failure, relating to limited study size, varying study populations, differences in criteria diagnosing ECG LVH, and echocardiographic threshold defining systolic function. Two previous studies of 172 and 229 consecutively hospitalised patients with heart failure demonstrated a significantly higher prevalence in those with preserved versus depressed systolic function: 51% *v* 25% and 49% *v* 36%, respectively.[6 7] This corroborates a report of the Framingham Heart Study, in which ECG LVH occurred in 22% of patients with HF-PSF compared with 14% of patients with left ventricular systolic dysfunction.[8] By contrast, no significant difference was observed in 137 patients in the Olmsted County study (17% *v* 19%)[9] or in 739 patients in the French hospital survey (31% *v* 31%),[10] while ECG LVH was actually less frequent in the Cook County study (22% *v* 42%).[11]

The CHARM programme describes by far the largest cohort to date for comparison of patients with heart failure with preserved and impaired LVEF. The diverse population and large number of outcome events enables precise assessment of risk for specific outcomes overall and within the subgroups. Our analysis reveals that the prevalence of ECG LVH was similar in all three CHARM trials (Alternative, 15.4%; Added, 17.1%; and Preserved, 14.7%; Overall 15.7%) despite a more frequent history of hypertension in the Preserved group. Possibly, the trial baseline blood pressure does not accurately reflect the mean lifetime blood pressure and concomitant LVH, owing to development of left ventricular systolic dysfunction and a consequent reduction in blood pressure. The mean duration of hypertension in each trial was also unknown. Finally, the QRS amplitude is affected not only by the left ventricular mass but also by impaired systolic function.[18] The geometric relationship representing interplay of wall thickness and chamber dilatation is an important factor in determining ECG voltage.[19] Our analysis, in which LVEF was an independent predictor of ECG LVH, supports this theory.

ECG LVH is a potent independent predictor of cardiovascular events in patients with hypertension.[20 21] Regression confers cardiovascular benefit, whereas progression imposes adverse prognostic consequences.[22 23] ECG LVH independently increases the risk of heart failure development, both in the general population and in patients at high cardiovascular risk.[2 3] For example, in a 4-year longitudinal study, 18% of patients with hypertension and LVH progressed to have reduced systolic function.[4] Conversely, treatment of hypertension compared with placebo or control reduced the incidence of heart failure by over 50%.[5] Once heart failure has developed, echocardiographic LVH remains an independent predictor of adverse events.[24]

Our study defines the previously unknown prognostic implications of ECG LVH in patients with heart failure, particularly in those with HF-PSF. Analysis of the CHARM-Overall programme revealed the baseline finding of ECG LVH is an independent predictor of cardiovascular death or hospital admission for patients with heart failure, significantly increasing the primary outcome by 27%. In addition, ECG LVH was associated with increased risk of the prespecified secondary and component outcomes, including cardiovascular death (50%) and major cardiovascular events (35%). It is of further interest that ECG LVH was associated with an increased risk of both sudden death and deaths attributed to progression of heart failure, the two major components of cardiovascular death.

The risk of cardiovascular death was increased by a similar magnitude in patients with reduced and preserved systolic function. Although adjusted risk of the primary outcome and hospitalisation due to heart failure appeared greater in patients with reduced compared to preserved systolic function, statistical testing for an interaction revealed no significant difference. The play of chance is not ruled out, as the lower numbers of patients and event rates in the CHARM-Preserved cohort reduces the statistical power. The difference may also be influenced by incorporating factors such as hypertension in the multivariate hazards model. This may override the variance attributable to ECG LVH more in patients with HF-PSF.

Sustained haemodynamic and neurohumoral stimulation causes myocyte hypertrophy and interstitial fibrosis due to disruption of the complex interaction between collagen synthesis and degradation.[25] Pharmacological intervention specifically targets the renin–angiotensin–aldosterone system to promote regression and structural remodelling, leading to functional normalisation. Angiotensin receptor blockers have a potential direct antihypertrophic effect mediated by complete blockade of angiotensin II at the AT1 receptor,[26] with meta-analyses suggesting that ACEIs and angiotensin receptor blockers have greatest efficacy in reducing left ventricular mass, independent of blood pressure reduction.[27 28] The Candesartan Assessment in the Treatment of Cardiac Hypertrophy Study showed that regimens based on candesartan and enalapril were equipotent in inducing echocardiographic LVH regression in patients with hypertension, with candesartan achieving a higher rate of full left ventricular mass index normalisation (36.3% *v* 28.6%).[29] In the CHARM population, the prognostic benefits of candesartan were not significantly altered by the presence of ECG LVH. This reflects the importance of the renin–angiotensin–aldosterone system blockade in this cohort of patients irrespective of the presence of LVH.

Several potential limitations of the present study merit consideration. ECG interpretation was performed by individual site investigators based largely on Sokolow–Lyon voltage criteria rather than by a single central laboratory with standardised methods. Despite superior correlations with echocardiographic LVH,[30] more complex ECG LVH criteria and scoring systems are not routinely employed in daily practice. The simplicity of the ECG LVH diagnostic criteria used in CHARM and their interpretation by individual investigators improves clinical applicability in large populations. A further limitation is the lack of serial ECG measurements, preventing assessment of the effects of ECG LVH regression on prognosis. Whether the favourable prognostic implications of regression of ECG LVH in hypertensive patients translates into similar benefits in heart failure patients remains likely but unproven. Moreover, the absence of routine echocardiographic assessments precludes other correlations that would have been enlightening in this population with heart failure.

In conclusion, LVH defined by simple, easily applicable ECG criteria is associated with a significantly increased risk of major cardiovascular events. This accessible and inexpensive tool identifies a subset of patients at particularly high cardiovascular risk. ECG LVH is an independent predictor of worse clinical outcomes in a broad spectrum of patients with symptomatic heart failure, including those with reduced and preserved left ventricular systolic function.

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