Left Ventricular Hypertrophy is a predictor of cardiovascular events in elderly hypertensives: hypertension in the the very elderly trial (HYVET)

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LEFT VENTRICULAR HYPERTROPHY IS A PREDICTOR OF CARDIOVASCULAR EVENTS IN ELDERLY HYPERTENSIVES. HYPERTENSION IN THE ELDERLY (HYVET) TRIAL

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Abstract

Objective. We assessed the prognostic value of electrocardiographic left ventricular hypertrophy (LVH) using Sokolow-Lyon (SL-LVH), Cornell Voltage (CV-LVH) or Cornell Product (CP-LVH) Criteria in 3043 hypertensive people aged 80 years and over enrolled in the Hypertension in the Very Elderly Trial.

Methods. Multivariate Cox proportional hazard models were used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for all-cause mortality, cardiovascular diseases, stroke and heart failure in participants with and without LVH at baseline. The mean follow-up was 2.1 years.

Results. LVH identified by CV- or CP-LVH Criteria was associated with a 1.6 to 1.9-fold risk of cardiovascular disease and stroke. The presence of CP-LVH was associated with an increased risk of heart failure (HR 2.38, 95% CL 1.16-4.86). In gender specific analyses, CV-LVH (HR 1.94, 95%Cl 1.06-3.55) and CP-LVH (HR 2.36, 95% CI 1.25-4.45) were associated with an increased risk of stroke in women and of heart failure in men, CV-LVH (HR 6.47, 95 % Cl 1.41-29.79) and CP-LVH (10.63, 95Cl % 3.58-31.57), respectively. There was no significant increase in the risk of any outcomes associated with SL LVH. LVH identified by these three methods was not a significant predictor of all-cause mortality.

Conclusions. Use of Cornell Voltage and Cornell Product criteria for LVH predicted the risk of cardiovascular disease and stroke. Only Cornell Product was associated with an increased the risk of heart failure. This was particularly the case in men. The

identification of electrocardiographic LVH proved to be important in very elderly hypertensive people.

Condensed abstract.

The prognostic value of electrocardiographic left ventricular hypertrophy (LVH) was assessed in 3034 hypertensive people aged 80 years or more in the Hypertension in the Very Elderly Trial. After adjustments, LVH by Cornell Voltage and Cornell Product Criteria significantly predicted a 1.6 to 1.9-fold increased risk of cardiovascular diseases and stroke. In gender-specific analyses, LVH by Cornel voltage and Cornel Product were significant predictors of stroke in women only, whereas they were predictors of heart failure in men only. LVH by Sokolow-Lyon criteria showed no significant relationship with any outcome. LVH was not a significant predictor of all-cause mortality.

Key words: electrocardiographic left ventricular hypertrophy, Sokolow-Lyon, Cornell Voltage, Cornell Product, hypertension, prediction, very elderly.

Introduction

The most common finding in both elderly and hypertensive hearts is left ventricular hypertrophy (LVH) [1]. It is an adaptive process following increased hemodynamic load and thus is evidence of target organ damage [1-3]. The presence of LVH is determined using echocardiography (ECHO) or electrocardiography (ECG) to classify hypertensive subjects as at high or very high risk for cardiovascular diseases (CVD) [3]. Although a normal ECG does not exclude the presence of anatomical or ECHO LVH, it does measure the electrical activity of the heart tissue [2-4]. ECHO and ECG LVH have been found to carry different prognostic information [5], however, ECG is easily available and inexpensive [2, 3]. Current guidelines have accepted ECG LVH as an important risk factor for CVD morbidity and mortality and recommend that a 12-lead ECG should be the first line method for the diagnosis of LVH in all hypertensive patients [2, 3].

The presence of ECG LVH in hypertension carries a 2-4-fold increase in the risk of CVD morbidity and mortality, depending on the criterion used [4]. In hypertensive elderly patients, the presence of ECG LVH increases the risk of mortality or morbidity independently in most [6-10], but not in all studies [11, 12].

In the studies of people aged at least 75 years, the prevalence of anatomical, x-ray LVH or ECHO LVH is very high at 44%-87% [12, 13] and the prevalence of ECG LVH 2-25% [12-15], depending on the age-subgroup, LVH criterion and hypertensive status used. Despite this, the information on the risks associated with LVH in very

elderly hypertensive subjects is scarce [10, 12] and to our knowledge, this information is missing in hypertensive subjects aged 80 years and more.

In the present paper, we compared the risk of all-cause mortality, fatal and nonfatal CVD, stroke and heart failure in participants in the Hypertension in the Very Elderly (HYVET) Trial with and without ECG LVH at baseline in all participants and separately for women and men.

Methods

HYVET was designed to establish the benefits and risks of treating patients aged 80 years or more with hypertension [16]. It was a randomized double-blind, placebo-controlled trial comparing the effect of indapamide SR 1.5mg or matching placebo with the optional addition of 2 or 4 mg perindopril, or matching placebo to reach a goal blood pressure (BP) of less than 150/80 mmHg. The detailed protocol for the HYVET trial has been published previously [17]. HYVET was performed in 195 centers in 13 countries from Western and Eastern Europe (n=2230), Australasia (n=19), Tunisia (n=70) and China (n=1526). Approval for the trial was obtained from the appropriate competent authorities and central or local ethics committees as required. Participants gave written informed consent. Those who were illiterate were consented appropriately with an independent witness who signed the consent form. The procedures followed were in accordance with institutional guidelines.

Patients were eligible if the mean of the four systolic BP (SBP) recordings during the placebo run-in period was between 160 and 199 mmHg, patient were included to the study. The average seated diastolic BP (DBP) had to be less than 110 mmHg. The standing SBP criterion was at least 140 mmHg. Exclusion criteria included contraindication to trial medication, accelerated hypertension, secondary hypertension, hemorrhagic stroke in the past 6 months, heart failure requiring treatment with antihypertensive medication, serum creatinine more than 150 mmol/l, serum potassium less than 3.5 mmol/l or more than 5.5 mmol/l, gout, a clinical diagnosis of dementia and requirement for nursing home care.

During the placebo run-in period, information was collected on current diseases, medication, BP, biochemistry, current smoking habits, alcohol intake, and antihypertensive treatment status before randomization. Body height and weight were measured and body mass index (BMI) was calculated (kg/m2). Diabetes was defined as reported diabetes, in receipt of antidiabetic treatment, or a random blood glucose measurement of more than 11.1 mmol/l. Previous CVD at presentation included prior stroke, myocardial infarction or heart failure.

Two clinical doctors (R.L.A. and N.B.) evaluated the resting 12-lead ECGs collected during the run-in period [15]. The voltages in the ECGs with calibration signal heights of 0.5 and 2 cm were recalculated to correspond to the voltages with signal height of 1 cm (1 mV). QRS duration was measured to the nearest 20 milliseconds when the paper velocity was 25 mm/sec (10 ms for 50 mm/sec) and the R-wave and S-wave amplitude heights were measured to the nearest 1 mm corresponding to 0.1 mV. Inter-rater (between R.L.A. and N.B.) and intra-rater reliability were calculated using blinded samples of ECGs. The inter-rater comparisons for measurements were very high (88–98%) and intra-rater comparisons 86–100%.

Three criteria were chosen to characterize ECG LVH, Sokolow-Lyon (SL), Cornell-Voltage (CV) and Cornell-Product (CP). Two of them (1 and 3 below) and their cut-points are on the list of the European Society of Hypertension (ESH) /European Society of Cardiology (ESC) 2007 guidelines [18].

- LVH by Sokolow-Lyon voltage (SL-LVH) criterion [19], was considered as present when the amplitude of SV1+ (max RV5 or RV6) was above 3.8 mV.

1. LVH by Cornell sex-specific voltage criterion (CV-LVH) was considered as present when the amplitude of RaVL+SV3 was more than 2.8 mV for men and more than 2.0 mV for women [20].

2. LVH by Cornell product criterion (CP-LVH) was considered as present when QRS duration (ms) multiplied by (RaVL+SV3) was more than 244 mV*ms for men and QRS duration multiplied by (RaVL+SV3+0.6 mV) more than 244 mV*ms for women [21].

Bundle Branch Block (BBB) was defined as a QRS duration equal or more than 120ms.

All fatal and non-fatal events that could be considered to be trial endpoints, were reviewed by an independent committee. The committee were blinded to trial treatment allocation and used predefined definitions from the protocol [16]. These analyses report results for death from any causes, fatal and nonfatal CVD, stroke and heart failure. The number of myocardial infarctions was small and therefore not included.

The differences in mean values and standard deviations in women and men were assessed using Student's t-test. Comparisons between proportions were performed using the chi-square test. The relationship between the endpoints, the presence of baseline SL-, CV-, and CP-LVH and other baseline variables (age, gender SBP, DBP, heart rate, BMI, serum cholesterol, hemoglobin, creatinine and uric acid concentration,

history of CVD, diabetes, antihypertensive drug treatment at baseline, smoking and alcohol use and randomization to intervention/placebo group) was determined using a Cox proportional hazard regression model. The variables selected have been associated with the presence of ECG LVH in previous studies [15, 22, 23]. Information was missing for serum uric acid in 17 participants, cholesterol in six, hemoglobin level in four, heart rate measurements in three and BMI in one participant. A p-value of 0.05 was taken as statistically significant. Multivariable Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% Confidence intervals (CI) for all-cause mortality, CVD, heart failure and stroke in participants with and without LVH at baseline. Gender, and the statistically significant predictors from the univariate analyses for at least one of the endpoints were selected for inclusion into the final multivariate model. They were increasing age, DBP, heart rate, race (Caucasians vs Chinese), smoking, the presence of diabetes, uric acid concentration, CVD at baseline and randomization to placebo/active treatment. The interaction between gender and the presence of CP-LVH for the risk of heart failure was statistically significant.

Analyses were performed on an intention-to-treat basis using the Statistical Analyses System (SAS Institute Inc., Cary, North Carolina, USA). This trial is registered with Clinical Trials.gov number NCT00122811.

Results

From the total 3845 participants randomized in the HYVET Study, 521 participants were excluded with missing, paced, uncodable or incomplete ECGs and 290 with BBB. This left 1884 women and 1150 men with information on all three ECG LVH criteria. The mean follow up was 2.1 years.

Table- 1 shows the baseline characteristics and Table 2 the incidence of fatal and nonfatal events and all-cause mortality according to the various definitions of presence or absence of ECG LVH at baseline in both men and women.

Regardless of the ECG criterion used, the presence of LVH did not predict all-cause mortality with statistical significance (Table 3). Persons with both CV-LVH and CP-LVH were at increased risk of CVD, stroke and heart failure. The risk associated with CV-LVH was, however, of borderline statistical significance. The adjusted HRs associated with CV-LVH were 1.60 (95% CI of 1.12-2.31) for CVD and 1.85 (95% Cl 1.05-3.27) for stroke. The corresponding HRs associated with of CP-LVH were 1.65 (95% CI 1.13-2.40) for CVD and 1.94 (95% CI 1.08-3.49) for stroke. SL-LVH predicted heart failure, but after adjustments only attained a borderline significance, HR 2.02 (95% Cl 0.98-4.16).

In gender-specific analyses, after adjustments, increase in the risk of CVD was markedly associated with the presence *of* CV-LVH, (HR 1.51, 95% CI 1.02-2.24) in women and with the presence CP-LVH in men (HR 2.41, 95% CI 1.20-4.84) (Table 4). Women were at an increased risk of stroke with LVH, the adjusted HR associated with

CV-LVH was 1.94 (95% Cl 1.06-3.55) and that of CP-LVH was 2.36 (95% Cl 1.25-4.45). For incident heart failure, statistically significant predictions were seen in men only, the adjusted HRs for CV-LVH and CP-LVH criteria were 6.47 (95% Cl 1.41-29.79) and 10.63 (95% Cl 3.58-31.57), respectively. The interaction between CP-LVH and gender was statistically significant for heart failure but not for stroke.

Discussion

Our data showed that the presence of ECG LVH identified by Cornell Voltage and Cornell Product criteria predicted CVD, stroke and heart failure in hypertensive very old people. CV-LVH and CP-LVH markedly predicted stroke in women, whereas their presence predicted heart failure in men only. The interaction between gender and CP-LVH for heart failure was significant. ECG LVH did not predict all-cause mortality.

Previous work in population based studies of older adults has shown associations between ECG-LVH and increased risk of CVD morbidity [10, 14] or mortality [5], stroke morbidity [12, 24] or mortality [14], and all-cause mortality [5, 14].

For example, The Bronx longitudinal Aging Study [14] included community dwelling people without dementia or known terminal illness and with the ability to walk. The study showed, that the presence of ECG LVH by Minnesota code was an independent predictor of myocardial infarction and all-cause mortality. The Cardiovascular Study in the Elderly (CASTEL) compared people in the general population with and without ECG LVH at baseline and did not, however, report an increased risk of mortality during 7- [12] or 14 years of follow-up [10].

In hypertensive middle-aged and older patients, despite the potential the prognostic significance of different ECG LVH criteria for CVD morbidity [6-8, 11, 25-26] and mortality [7, 10, 25-27], coronary heart disease morbidity [7, 9] and mortality [26, 27], stroke morbidity [7, 9] and mortality [27], as well as mortality from all causes [7, 28]. Differences in baseline characteristics and methodology between studies [6-9, 11]

mean that the results from these studies are not fully comparable. For instance, for Sokolow-Lyon criterion, the cut point of 3.5 mV in the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS) [6], while the cut point was 3,8 mV in our study. The mean age of participants in the studies was lower than for the participants in HYVET. The history of CVD in the JATOS trial [6] and in the study by Aronow et al. [9] at baseline was more prevalent than in our study. The JATOS Trial [6] evaluated the effect of strict or mild antihypertensive BP control. The systolic hypertension in Europe Trial (SYST-EUR) [7] and the European Working Party on high blood pressure Trial (EWPHE) [11] compared the effect of antihypertensive drug treatment with placebo and they defined LVH using voltage as an increasing variable.

Contrary to our study, the risk of total mortality in elderly people with ECG LVH or increasing voltage has shown to have been increased in most studies [5, 7, 11, 14, 27, 28], although in the EWPHE study [11], the statistical significance of the risk disappeared after an adjustment for age. In these previous studies, the follow-up was longer and the mean age lower than in our study. Where SL- CV- or CP-LVH criteria were used, the prevalence of LVH was higher than in our study [5, 28]. Furthermore, in the population based Castel Study [12], the mean age of participant was 83 years, and no significant increase in the risk of all-cause mortality from LVH was found during the 7-year follow-up. It may be that our finding and that of the CASTEL study are due to attrition and younger excess mortality in hypertensive elderly people with LVH i.e. those who are at the highest risk die prior to reaching the age of 80. It also may be possible that with cardiac ischaemia or previous MIs, the ECG signs of LVH would get

less, thus resulting to reversal of the true relationship. Despite the anomalous failure to find a relationship between LVH and total mortality the relationships were consistent for other end-points.

In agreement with our study, ECG LVH in JATOS [6] and increasing voltage in the Syst-Eur Trial [7] predicted incident CVD events. The presence of CV- and CP -LVH predicted the risk of stroke, but the prediction was restricted to the female gender. The gender specific thresholds of CV- and CP-LVH criteria may not be valid in very old hypertensive men because they predicted only one out of 40 strokes in this gender.

Heart failure is common in older people. Hospitalization rates for heart failure increase steeply with increasing age and the condition is imposing a major burden on the health care system [29]. In older hypertensive people in the Syst-Eur Study, increasing ECG LVH voltage sum [7] predicted an increased risk of heart failure. In the population based Cardiovascular Health Study in the elderly, a higher ECG LVH mass was associated with an increased risk of heart failure [30]. People with heart failure requiring treatment with antihypertensive medication were excluded from the HYVET study, thus, the incidence of heart failure was lower, 56 (1.86 %) heart failure events during the follow-up (8.9 events/1000 patient years) compared with the heart failure incidence of 19.2 events/1000 patient years in a general population [29] and 48.4/1000 patient years [31] in Medicare beneficiaries aged 80-84 years..

Heart failure and frailty are also related [32]. Frail patients have decreased physiologic reserves, among other things loss of weight and muscle mass [32]. Male gender itself

and high BP are among independent risk factors for heart failure [30]. In our study, CP-LVH and CV-LVH were predictors of heart failure in men. In the Losartan Intervention for Endpoint (LIFE) Study, BMI was higher in people with CP-LVH [23], while in our study BMI was similar in men with and without both CP- and CV-LVH.

The LIFE Study showed that prolonged QRS duration (QRSd) was independently associated with increased cardiovascular and all-cause mortality [32]. In the Framingham Study [34] QRSd 100-119 ms predicted a 1.4-fold significant increase in the risk of incident heart failure compared with QRSd <110ms. In the Multi-Ethnic Study of Arteriosclerosis (MESA) [35], the risk of heart failure associated with longer QRS duration (101-110ms vs<100) was 1.9. These observed prognostic value of QRSd may be related not only to the increased left ventricular mass, but also in part to the fact that delayed conduction may be a marker of left ventricular structural abnormalities [36] or it is one of the factors increasing susceptibility to reentrant ventricular arrhythmias [33]. In our study, CP-LVH criterion only included the measurement of QRSd and it predicted an increase in the risk of CVD and stroke. CP-LVH was also a predictor of heart failure in men but not in women. After excluding people with BBB, the mean of QRSd was significantly longer in men than in women (83.1ms vs 81.5ms, $p<0.001$). At baseline, men with CP LVH had more prevalent CVD than women (13.5% vs 10.3% $p<0.004$), and such disease may have led to changes in the myocardial structure. The presence of LVH may be a sign of subclinical heart failure, especially for CP-LVH.

The presence of ECG LVH and increased left ventricular mass [35, 37] are risk factors for incident atrial fibrillation, which itself is a risk factor for embolic stroke [37]. In our study, atrial fibrillation was present in 187 patients, and 6.2% with atrial fibrillation suffered a stroke compared to 3% without it (p=0.03). After additional adjustments for atrial fibrillation, the increase in the HRs for stroke and other events in Tables 3 and 4 as well as for heart failure in men and women separately remained virtually the same.

The main strength of our study is the high number of hypertensive people aged 80 years or more. A limitation is the small number of some events, particularly in men (table 2). Also, HYVET patients were community dwelling and likely to be generally healthier than those in general population. Thus the results of our study may not be generalizable to a less healthy population. However as this age group is growing fast in Western countries, it is important to gain greater understanding of their CVD risk.

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The HYVET trial is registered with ClinicalTrials.gov number NCT00122811

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