Left ventricular hypertrophy and risk of fatal and non-fatal stroke. EUROSTROKE: a collaborative study among research centres in Europe

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Background: This study investigated the association between electrocardiographically assessed left ventricular hypertrophy (LVH) and fatal, non-fatal, haemorrhagic and ischaemic stroke in four European cohorts participating in EUROSTROKE.

Methods: EUROSTROKE is a collaborative project among ongoing European cohort studies to investigate differences in incidence of, and risk factors for, stroke between countries. EUROSTROKE is designed as a nested case-control study. For each stroke case, two controls were sampled. Strokes were classified according to MONICA criteria or reviewed by a panel of four neurologists. LVH was assessed according to the Minnesota code or the automated diagnostic MEANS classification system. For this analysis, data on LVH and stroke were available from cohorts in Cardiff (84 cases/200 controls), Kuopio (60/116), Rotterdam (114/334), and Novosibirsk (62/168). Results are adjusted for age and sex.

Results: LVH was associated with a twofold increased risk of stroke (odds ratio 2.1 (95% CI 1.3 to 3.5). The risk was particularly pronounced for fatal stroke (4.0 (95% CI 2.1 to 7.9)), whereas the risk was non-significantly increased for non-fatal stroke (1.5 (95% CI 0.8 to 2.7)). The increased risk was more pronounced in smokers: for total stroke 3.5 (95% CI 1.5 to 8.1) versus 1.6 (95% CI 0.8 to 3.1) in non-smokers. Adjustment for systolic blood pressure and body mass index attenuated the associations. LVH was not preferentially associated with a particular type of stroke, although the association with cerebral infarction was stronger.

Conclusion: This analysis of the EUROSTROKE project indicates that LVH assessed by electrocardiogram is a predictor of stroke. The association seems to be stronger for fatal stroke than for non-fatal stroke and is more pronounced in smokers.

METHODS
The rationale and design of EUROSTROKE have been described in detail elsewhere. In short, EUROSTROKE is a collaborative study among European research centres to investigate (1) the variation in incidence of fatal and non-fatal ischaemic and haemorrhagic stroke among populations in different European countries; (2) whether the observed differences in stroke incidence across countries can be explained by differences in prevalence of established cardiovascular risk factors; (3) the relative importance of smoking and some selected dietary factors (potassium intake, alcohol consumption), haemostatic disturbances (fibrinogen) and comorbidity (rheumatic heart disease, atrial fibrillation) compared with established risk factors as determinants of the occurrence of ischaemic and haemorrhagic stroke. The EUROSTROKE database is drawn from ongoing European population-based prospective follow up studies (cohorts) and is designed as a case-control study nested within these ongoing studies. For each stroke case, two controls were sampled. Controls were matched on day of baseline examination only. Apart from its objectives, the EUROSTROKE database allows for aetiological analyses looking into various risk factors for stroke. EUROSTROKE formally started on 1 January 1994. At present, data from four cohorts were available for analysis.

EUROSTROKE case review board
Stroke was defined as a clinical event of rapid onset consisting of neurological deficit lasting more than 24 hours unless death supervenes, or if is lasts less than 24 hours, an appropriate lesion to explain the deficit is seen in a brain image. The event
could not be directly caused by trauma to the brain, tumour, or infection. This definition included subjects presenting with signs and symptoms suggestive of a subarachnoid haemorrhage, an intracerebral haemorrhage, ischaemic cerebral infarction, and subjects with a transient ischaemic attack, provided neuroimaging has been performed. A case reviewing panel consisting of four neurologists classified stroke events occurring in EUROSTROKE based on the information that was obtainable such as patients history, results from a lumbar puncture, computed tomography or magnetic resonance images, findings from a necropsy report. Final codes from existing and operating registries, such as, for example, the FINMONICA registry were not reviewed separately, but used as coded. Based on the information present, the neurologist classified the event into first and recurrent stroke, and into subarachnoid haemorrhage, intracranial haemorrhage, intra- cerebral infarction, or unspecified stroke. In addition, the certainty of the diagnosis was assessed in definite, probable, possible, and no stroke. Events were classified by two neurologists; in case of disagreement a third arbitrated.

This analysis is restricted to definite and probable events. An incident stroke was considered to have occurred when (1) the event had led to a hospitalisation and the hospital discharge record indicated a diagnosis of a new stroke. The clinical diagnosis was based on signs and symptoms, and neuroimaging investigations during hospital stay (definite stroke); or (2) in case of no hospitalisation, signs and symptoms associated with the event obtained from the general practitioner’s records were highly suggestive of a stroke according to the neurologists (probable stroke) or (3) in case of out hospital death, when the general practitioner reported that the cause of death was a cerebrovascular accident and a cardiac cause was judged by the general practitioner to be highly unlikely (probable stroke).

Finland
The Finnish contribution to EUROSTROKE comes from the Kuopio Ischemic Heart Disease Risk Factor study, which is a population-based prospective cohort study comprised of an age stratified random sample of 2682 men aged 42, 48, 54 and 60 years. The baseline examination was performed between 1984 and 1989. Fatal and non-fatal stroke cases were collected through the national mortality statistics and the FINMONICA stroke registries. Stroke was defined according to FINMONICA criteria and definitions. Case ascertainment from the baseline examination to 1 January 1993 revealed 74 stroke cases. Controls subjects (n=148) were randomly drawn from the cohort that remained free from stroke during follow up.

The Netherlands
The Dutch contribution to EUROSTROKE comes from the Rotterdam Study, which is a population-based prospective follow up study among 7983 subjects, aged 55 years or over, living in the suburb of Ommoord in Rotterdam, the Netherlands. Baseline data were collected from March 1990 to July 1993. In the Rotterdam Study, information on incident fatal and non-fatal events is obtained from the general practitioners (GPs) working in the study district of Ommoord as described earlier. In short, the GPs involved report all possible cases of stroke to the Rotterdam research centre. Events are presented in coded information following the International Classification of Primary Care (ICPC). With respect to the vital status of the participants, information is obtained at regular intervals from the municipal authorities in Rotterdam and also death of a participant is reported. When an event or death has been reported, additional information is obtained by interviewing the GP on the query: “Do you suffer from diabetes mellitus?”. In the Rotterdam study diabetes mellitus was considered present when subjects used blood sugar lowering drugs.

Cardiovascular risk factors
Because EUROSTROKE is based on 10 ongoing cohort studies, information on cardiovascular risk factors in each of the participating centres was already collected before the formal start of the EUROSTROKE project. Whenever possible, an exhaustive attempt was made to further harmonise the collected information to make comparison across studies possible. Nevertheless, any baseline measurements could not be further standardised beyond the attempts done in each individual study.

In each of the centres information on smoking, alcohol consumption, and medical history was obtained by questionnaire. The subject’s smoking behaviour was categorised into current, former or never. Alcohol consumption was categorised into current drinkers and non-current drinkers (former and never). In addition, an estimate of grams of alcohol per day was obtained. Presence of diabetes mellitus was generally based on the query: “Do you suffer from diabetes mellitus?”. In the Rotterdam study diabetes mellitus was considered present when subjects used blood sugar lowering drugs.

Key points
- Stroke is a major cause of morbidity and mortality.
- ECG LVH can be easily assessed.
- LVH predicts stroke.
- Association seems more prominent in smokers.
whereas in the Novosibirsk study presence of diabetes mellitus was not evaluated for the entire cohort. Information on a history of stroke was obtained by direct questioning at baseline “Did you ever suffer from a stroke?”. A similar approach was taken for myocardial infarction. Presence of angina pectoris was based on either the cardiovascular Rose questionnaire or direct questioning.

In general, systolic and diastolic blood pressure were measured twice at one occasion in sitting position. In Cardiff, only one blood pressure measurement was performed. Height and weight were measured and body mass index (kg/m²) was calculated. In all four centres an electrocardiogram was made. In Cardiff, Kuopio and Novosibirsk, LVH was assessed according to the Minnesota classification system (codes 3.1, 3.3, 3.4). In Rotterdam, an automated diagnostic classification system of the Modular Electrocardiogram Analysis System (MEANS) was used in which LVH diagnosis was assessed on the parameters voltage, shape and repolarisation, as detailed elsewhere. Apart from Rotterdam, a fasting blood sample was taken for determination of serum lipids (total cholesterol, HDL cholesterol). For the present analysis hypertension was defined as a systolic blood pressure of 160 mm Hg or over, or a diastolic blood pressure of 95 mm Hg or over, or current use of blood pressure lowering drugs.

Data analysis

Complete data on both stroke and LVH were available for Cardiff (84 cases/200 controls), Kuopio (60 cases/116 controls), Rotterdam (114 cases/334 controls), and Novosibirsk (62 cases/168 controls).

The analyses were first performed for each centre separately. To identify potential confounding variables, cardiovascular risk factors that were related to stroke were examined using logistic regression models and to LVH using logistic regression analysis. Initially adjustments were made for age and sex, and subsequently for potential confounding cardiovascular risk factors.

An interaction term (LVH × centre) was used to study whether the association between LVH and stroke differed across the four centres (heterogeneity). Interaction term (LVH × sex) was used to evaluate whether the association differed between men and women. Similar analyses were performed in strata of smoking and hypertension. Results are presented as odds ratios, with their corresponding 95% confidence intervals (95% CI). Separate analyses were performed for total stroke, first ever stroke, fatal stroke (death within 28 days after onset), non-fatal stroke, and for haemorrhagic stroke and cerebral infarction.

In the analysis in which a history of diabetes mellitus was used, analyses were initially performed excluding data from Novosibirsk, because in this centre such data were not available. Additional analyses were performed in which history of diabetes was imputed for the Novosibirsk centre. The imputation was based on the prevalence observed in Cardiff and Kuopio combined, an estimate comparable to what has been reported for Novosibirsk area. A dummy variable (yes/no) for the imputation was added to the model. As the magnitude of findings did not differ between the two approaches only the latter is presented. The analyses have been performed using STATA version 4.0.

RESULTS

General characteristics of the study populations are given in table 1. Characteristics of the stroke events are presented in table 2. Of all strokes, 73% had been hospitalised. Neuroimaging (CT/MRI) had been performed in 55% of the cases. Among the fatal strokes, 26.2% were a haemorrhagic, 33.8% a cerebral infarctions and 40.0% could not be specified with the available information. The corresponding figures for non-fatal stroke were 9.6%, 80.4% and 10.0%, respectively. In analyses in which
LVH and risk of stroke

Figure 1 Left ventricular hypertrophy and risk of stroke, by centre. Results are adjusted for age and sex, when appropriate.

Table 3 The association of left ventricular hypertrophy and risk of stroke

<table>
<thead>
<tr>
<th></th>
<th>Model I</th>
<th>Model II</th>
<th>Model III</th>
<th>Model IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>All strokes</td>
<td>2.13 (1.29 to 3.50)</td>
<td>1.72 (1.02 to 2.89)</td>
<td>1.62 (0.93 to 2.81)</td>
<td>1.62 (0.43 to 2.81)</td>
</tr>
<tr>
<td>First ever</td>
<td>2.13 (1.27 to 3.56)</td>
<td>1.70 (0.99 to 2.92)</td>
<td>1.65 (0.95 to 2.87)</td>
<td>1.57 (0.89 to 2.78)</td>
</tr>
<tr>
<td>Fatal</td>
<td>4.02 (2.05 to 7.89)</td>
<td>3.14 (1.55 to 6.36)</td>
<td>2.93 (1.37 to 6.26)</td>
<td>2.76 (1.25 to 6.11)</td>
</tr>
<tr>
<td>Non-fatal</td>
<td>1.52 (0.84 to 2.76)</td>
<td>1.19 (0.64 to 2.23)</td>
<td>1.19 (0.64 to 2.24)</td>
<td>1.19 (0.63 to 2.28)</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>1.52 (0.45 to 5.10)</td>
<td>1.08 (0.30 to 3.86)</td>
<td>1.12 (0.31 to 4.10)</td>
<td>1.10 (0.29 to 4.19)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>1.67 (0.92 to 3.04)</td>
<td>1.34 (0.72 to 2.53)</td>
<td>1.34 (0.72 to 2.53)</td>
<td>1.35 (0.72 to 2.59)</td>
</tr>
<tr>
<td>Cerebral infarction*</td>
<td>2.21 (1.32 to 3.69)</td>
<td>1.82 (1.07 to 3.11)</td>
<td>1.70 (0.98 to 2.96)</td>
<td>1.74 (0.99 to 3.04)</td>
</tr>
</tbody>
</table>

Table 4 Stratified analysis of the association of LVH with stroke and cerebral infarction

<table>
<thead>
<tr>
<th></th>
<th>Cases/controls</th>
<th>Stroke</th>
<th>Cerebral infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (yes)</td>
<td>131/245</td>
<td>3.47 (1.49 to 8.08)</td>
<td>91/245</td>
</tr>
<tr>
<td>Smoking (no)</td>
<td>185/567</td>
<td>1.61 (0.84 to 3.11)</td>
<td>126/567</td>
</tr>
<tr>
<td>Hypertension (yes)</td>
<td>181/317</td>
<td>1.89 (1.00 to 3.58)</td>
<td>117/317</td>
</tr>
<tr>
<td>Hypertension (no)</td>
<td>139/501</td>
<td>2.07 (0.91 to 4.71)</td>
<td>103/501</td>
</tr>
<tr>
<td>Men</td>
<td>230/543</td>
<td>2.10 (1.12 to 3.88)</td>
<td>162/543</td>
</tr>
<tr>
<td>Women</td>
<td>90/275</td>
<td>2.23 (0.95 to 5.22)</td>
<td>58/275</td>
</tr>
</tbody>
</table>

Results are adjusted for age and sex, when appropriate.
prevalence of the exposure of interest (LVH), it may bias a true positive association towards a reduced odds ratio or a null finding. We have no means to evaluate whether this indeed did take place. Secondly, the association with fatal stroke may be biased towards a positive finding when in the assessment a large proportion of the stroke cases was misclassified—that is, had died from coronary heart disease rather than from stroke. Given the diagnostic procedures in the participating centres this is unlikely to have happened. Thirdly, it has been well established that the sensitivity of the ECG to detect LVH is limited. Data from the Framingham Heart Study indicated a sensitivity of 6.9% and a specificity of 98.8% compared with echocardiography as gold standard.26 The ultimate consequence of this notion is that most probably the reported associations under study are an underestimation of the “true” association; as misclassification occurred in both cases and controls, most probably in a random fashion. Alternatively, a recent paper indicated that ECG-LVH and LVH assessed by echocardiography carry to some extent different prognostic information.27 Finally, we acknowledge that the diagnoses of LVH have been made using different approaches. We used whatever approach had been taken in the individual cohort. Some may have a stronger prognostic implication. However, in all cohorts, ECG-LVH was related to risk of stroke without showing differences in associations across the cohorts (fig 1). Strengths of this study are the fairly large number of well diagnosed and classified events for both men and women, presence of data on a large number of potential confounders, a wide age range, and risk factors assessment before the occurrence of the stroke event.

Several studies have evaluated the association between LVH and stroke (table 5). Direct comparison between studies is hampered by differences in population distribution, in selection of population, in methods of assessing LVH, in stroke distribution (fatal/non-fatal, type of stroke) and in adjustment for several potential confounding variables. In general, an increased stroke risk was found among subjects with LVH. In reports of the Framingham Heart study, with different samples from the populations and duration of follow up, LVH was associated with a sixfold increased risk of stroke among middle aged men and women 7 and with a 2.3-fold increased risk in the elderly. Results from Dunn and coworkers in the United Kingdom showed that among hypertensives the relative contribution of LVH to death from stroke decreased with age. In the Copenhagen City Heart Study in Denmark weaker than in the Framingham Heart Study, associations were found for men and no relation was seen for women (table 5). Few studies, however, have distinguished between fatal and non-fatal stroke. In a community-based cohort study among 459 subjects aged 75 to 85 years, who were followed up for 10 years, baseline LVH was associated with a threefold increased risk of fatal stroke (p=0.07), whereas a non-significant increased risk of non-fatal stroke was found (odds ratio 1.1).31 The analyses were, however, based on a limited number of fatal (n=15) and non-fatal (n=20) events. The present EUROSTROKE analysis confirms the increased risk of stroke associated with LVH. In addition, our findings point towards a stronger association of LVH with fatal stroke than with non-fatal stroke, a tendency observed for cerebral infarction only. In this analysis, the increased risk was more pronounced in smokers than in non-smokers. As none of the studies reported such a finding, future studies are needed to confirm this potential effect modification of smoking in stroke risk. It has not been clear by which mechanism smoking increases the risk of stroke. This new finding that LVH may be a condition required for stroke to occur in smokers may suggest that the underlying mechanism is related to either arrhythmias32-33 or other cardiac events.

Several hypotheses have been given to explain why LVH predisposes for coronary heart disease and death. Yet, the mechanisms for stroke may be less clear. Firstly, LVH may be a marker for presence of longstanding increased blood pressure and as such it may reflect cardiovascular end-organ damage, which in itself is associated with increased risk of stroke. Our finding that when differences in blood pressure were taken into account the association between LVH and stroke was reduced, favours this view. Secondly, LVH has been implicated as an important factor in triggering cardiac arrhythmias,34-36 which may increase the risk of stroke, in particular ischaemic stroke.

Increased blood pressure has consistently been reported as a major determinant of LVH. The increased stroke risk of LVH...
and among smokers further supports the large potential for prevention of stroke by lowering of blood pressure and discouraging starting and encouraging quitting smoking.

In conclusion, this analysis of the EUROSTROKE project indicates that LVH assessed by electrocardiogram is a powerful predictor of stroke. The association seems to be stronger for fatal stroke than for non-fatal stroke and is more pronounced in smokers.

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