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CHA_2DS_2-VASc score, left atrial size and atrial fibrillation as stroke risk factors in the Tromsø Study

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To cite: Tiwari S, Løchen M-L, Jacobsen BK, *et al*. CHA_2DS_2-VASc score, left atrial size and atrial fibrillation as stroke risk factors in the Tromsø Study. *Open Heart* 2016;**3**:e000439. doi:10.1136/openhrt-2016-000439

▸ Additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/openhrt-2016-000439).

Received 18 March 2016
Revised 29 June 2016
Accepted 30 June 2016

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ABSTRACT

Objective: CHA_2DS_2-VASc score, left atrial (LA) size and atrial fibrillation (AF) have individually been associated with stroke risk. Our aim was to investigate the predictive ability of combinations of these factors for the odds of incident stroke in a population-based cohort study.

Methods: We followed 2844 participants from the Tromsø Study from 1994 to 2012. Information on LA size and CHA_2DS_2-VASc score (age, sex, congestive heart failure, hypertension, vascular disease, stroke and diabetes) were obtained at baseline. AF status was recorded from medical records. The outcome measure was all strokes. The association between covariates and stroke was investigated by means of multivariate logistic regression analysis.

Results: A total of 325 participants (45% women, mean age at baseline 59.3 years) had a stroke. Incidence rates for stroke were 6.4 in women and 8.4 in men per 1000 person-years. Participants with CHA_2DS_2-VASc ≥1 and LA size <2.8 had ~4 times (95% CI 2.6 to 5.3) increased odds of stroke, whereas participants with CHA_2DS_2-VASc ≥1 and LA size ≥2.8 had ~9 times (95% CI 5.3 to 16.4) increased odds of stroke, compared with participants with CHA_2DS_2-VASc score 0, irrespective of AF status. Adjustment for significant covariates had minimal impact on the OR estimates.

Conclusions: Combining CHA_2DS_2-VASc score ≥1 and enlarged LA size identified participants with high odds of stroke regardless of AF status.

KEY QUESTIONS

What is already known about this subject?

- CHA_2DS_2-VASc score, left atrial size (LA) and atrial fibrillation (AF) have previously been shown to be associated with stroke risk for each factor separately.

What does this study add?

- This study provides long-term results for the association between combinations of CHA_2DS_2-VASc score, LA and AF with stroke risk in a large general cohort. Participants with higher CHA_2DS_2-VASc score and enlarged LA size had approximately nine times increased odds of stroke irrespective of AF status.

How might this impact on clinical practice?

- Our study may indicate that Holter monitoring in people with no known AF, but with increased risk of stroke due to high CHA_2DS_2-VASc score and risk of AF, may be important. In addition, the risk factors that increase the CHA_2DS_2-VASc score as well as AF risk factors should be monitored and managed properly.

INTRODUCTION

Ischaemic stroke is the most devastating complication resulting from atrial fibrillation (AF), and AF-related strokes are more severe.[1]

The CHA_2DS_2-VASc score estimates stroke risk in non-anticoagulated patients with AF.[2] It combines common risk factors for stroke such as congestive heart failure, hypertension, age, diabetes, previous stroke/transient ischaemic attack (TIA), vascular disease and sex. A previous prospective study investigated the CHA_2DS_2-VASc score among non-AF high-risk patients, and concluded that the score strongly predicts new onset of ischaemic stroke, myocardial infarction, cardiovascular death and combined cardiovascular end points, including congestive heart failure.[3] A study with a mean follow-up of 1.1 years using continuous monitoring in stroke-free patients without previously diagnosed AF and elevated stroke risk found that 30% of the patients had AF.[4]

Left atrial (LA) size is associated with increased cardiovascular disease risk, including AF and stroke.[5–9]

How to combine these factors to identify stroke risk has been unclear, as most of the studies have assessed the association with stroke risk for each factor separately. Our aim was to investigate the predictive ability of combinations of CHA_2DS_2-VASc score, LA size and AF status for odds of incident stroke in the population-based Tromsø Study with 18 years of follow-up.

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METHODS

Study population

The Tromsø Study is a prospective cohort study conducted in the municipality of Tromsø, Norway.[10] It was initiated in 1974 with the emphasis on epidemiology and surveillance of modifiable risk factors for cardiovascular diseases. In the fourth survey (Tromsø 4) in 1994–1995, all inhabitants 25 years or older were invited and 27 158 persons (77% of the eligible population) participated. Among them, all individuals aged 55–74 years and 5–10% random samples of the other age groups (aged 25–54 and 75–84 years) were invited for a second visit, which included extensive examinations. The selection of participants eligible for the second visit was based on economical and scientific reasons and was performed before they attended the first visit. The 6902 individuals who attended the second visit were randomly allocated based on simple randomisation with computer-generated random numbers to one of two lines of examination, one of which comprised echocardiographic examination.[11] The attendance rate was 88%.[12] Figure 1 shows that after exclusions, 2844 participants were included. All participants have given informed consent, the Tromsø Study complies with the Declaration of Helsinki and has been approved by the Regional Committee for Medical and Health Research Ethics, the Data Inspectorate and the Norwegian Directorate of Health.

Baseline characteristics

Questionnaire data were used to define predictor variables on diabetes (yes/no), antihypertensive medication use (current/previous/never), smoking (current/previous/never), palpitations (yes/no) and prevalent coronary heart disease (CHD) (yes/no). Prevalent CHD was defined as self-reported previous myocardial infarction. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and body surface area (BSA) was calculated by Du Bois formula (BSA=(Weight$^{0.425}$×Height$^{0.725}$)×0.007184). Blood pressure and heart rate were recorded three times with 1 min intervals after 2 min resting, by trained technicians using an automatic device (Dina map Vital Signs Monitor 1846, Criticon). For the analysis, the mean from the second and third readings was used. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or current antihypertensive medication use.

Plasma creatinine was analysed by a modified Jaffe reaction, but since creatinine-based estimation of glomerular filtration rate (GFR) is better validated for enzymatic creatinine measurements, 111 plasma samples from the 1994/1995 survey were thawed and reanalysed with an enzymatic method (Modular P/Roche). Values were fitted to a linear regression model, and recalibrated creatinine values were calculated for all participants. Estimated GFR was calculated according to the CKD-EPI formula[13] and renal failure was defined as having GFR <60 mL/min/1.73 m^2. Non-fasting total cholesterol was analysed by enzymatic methods with commercial kits and serum high-density lipoprotein (HDL) cholesterol was measured after the precipitation of lower-density lipoprotein with heparin and manganese chloride. All blood sample analyses were performed at the Department of Clinical Chemistry, University Hospital of North Norway.

We calculated CHA_2DS_2-VASc score, which aids in identifying additional stroke risk factors for patients with AF. To calculate the score, the variables used were age (<65:0 for both sexes, 65–74: +1, ≥75: +2), sex (female ≥65: +1), history of congestive heart failure (+1), hypertension (+1), stroke/TIA/thromboembolism (+2), vascular disease (+1) and diabetes mellitus (+1).[14 15]

Echocardiography

Echocardiographic examinations were performed on all participants by two expert cardiologists using a VingMED CFM 750 (VingMED Sound A/S, Horten, Norway) with a combined 3.25 MHz mechanical and 2.5 MHz Doppler probe. The examinations were performed using the standard apical and parasternal long-axis and short-axis views. Standard two-dimensional guided M-mode registrations of anteroposterior LA size, internal dimensions of the left ventricle and wall thickness of the septum and posterior wall were made from leading edge to leading edge convention.[16] In this study, LA size was indexed by BSA. Heart failure was defined as left ventricular ejection fraction <0.5.

Atrial fibrillation

All participants were followed with respect to incident clinical AF documented by an ECG before or until date of stroke. The national personal identification number of participants was linked to the diagnosis registry at the University Hospital of North Norway (outpatient clinic included), using the following diagnostic codes: ICD-9 codes 427.0–427.99 and ICD-10 codes I47 and I48. In addition, we performed manual text search for participants without an arrhythmia diagnosis but with a diagnosis of cerebrovascular or cardiovascular events. An independent committee adjudicated all events. Types of AF were categorised into paroxysmal (paroxysmal or persistent), permanent or unclassified. We combined paroxysmal and persistent AF because it was difficult to make absolute decisions about the correct type. All AF types were merged in the multivariable analysis. Participants with transient AF occurring only during an acute myocardial infarction, in connection with cardiac surgery, or in the last 7 days of life, were not classified as having AF. The adjudication of AF is described in detail previously.[6 17]

Reproducibility

A reproducibility study of the echocardiographic data was performed in a subsample of 58 participants by 2 cardiologists. All participants were examined twice with 1-week interval by both observers. Data concerning the

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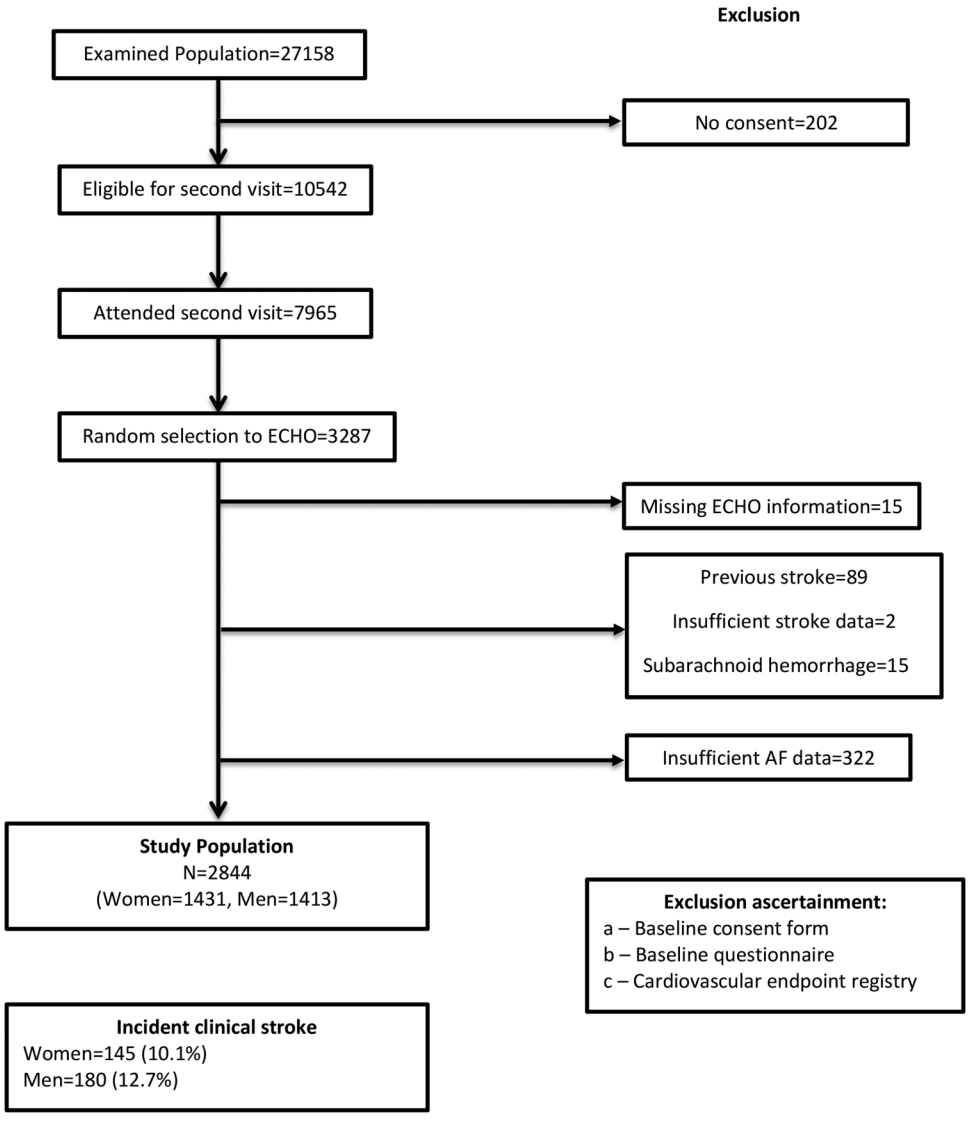

Figure 1 Study population, the Tromsø Study 1994–2012.

reproducibility of the echocardiography are given elsewhere.[12] This study shows that the validity of the echocardiographic measurements is good due to the use of a representative sample from a general population with a large age-span and a high attendance rate. The reliability of measurements from independently recorded heartbeats is good, and the reliability is further strengthened by 83% of the examinations being performed by one observer. There was no systematic measurement variability invalidating the data.

Classification of LA size

We indexed the LA size by BSA and categorised into two groups as normal or moderately enlarged (<2.8 cm/m^2) and severely enlarged (≥2.8 cm/m^2) left atria.

Classification of combined analytical groups

We combined CHA_2DS_2-VASc score, LA size and AF together and made the following groups:

Group 1=CHA_2DS_2-VASc score=0;
Group 2=CHA_2DS_2-VASc score ≥1 and normal or moderately enlarged LA (<2.8 cm/m^2) and AF;
Group 3=CHA_2DS_2-VASc score ≥1 and normal or moderately enlarged LA (<2.8 cm/m^2) and no AF;
Group 4=CHA_2DS_2-VASc score ≥1 and severely enlarged LA (≥2.8 cm/m^2) and AF;
Group 5=CHA_2DS_2-VASc score ≥1 and severely enlarged LA (≥2.8 cm/m^2) and no AF.

End points

We followed all participants who attended Tromsø 4 for incident cases of stroke, as described previously.[18] With the exclusion of subarachnoid haemorrhage, we combined ischaemic stroke, haemorrhagic stroke and unclassified stroke as one common end point. The combined stroke end point was preferred as the result for ischaemic stroke only and the combined end point were similar, but with narrower CIs for combined stroke.

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Norway has a unique personal identification system that allows exact matching of population register data. The identification number of participants of the 1994–1995 survey was linked to the diagnosis registry at the University Hospital of North Norway (the outpatient clinic included), the only hospital in this area, and to the National Causes of Death Registry at Statistics Norway. Cases of possible non-fatal and fatal stroke were identified by a broad search for the following diagnosis codes of cerebrovascular disease: International Classification of Diseases (ICD) 8 and 9 codes 430–438, and ICD 10 codes I60–I69 (cerebrovascular diseases). In addition, systematic manual and electronic text searches were performed in the medical records for patients with ICD 8 and 9 diagnosis codes 410–414 and 798–799, and ICD 10 codes I20–I25 and R96, R98 and R99. Adjudication of hospitalised and out-of-hospital events was performed by an independent end point committee based on data from hospital and out-of-hospital medical records, autopsy records and death certificates. For the computation of stroke incidence (excluding subarachnoid haemorrhage), we followed 2844 participants (figure 1) until the date of first stroke or date of censoring due to death, migration or end of follow-up at 31 December 2012, whichever came first. Those who had died or emigrated from Tromsø during follow-up were identified through the Population Register of Norway.

Statistical analysis

We present the characteristics of the study population with and without stroke as means and SDs for continuous variables and proportions of group total for categorical variables. Differences between groups were assessed by t-test, χ^2 test and Fisher's exact test. To estimate ORs for stroke, we used both age-adjusted and multivariable logistic regression analysis adjusted for smoking, total/HDL cholesterol ratio, BMI, GFR and palpitations. The variables that were included in the final multivariable model were chosen based on known risk factors for stroke or variables significant in our univariable analysis. We have chosen logistic and not Cox proportional hazard regression analysis because the covariate AF is taken from the end point registry without knowledge of when the AF started, although both methods gave similar results. We tested for interactions between LA size and AF and sex, and the p values were 0.162 and 0.004, respectively. We calculated the c-statistic of the model to predict its clinical usefulness for distinguishing high-risk from low-risk participants. In addition, Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) were calculated to quantify improvement in model performance. A two-sided p value of <0.05 was considered statistically significant. Statistical analysis was performed using STATA V.12 (Stata, College Station, Texas, USA). The NRI and IDI were calculated with user written program by Liisa Byberg.

RESULTS

Incident stroke was identified in 145 women (10.1%) and 180 men (12.7%) (figure 1) during a mean follow-up of 15.5 years (44 147 person-years). The incidence rate (per 1000 person-years) of stroke was 6.4 in women and 8.4 in men. Table 1 shows the baseline characteristics for participants with and without stroke. Participants who developed stroke were significantly older, had higher blood pressure, prevalence of CHD, diabetes and used antihypertensive medication. They also had higher BMI and total/HDL cholesterol ratio (not statistically significant in men) and renal failure (not statistically significant in women). There were no significant differences in smoking and palpitations.

Table 2 shows CHA_2DS_2-VASc score, LA size and AF status, for participants with and without stroke. Participants with stroke had increasing CHA_2DS_2-VASc score, larger LA size and higher prevalence of AF (not statistically significant in men).

The incidence rate of stroke increased with increase in CHA_2DS_2-VASc score for both sexes and the increase with increasing score was much steeper in those with no AF (see online supplementary table S1).

Table 3 shows the OR for stroke according to CHA_2DS_2-VASc score, indexed LA size and AF. The CHA_2DS_2-VASc and AF status were significant predictors of subsequent stroke. For AF, the increased risk was related to the first half of the follow-up period. Compared with participants in the reference group (CHA_2DS_2-VASc=0), participants with CHA_2DS_2-VASc ≥1 and LA size <2.8 had ~4 times (95% CI 2.6 to 5.3) increased odds of stroke, irrespectively of the presence of prevalent AF. Similarly, participants with CHA_2DS_2-VASc ≥1 and LA size ≥2.8 had ~9 times (95% CI 5.3 to 16.4) times increased odds of stroke. Those with CHA_2DS_2-VASc ≥1, LA size ≥2.8 and no AF (group 5) had the highest odds, increasing from 12.1 (95% CI 6.3 to 23.2) to 12.5 (95% CI 6.4 to 24.3) after adjustment for significant covariates, but was not significantly greater than for those with AF. This conclusion was unchanged when sex-specific analysis was conducted. Including eight participants with AF in the terminal 7 days of life, where three died from stroke, did not change our results. Adding palpitations to the multivariable model caused no changes in the point estimates. In addition to CHA_2DS_2-VASc score and AF status, total/HDL cholesterol ratio and low GFR were significant risk factors. Men had higher overall risk, but there was no sex interaction for the risk factors. The model with CHA_2DS_2-VASc, LA size groups and AF status and the other predictor variables together (Model 2) gave better prediction than a model with the predefined groups only (Model 1) (Harrell's c=0.68 vs 0.66, p=0.003). The unadjusted ORs for stroke according to the three different components of the combined analytical groups group are given in online supplementary table S2.

For the full model, NRI was 5.8%, p=0.01 and IDI was 0.7%, p=0.001. Adding only AF status and LA size to

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Table 1 Unadjusted baseline characteristics of women and men by future stroke status

Baseline characteristics	Women			Men		
	Stroke (n=145)	No stroke (n=1286)	p Value	Stroke (n=180)	No stroke (n=1233)	p Value
Age (years)	66.7 (6.3)	59.1 (10.6)	<0.0001	63.6 (7.1)	58.0 (10.6)	<0.0001
Systolic blood pressure (mm Hg)	157.1 (26.9)	142.0 (23.0)	<0.0001	153.0 (22.4)	142.9 (19.3)	<0.0001
Diastolic blood pressure (mm Hg)	86.6 (15.2)	80.7 (12.3)	<0.0001	88.7 (13.1)	84.1 (11.4)	<0.0001
Body mass index (kg/m^2)	27.2 (4.7)	25.8 (4.4)	0.0003	26.5 (3.4)	26.1 (3.3)	0.1054
Total cholesterol (mmol/L)	7.20 (1.10)	6.82 (1.33)	0.0010	6.62 (1.18)	6.52 (1.21)	0.2924
HDL cholesterol (mmol/L)	1.61 (0.41)	1.69 (0.42)	0.0367	1.37 (0.40)	1.41 (0.39)	0.3038
Total/HDL cholesterol ratio	4.72 (1.43)	4.28 (1.40)	0.0003	5.17 (1.73)	4.96 (1.58)	0.0893
Smoking, % (n)			0.736			0.995
No smoking	46.2 (67)	45.7 (587)		20.0 (36)	20.0 (247)	
Previous smoking	22.1 (32)	24.8 (319)		45.6 (82)	45.2 (557)	
Current smoking	31.7 (46)	29.6 (380)		34.4 (62)	34.8 (429)	
Hypertension, % (n)	73.8 (107)	52.5 (675)	<0.0001	77.8 (140)	56.5 (696)	<0.0001
Current antihypertensive treatment, % (n)	20.8 (30)	11.5 (148)	<0.0001	19.1 (34)	10.5 (129)	<0.0001
Coronary heart disease, % (n)	5.6 (8)	2.6 (33)	0.06	15.7 (28)	6.5 (80)	<0.0001
Heart failure, % (n)	0 (0)	0.4 (4)		6.5 (9)	1.3 (13)	<0.0001
Palpitations, % (n)	37.6 (41)	30.2 (330)	0.110	18.5 (29)	18.7 (213)	0.953
Diabetes, % (n)	6.0 (8)	1.9 (24)	0.011	6.2 (11)	2.1 (26)	0.002
HbA1c (%)	5.6 (1.0)	5.4 (0.7)	0.0060	5.6 (0.9)	5.4 (0.6)	<0.0001
GFR <60, % (n)	2.8 (4)	1.5 (19)	0.280	3.4 (6)	0.9 (11)	0.014

Mean (SD) or percentage (number of participants). The Tromsø Study 1994–1995. GFR, glomerular filtration rate; HDL, high-density lipoprotein.

Table 2 Unadjusted CHA_2DS_2-VASc score, indexed left atrial size and atrial fibrillation status in women and men according to future stroke status

	Women			Men		
	Stroke (n=145)	No stroke (n=1286)	p Value	Stroke (n=180)	No stroke (n=1233)	p Value
CHA_2DS_2-VASc score, % (n)						
0	13.8 (20)	38.7 (497)	<0.0001	10.6 (19)	34.1 (421)	<0.0001
1	17.2 (25)	26.4 (340)		40.6 (73)	41.9 (517)	
2	11.7 (17)	8.9 (115)		36.7 (66)	19.2 (237)	
3	44.1 (64)	23.1 (297)		8.3 (15)	4.3 (53)	
4 or more	13.1 (19)	2.9 (37)		3.9 (7)	0.4 (5)	
LA size indexed by BSA (cm/m^2)						
<2.2	37.0 (50)	53.1 (658)	<0.0001	54.1 (92)	63.6 (762)	0.014
2.2–2.79	47.4 (64)	42.3 (524)		41.8 (71)	34.8 (417)	
≥2.8	15.6 (21)	4.7 (58)		4.1 (7)	1.7 (20)	
Atrial fibrillation (AF)						
AF, % (n)	26.9 (39)	12.5 (161)	<0.0001	19.4 (35)	17.7 (218)	0.564
AF before or until up to date of stroke, % (n)						
No AF	73.1 (106)	87.5 (1125)	<0.0001	80.6 (145)	82.3 (1015)	0.329
Paroxysmal/persistent AF	12.4 (18)	5.5 (71)		6.7 (12)	8.0 (99)	
Permanent AF	14.5 (21)	6.6 (85)		12.8 (23)	9.0 (111)	
Unclassified AF	0	0.4 (5)		0	0.7 (8)	
AF after stroke, % (n)						
No AF	81.1 (86)			84.8 (123)		
Paroxysmal/persistent AF	10.4 (11)			6.9 (10)		
Permanent AF	8.5 (9)			7.6 (11)		
Unclassified AF	0			0.7 (1)		

Percentage (number of participants). The Tromsø Study 1994–1995.

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Table 3 OR (95% CI) for stroke according to CHA_2DS_2-VASc score, indexed left atrial size and atrial fibrillation combined: the Tromsø Study 1994–2012

	Model 1	Model 2
CHA_2DS_2-VASc and LA size		
CHA_2DS_2-VASc=0, Group 1 (n=957)	1 (Ref.)	1 (Ref.)
CHA_2DS_2-VASc ≥1		
LA size <2.8, Group 2 (n=1713)	3.9 (2.7 to 5.5)	3.7 (2.6 to 5.3)
LA size ≥2.8, Group 3 (n=96)	9.7 (5.6 to 16.7)	9.4 (5.3 to 16.4)
Atrial fibrillation (AF)*		
No AF, Group 1 (n=2391)	1 (Ref.)	1 (Ref.)
Late AF, Group 2 (n=266)	1.0 (0.7 to 1.6)	1.0 (0.6 to 1.5)
Early AF, Group 3 (n=142)	2.8 (1.9 to 4.2)	2.6 (1.7 to 3.9)
Previous AF, Group 4 (n=45)	2.4 (1.2 to 5.0)	2.2 (1.1 to 4.5)
Combined analytical group		
CHA_2DS_2-VASc=0, Group 1 (n=957)	1 (Ref.)	1 (Ref.)
CHA_2DS_2-VASc ≥1 and LA size <2.8		
AF, Group 2 (n=331)	5.0 (3.3 to 7.7)	4.9 (3.1 to 7.6)
No AF, Group 3 (n=1382)	3.6 (2.5 to 5.1)	3.5 (2.4 to 5.0)
CHA_2DS_2-VASc ≥1 and LA size ≥2.8		
AF, Group 4 (n=43)	7.1 (3.3 to 15.5)	6.3 (2.8 to 14.3)
No AF, Group 5 (n=53)	12.1 (6.3 to 23.2)	12.5 (6.4 to 24.3)
Smoking (no/yes)	1.1 (0.8 to 1.4)	
Total/HDL cholesterol ratio	1.1 (1.1 to 1.2)	
BMI (kg/m^2)	1.1 (1.02 to 1.1)	
GFR <60 mL/min/1.73 m^2	2.6 (1.3 to 5.5)	

Model 1: Unadjusted.
Model 2: Adjusted for smoking, Total/HDL cholesterol ratio, BMI, GFR.
*AF, any diagnosis of AF before or until up to date of stroke; early AF, AF diagnosed from 1994 to 2002; Late AF, AF diagnosed from 2003 to 2012; previous AF, AF at baseline.

CHA_2DS_2-VASc has an NRI and IDI of 2.6%, p=0.21 and 0.2%, p=0.08, respectively.

Among the participants with CHA_2DS_2-VASc score ≥1 without AF before stroke, 23% reported palpitations at baseline. Palpitations were not an independent predictor of stroke and the incidence was similar in those with and without palpitations (14% vs 13%) in this group.

DISCUSSION

CHA_2DS_2-VASc score, LA size, AF status and stroke risk

We found that adding LA size to elevated CHA_2DS_2-VASc score gave additional stratification of stroke risk irrespective of AF status. To the best of our knowledge, this is a novel finding.

The highest stroke risk was among participants with high CHA_2DS_2-VASc score and severely enlarged LA size. Self-reported palpitations did not independently predict stroke risk, despite an increased risk of AF[17] with enlarged LA size.[6]

Several studies have shown an association with stroke for CHA_2DS_2-VASc score and LA size. A 5-year follow-up study of high-risk patients found that CHA_2DS_2-VASc score strongly predicted ischaemic stroke among non-AF patients.[3] A prospective study among patients with heart failure found that CHA_2DS_2-VASc score was associated with the risk of ischaemic stroke with or without AF.[19] Another study on LA dimension and stroke risk in a Chinese population without AF with long follow-up found an association between increased LA size and incident stroke in women, but not in men.[7] However, in the Framingham Heart Study, LA enlargement was a significant predictor of stroke in men only after multivariable adjustment also adjusted for AF.[8] We did not confirm any sex interactions with LA size. We found a higher incidence of stroke in men compared with women, which is in line with previous findings from the Tromsø Study.[18]

There is an ongoing discussion on how to manage intermediate-risk AF patients with one additional risk factor of the CHA_2DS_2-VASc score beyond sex.[20–22] Evidence from two large studies suggested that anticoagulation should be considered in these patients and that the risk factors carried various risk with age 65–74 years associated with the highest stroke rate. Our study did not have enough power to further elucidate this matter.

Incidence of stroke among AF patients

We found that the incidence of stroke was 23.3% among those with ever-diagnosed AF. On the other hand, among patients who had stroke, 22.8% had diagnosed AF before the stroke and 12.9% had AF diagnosed after stroke. This is similar to a cross-sectional study of patients in nationwide Swedish health registers with a 5-year inclusion period. They found that 22.1% of

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ischaemic stroke patients had previously diagnosed AF at the time of stroke and 8.1% were diagnosed after the stroke, leaving around 30% of patients who had stroke with AF as likely contributing cause.[23]

High CHA_2DS_2-VASc score and undiagnosed AF

We found that even among those with no known AF prior to stroke, the CHA_2DS_2-VASc score was a strong predictor of stroke and about 13% developed AF after stroke. In a cross-sectional study, the likelihood of AF among patients with stroke was directly correlated to the CHA_2DS_2-VASc score.[23] We have identified a group of participants with high risk of stroke and no AF, and we believe that Holter monitoring might be valuable in the follow-up of these individuals as they have an increased risk of AF. We assume the increased stroke risk in participants without AF probably was due to undiagnosed paroxysmal and/or persistent AF. In addition, the risk factors that increase the CHA_2DS_2-VASc score as well as AF risk factors should be monitored and managed properly.

Strengths

The study was performed in a large population-based cohort of both sexes, with a high attendance rate and a long follow-up. Another strength was the thorough case validation and search methods. The hospital discharge list may be incomplete, and we found some people who were not registered with an AF diagnosis, but where ECG or medical texts documented AF. The reproducibility study of the echocardiographic data collection gave coefficients of variation similar to other studies and have been presented in detail previously.[12] There was no systematic measurement variability invalidating the data in this reproducibility study.

Limitations

Stroke information was collected through linkage to the hospital diagnosis registry and the National causes of Death Register at Statistics Norway; this could have led to underestimation of non-fatal strokes, if they were not referred to hospital. Although a detailed search method was used, there may still be individuals with undiagnosed AF. Participants with asymptomatic or paroxysmal AF often fail to get their arrhythmia documented. We included only participants having hospital-diagnosed AF before stroke, and any AF only recorded by the patient's general practitioner were missed. The Tromsø Study estimated LA size by M-mode diameter measurement. As LA size is best evaluated by estimation of volume, our OR estimates are probably attenuated. The external validity refers to a Caucasian population, and may not be generalisable to other groups.

CONCLUSIONS

Our study concludes that a combination of CHA_2DS_2-VASc score ≥1 and enlarged LA size is an important risk factor for stroke irrespective of AF status.

Correction notice This paper has been updated since it published Online First. In the methods section, references to CHA_2DS_2 have been updated to CHA_2DS_2-VASc.

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Acknowledgements An abstract of this paper was presented as a poster presentation at The ESC (European Society of Cardiology) Congress in Rome, Italy, in 2016.

Contributors ST contributes to data analysis and writing of manuscript. M-LL contributes to conception and design of study, data collection and interpretation and revision of manuscript. BKJ contributes to statistical support, data interpretation and revision of manuscript. LAH contributes to data interpretation and revision of manuscript. AN contributes to data collection and interpretation and revision of manuscript. IN contributes to data collection and interpretation and revision of manuscript. EBM contributes to data collection and interpretation and revision of manuscript. HS contributes to conception and design of study, data collection and interpretation and revision of manuscript.

Funding Sweta Tiwari receives a PhD Fellowship from UiT The Arctic University of Norway.

Competing interests None declared.

Ethics approval Regional Committee for Medical and Health Research Ethics, the Data Inspectorate and the Norwegian Directorate of Health.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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REFERENCES

1. Ahmad Y, Lip GY, Lane DA. Recent developments in understanding epidemiology and risk determinants of atrial fibrillation as a cause of stroke. *Can J Cardiol* 2013;29(7 Suppl):S4–13.
2. Lip GY, Nieuwlaat R, Pisters R, *et al*. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;137:263–72.
3. Chan YH, Yiu KH, Lau KK, *et al*. The $CHADS_2$ and CHA_2DS_2-VASc scores predict adverse vascular function, ischemic stroke and cardiovascular death in high-risk patients without atrial fibrillation: role of incorporating PR prolongation. *Atherosclerosis* 2014;237:504–13.
4. Ziegler PD, Glotzer TV, Daoud EG, *et al*. Detection of previously undiagnosed atrial fibrillation in patients with stroke risk factors and usefulness of continuous monitoring in primary stroke prevention. *Am J Cardiol* 2012;110:1309–14.
5. Bangalore S, Yao SS, Chaudhry FA. Role of left atrial size in risk stratification and prognosis of patients undergoing stress echocardiography. *J Am Coll Cardiol* 2007;50:1254–62.
6. Tiwari S, Schirmer H, Jacobsen BK, *et al*. Association between diastolic dysfunction and future atrial fibrillation in the Tromsø Study from 1994 to 2010. *Heart* 2015;101:1302–8.
7. Lai CL, Chien KL, Hsu HC, *et al*. Left atrial dimension and risk of stroke in women without atrial fibrillation: the Chin-Shan Community Cardiovascular Cohort study. *Echocardiography* 2011;28:1054–60.
8. Benjamin EJ, D'Agostino RB, Belanger AJ, *et al*. Left atrial size and the risk of stroke and death. The Framingham Heart Study. *Circulation* 1995;92:835–41.
9. Gerdts E, Wachtell K, Omvik P, *et al*. Left atrial size and risk of major cardiovascular events during antihypertensive treatment: losartan intervention for endpoint reduction in hypertension trial. *Hypertension* 2007;49:311–16.

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10. Jacobsen BK, Eggen AE, Mathiesen EB, *et al*. Cohort profile: the Tromsø Study. *Int J Epidemiol* 2012;41:961–7.
11. Lindekleiv H, Løchen ML, Mathiesen EB, *et al*. Echocardiographic screening of the general population and long-term survival: a randomized clinical study. *JAMA Intern Med* 2013;173:1592–8.
12. Schirmer H, Lunde P, Rasmussen K. Mitral flow derived Doppler indices of left ventricular diastolic function in a general population; the Tromsø Study. *Eur Heart J* 2000;21:1376–86.
13. Levey AS, Stevens LA, Schmid CH, *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–12.
14. January CT, Wann LS, Alpert JS, *et al*. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;64:e1–76.
15. Camm AJ, Lip GY, De Caterina R, *et al*. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;33:2719–47.
16. O'Rourke RA, Hanrath P, Henry WN, *et al*. Report of the Joint International Society and Federation of Cardiology /World Health Organization Task Force on Recommendations for Standardization of Measurements from M-mode Echocardiograms. *Circulation* 1984;69:854A–7A.
17. Nyrnes A, Mathiesen EB, Njølstad I, *et al*. Palpitations are predictive of future atrial fibrillation. An 11-year follow-up of 22,815 men and women: the Tromsø Study. *Eur J Prev Cardiol* 2013;20:729–36.
18. Vangen-Lønne AM, Wilsgaard T, Johnsen SH, *et al*. Time trends in incidence and case fatality of ischemic stroke: the Tromsø Study 1977–2010. *Stroke* 2015;46:1173–9.
19. Melgaard L, Gorst-Rasmussen A, Lane DA, *et al*. Assessment of the CHA_2DS_2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. *JAMA* 2015;314:1030–8.
20. Huisman MV. Patients with atrial fibrillation and a CHA_2DS_2-VASc score of 1: are they at low or high stroke risk? *J Am Coll Cardiol* 2015;65:1395–7.
21. Lip GY, Skjøth F, Rasmussen LH, *et al*. Oral anticoagulation, aspirin, or no therapy in patients with nonvalvular AF with 0 or 1 stroke risk factor based on the CHA_2DS_2-VASc score. *J Am Coll Cardiol* 2015;65:1385–94.
22. Chao TF, Liu CJ, Wang KL, *et al*. Should atrial fibrillation patients with 1 additional risk factor of the CHA_2DS_2-VASc score (beyond sex) receive oral anticoagulation? *J Am Coll Cardiol* 2015;65:635–42.
23. Friberg L, Rosenqvist M, Lindgren A, *et al*. High prevalence of atrial fibrillation among patients with ischemic stroke. *Stroke* 2014;45:2599–605.

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