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ORIGINAL ARTICLE

Cardiac Organ Damage in Young Adults with Cryptogenic Ischaemic Stroke: The SECRETO Study

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Abstract

Introduction Cardiac organ damage (OD) is associated with increased risk of cardiovascular disease. However, limited knowledge exists on cardiac OD in young patients with cryptogenic ischaemic stroke (CIS).

Aim To explore prevalence and covariates of cardiac OD in patients with CIS compared to controls participating in the SECRETO study.

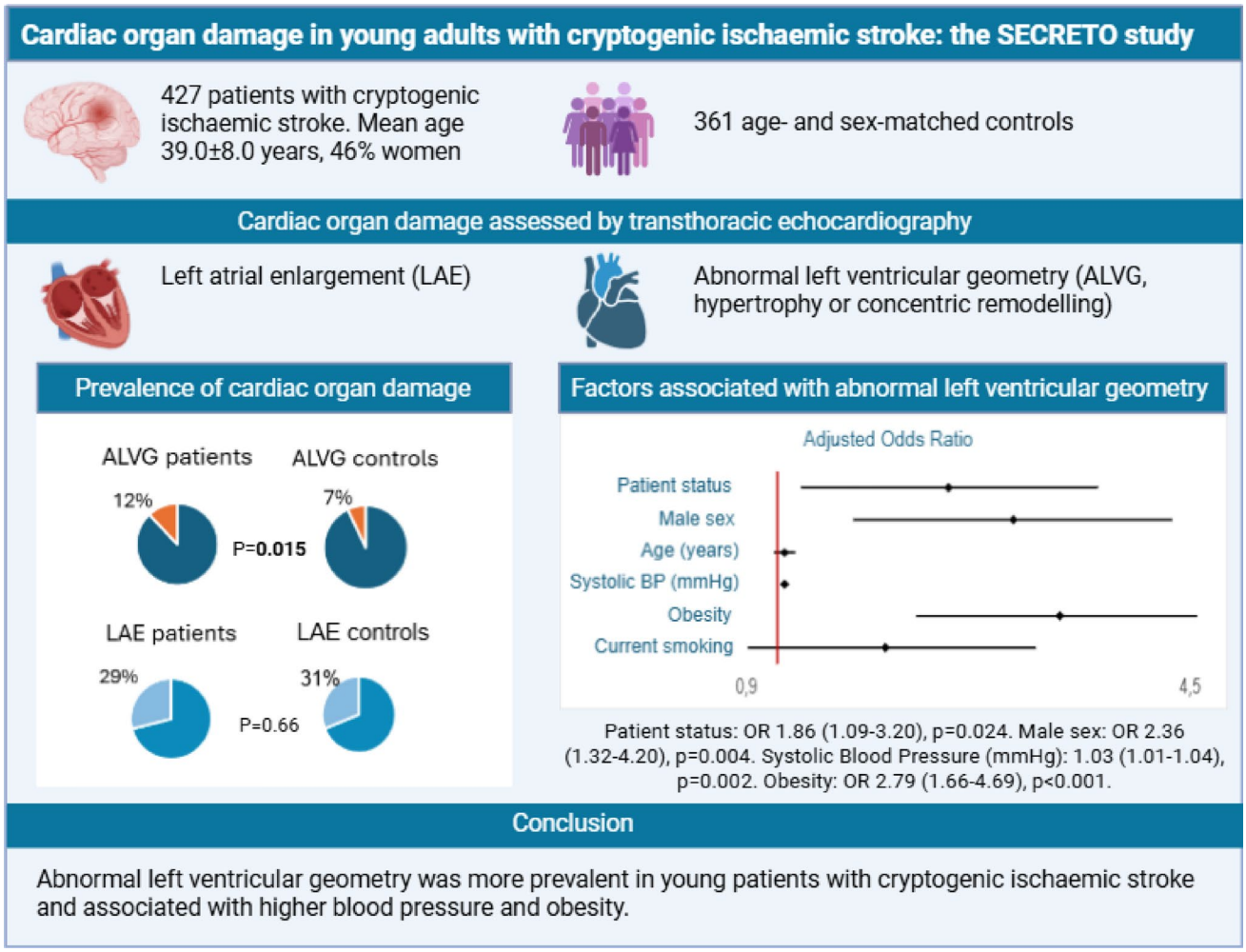
Methods We analysed data from 427 patients with CIS aged <50 years and 361 age- and sex-matched controls. OD was defined as presence of abnormal left ventricular (LV) geometry (LV hypertrophy or concentric remodelling) or left atrial enlargement (LAE) assessed by echocardiography, using sex-specific threshold values.

Results Compared to controls, patients had higher prevalences of obesity and tobacco smoking, patent foramen ovale (PFO) (52% vs. 25%) and abnormal LV geometry (12% vs. 7%, all $p < 0.01$), while presence of LAE did not differ. In multivariable analyses, CIS was associated with presence of abnormal LV geometry (odds ratio 1.86 [95% confidence interval 1.09–3.20], p=0.024). In separate multivariable analyses in patients only, obesity was associated with both abnormal LV geometry and LAE (both $p < 0.01$), and higher systolic blood pressure only with presence of abnormal LV geometry ($p < 0.001$). No significant association with PFO was found.

Conclusion In young patients with CIS participating in the SECRETO study, abnormal LV geometry was more prevalent compared to age- and sex-matched controls and associated with presence of higher blood pressure and obesity. The results point to the importance of blood pressure and weight control in CIS to prevent progression of cardiac OD and recurrent cardiovascular events.

Extended author information available on the last page of the article

Graphical Abstract



Keywords Ischaemic stroke · Organ damage · Blood pressure · Hypertension · Obesity

1 Introduction

An estimated 10% of ischaemic strokes occur in young adults below 50 years of age [1, 2]. Despite a decrease in total stroke globally, an increase in ischemic stroke in young adults has been observed in several regions [1, 2]. Among ischaemic strokes in young adults, 20–40% are of undetermined aetiology, termed cryptogenic ischaemic stroke (CIS) [3, 4]. The most frequent traditional risk factors for ischaemic stroke in this age group are dyslipidaemia, tobacco smoking and hypertension [5]. However, non-traditional risk factors like migraine, thrombophilia and autoimmune diseases have a stronger association with ischaemic stroke in individuals younger than 35 years of age [6], and in particular in patients with CIS and a patent foramen ovale (PFO) [7].

Hypertension is the leading risk factor for ischaemic stroke world-wide [8], and the risk is higher when hypertension starts at a younger age [9]. Blood pressure (BP) control is often less effective among younger compared to older adults [10], and longer duration of recognised hypertension is associated with a higher stroke risk, independent of age and BP level [11]. Furthermore, obesity has emerged as a new driver of ischaemic stroke in young individuals [12, 13]. A Danish population-based study found an increased body mass index (BMI) in childhood to be associated with incident ischaemic stroke before the age of 55 years [14].

From non-stroke populations it is well known that chronic hypertension and obesity lead to development of cardiac organ damage such as left ventricular (LV) hypertrophy (LVH), concentric LV remodelling and left atrial enlargement (LAE) which in turn predispose to ischemic stroke [15–18]. In older patients with ischaemic stroke a higher

prevalence of cardiac organ damage has been reported compared to controls at similar age [19, 20]. However, there is limited knowledge about presence of cardiac organ damage in young patients with CIS. Thus, the aim of this analysis was to explore presence and covariates of different types of cardiac organ damage in young adults with CIS participating in the multicentre Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome (SECRETO) study.

2 Methods

2.1 Study Population

The SECRETO study was designed as an international prospective multi-centre case-control study of young adults (18–49 years) presenting with an imaging-positive first-ever ischaemic stroke of undetermined aetiology. The rationale, study design, pre-defined inclusion and exclusion criteria, and the minimum diagnostic investigations have previously been published [21]. Study investigations included cerebral magnetic resonance imaging, imaging of cervicocephalic arteries, transcranial Doppler scan with bubble test when available, standardised transthoracic and transoesophageal echocardiogram, and at least 24 hours of heart rhythm monitoring. Strokes that were of unknown, uncertain or with no likely direct cause after the initial investigations were classified as CIS and eligible for inclusion into the SECRETO study [21]. The study participants were recruited from 19 European centres in 13 countries between 2013 and 2022. Stroke-free controls were recruited locally and matched according to age (within 5 years), sex, and ethnicity in a 1:1 fashion, preferably from population-based registries. However non-related volunteers could also serve as controls if population-based controls were unavailable [21]. For the present analysis, 18 sites contributed with at least one transthoracic echocardiography examination (TTE) of patients and 10 sites contributed with TTE of stroke-free controls. In total 608 patients and 557 controls were recruited to the SECRETO study, TTE was performed in 598 patients and 420 controls, and TTE studies from 493 patients and 378 controls were received at the SECRETO echocardiography core laboratory (Figure S1). Among these, echocardiograms from 427 patients (87%) and 361 controls (96%) had correct image format and sufficient image quality for analyses, forming the basis for the present analysis (Figure S1). Age and prevalences of obesity and hypertension did not differ between included and excluded participants (all $p > 0.3$).

2.2 Ethics

The SECRETO study was approved by the by the Regional Ethics Committees of the participating hospitals. In Finland, the study was approved by the Regional Ethics Committee of Helsinki and Uusimaa district (362/13/03/00/12) and in Norway by the Regional Ethics Committee of Western Norway (2015/2344). It was performed in line with the principles of the Declaration of Helsinki. All participants or their proxy provided written informed consent prior to inclusion. The study is registered at https://www.clinicaltrials.gov/ (Unique identifier: NCT01934725, 29th August 2013).

2.3 Baseline Clinical Data

Medical history was obtained using a structured interview and by reviewing medical records. Anthropometrics, BP and heart rate were measured at the initial study visit in a standardised manner [22].

2.4 Cardiovascular Risk Factors

Hypertension was defined as known hypertension, use of antihypertensive drugs at the time of the incident stroke or having a mean of two clinic BP measures ≥140 mmHg systolic or ≥90 mmHg diastolic at the initial study visit. The participants were instructed 5 minutes of initial rest before two clinic BP measurements with 1-minute interval. Current tobacco smoking was self-reported. The BMI was calculated from body weight in kilograms divided by the squared body height in meters. Obesity was defined as a BMI ≥30 kg/m^2. Increased waist circumference was defined as a measure ≥88cm in women and ≥102 cm in men. Hypercholesterolaemia was considered present if known hypercholesterolaemia or use of lipid-lowering medication at the time of the stroke. A new diagnosis of hypercholesterolaemia in patients with CIS was registered if the low-density lipoprotein cholesterol was ≥4.9 mmol/L at the incident hospitalisation. Diabetes mellitus (DM) was identified as known DM or use of antidiabetic medicines at the time of inclusion to the study. A new diagnosis of DM in patients with CIS was registered if the glycated haemoglobin A1c (HbA_{1c}) was ≥ 48 mmol/mol at the incident hospitalisation. Known cardiovascular disease was identified as a history of coronary artery disease, myocardial infarction, heart failure, or peripheral artery disease. None of the cases or controls had known atrial fibrillation.

2.5 Echocardiographic Examination

TTE was performed at the study centres according to the previously published performance protocol and sent to the study Echocardiography Core Laboratory at the University

Table 1 Clinical characteristics in patients and controls participating in the SECRETO study

Variable	Patients (n = 427)	Controls (n = 361)	*P* value
Age (years)	39.0 ± 8.0	39.7 ± 7.8	0.178
Women (%)	46	43	0.361
Height (m)	1.74 ± 0.10	1.74 ± 0.09	0.790
Weight (kg)	82.9 ± 18.6	80.7 ± 17.2	0.091
BMI (kg/m^2)	27.4 ± 5.7	26.6±5.0	**0.037**
Obesity (%)	27	19	**0.013**
Increased waist circumference (%)	40	28	**<0.001**
Clinic systolic BP (mmHg)	126 ± 15	127 ± 14	0.200
Clinic diastolic BP (mmHg)	77 ± 12	78 ± 11	0.371
Heart rate (bpm)	69 ± 13	67 ± 12	0.131
Hypertension (%)	35	30	0.158
Hypertension treatment (%)	30	26	0.176
Current tobacco smoking (%)	31	15	**<0.001**
HbA_{1c} (mmol/mol)	35 ± 7	NA	
Total cholesterol (mmol/L)	4.6 ± 1.0	NA	
Low-density lipoprotein (mmol/L)	3.0 ±0.9	NA	
History of CVD (%)	2	1	0.213

BMI: body mass index; BP: blood pressure; HbA_{1c}: glycated haemoglobin A_{1c}; CVD: cardiovascular disease; NA: not available

Bold values represent statistically significant results ($p < 0.05$)

of Bergen, Norway, for blinded central analysis [23]. The TTE's were analysed by a junior researcher and proofread by a senior cardiologist in accordance with current international guidelines [24]. LV mass was calculated using a necropsy validated formula and indexed to body height$^{2.7}$ to avoid underestimation in obese participants [25]. LVH was considered present if the LV mass exceeded 47 g/m$^{2.7}$ in women and 50 g/m$^{2.7}$ in men [26]. Concentric LV remodelling was considered present if the relative wall thickness (the ratio between 2 x LV posterior wall thickness and LV internal diameter at end-diastole) was ≥0.43 while the LV mass was within the normal range. Abnormal LV geometry was defined as presence of LVH or LV concentric remodelling. LAE was considered present if left atrial volume indexed for height^2 was >16.5 ml/m^2 in women and >18.5 ml/m^2 in men [26, 27]. LV filling pressure was estimated by the ratio between the early transmitral flow velocity and the early diastolic mitral annulus velocity (E/e′ ratio). PFO was diagnosed when either a spontaneous or Valsalva manoeuvre-induced right-to-left shunt across the atrial septum was evident with colour Doppler on transthoracic images and confirmed with a bubble study in the transoesophageal echocardiographic examination [23].

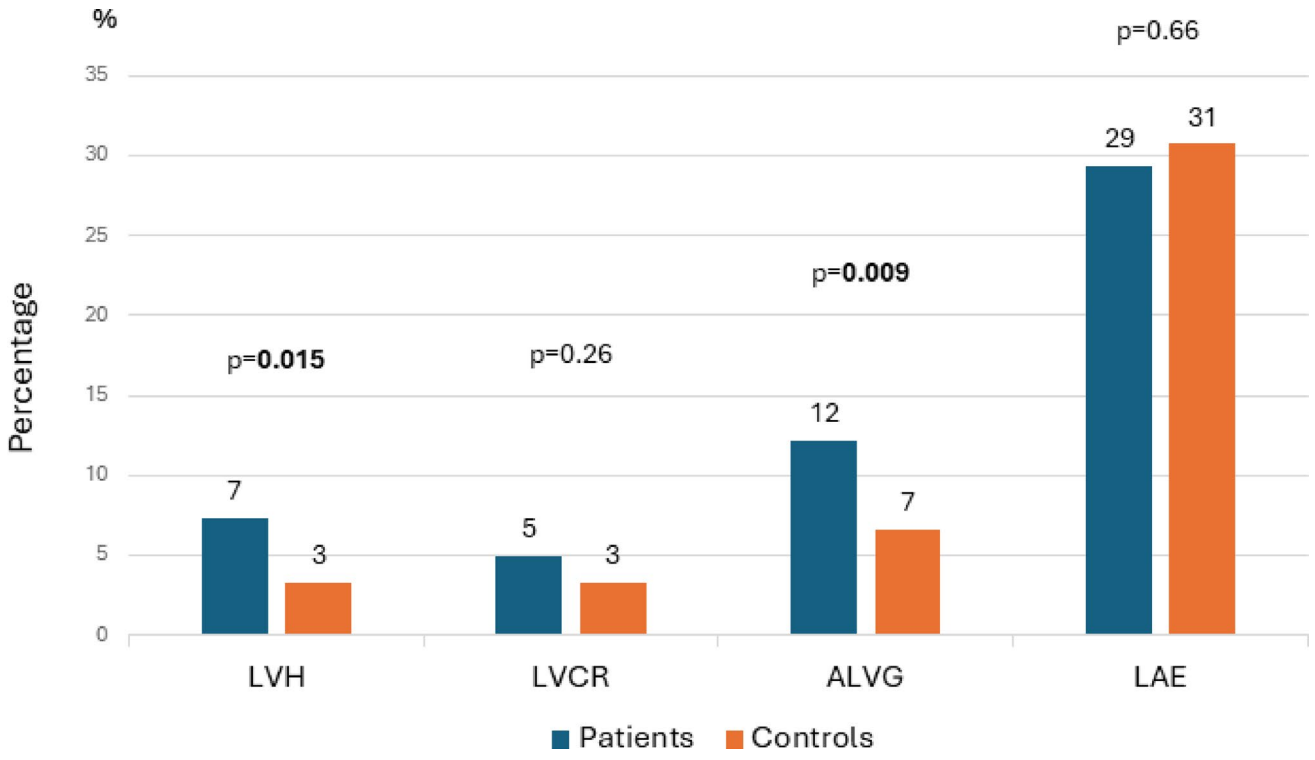


Fig. 1 Prevalence of types of organ damage in patients with cryptogenic ischemic stroke and stroke-free controls. LVH: left ventricular hypertrophy; LVCR: left ventricular concentric remodelling; ALVG: abnormal left ventricular geometry; LAE: left atrial enlargement. Bold values represent statistically significant results ($p < 0.05$).

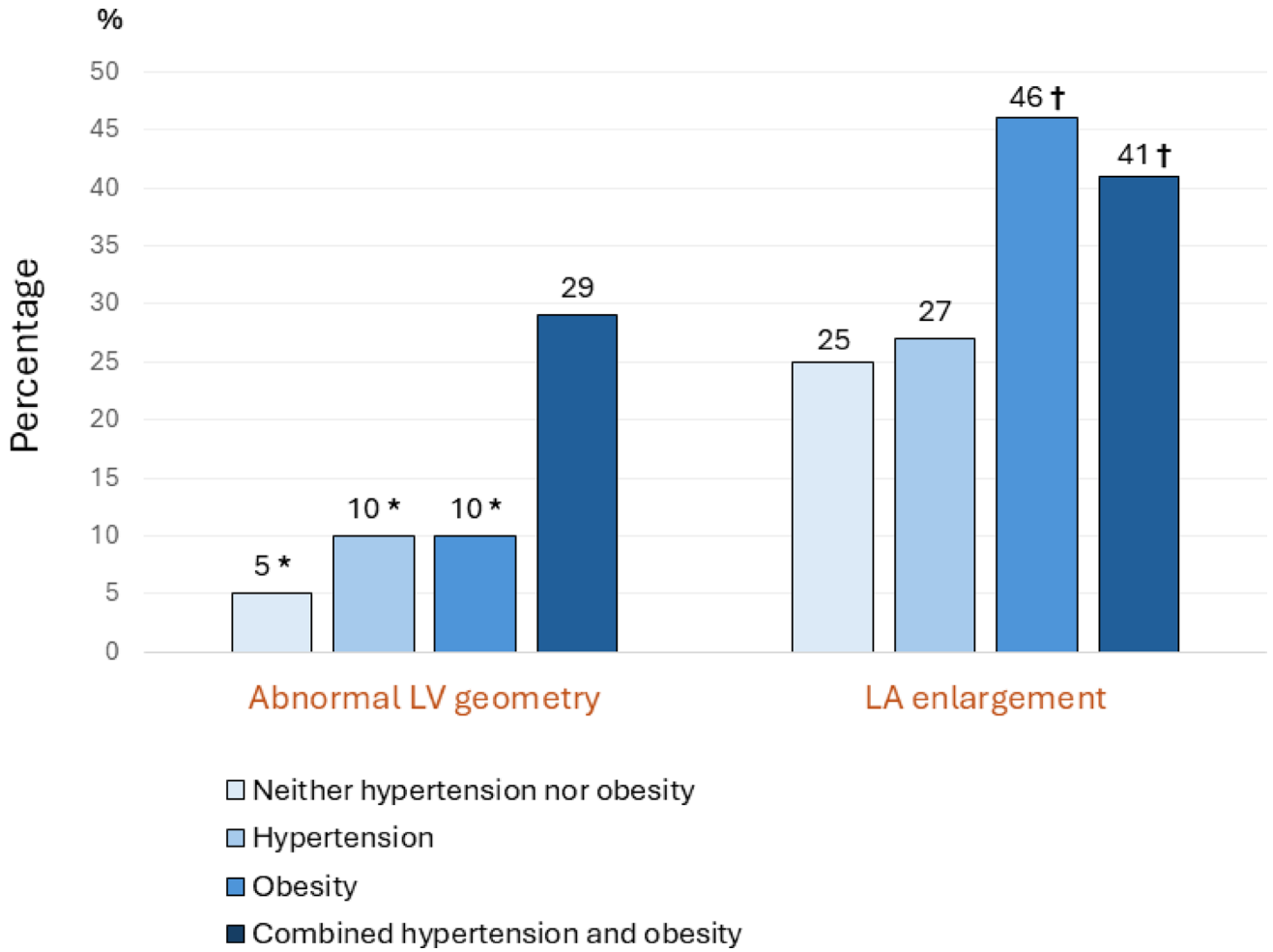


Fig. 2 Prevalences of organ damage in participants with hypertension, obesity or combined hypertension-obesity compared to those without these risk factors. *$p < 0.001$ versus Combined hypertension and obesity group. †$p < 0.05$ versus Neither hypertension nor obesity group.

Table 2 Echocardiographic findings in patients and controls participating in the SECRETO study

Variable	Patients (n = 427)	Controls (n=361)	*P* value
LV end-diastolic diameter (cm)	5.05 ± 0.55	5.05 ± 0.47	0.998
LV end-systolic diameter (cm)	3.50 ± 0.47	3.48 ± 0.39	0.483
LV end-diastolic septal thickness (cm)	0.93 ± 0.24	0.91 ± 0.19	0.112
LV end-diastolic posterior wall thickness (cm)	0.75 ± 0.17	0.74 ± 0.16	0.559
LV RWT	0.30 ± 0.08	0.30 ± 0.07	0.327
LV mass index ($g/m^{2.7}$)	33.7 ± 10.4	32.7 ± 8.3	0.117
LV ejection fraction (%)	57 ± 5	58 ± 4	**0.003**
Average E/e'	6.7 ± 1.8	6.6 ± 1.5	0.318
LA volume index (ml/m^2)	15.7 ± 4.6	16.0 ± 4.4	0.304
Presence of patent foramen ovale (%)	52	25	**<0.001**

LV left ventricular, *RWT* relative wall thickness, *LA* left atrial, *E* early transmitral flow velocity; e': early diastolic mitral annular velocity. Bold values represent statistically significant results ($p < 0.05$).

2.6 Statistical Analysis

Data management and statistical analyses were performed in IBM SPSS Statistics version 29 (IBM SPSS Statistics, Armonk, New York, USA). Continuous data were reported as mean values and standard deviation (SD). Categorical variables were reported as percentages. Group comparisons were performed using the student's *t* tests or Pearson chi-squared tests, as appropriate. Univariable logistic regression analyses were used to explore covariates of the different types of cardiac organ damage. Due to the low prevalence of LVH and LV concentric remodelling, these types of cardiac organ damage could not be assessed separately in multivariable analyses in the patient group and were therefore grouped together as abnormal LV geometry. The multivariable models were adjusted for significant variables identified in univariable analyses in the total cohort, adjusting also for presence of PFO and patient/control status, and

Table 3 Covariates of cardiac organ damage in the total study cohort; multivariable logistic regression analyses

Variable	LV hypertrophy (n=43)		Abnormal LV geometry (n=76)		LA enlargement (n=234)	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Patient status	2.28 (1.12–4.64)	**0.023**	1.86 (1.09–3.20)	**0.024**		
Sex	2.37 (1.12–5.04) *	**0.025**	2.36 (1.32–4.20)*	**0.004**	2.17 (1.56–3.03)†	**<0.001**
Age (years)			1.03 (0.99–1.07)	0.127	1.03 (1.01–1.05)	**0.012**
Systolic BP (mmHg)	1.03 (1.01–1.05)	**0.002**	1.03 (1.01–1.04)	**0.002**	1.01 (1.00–1.02)	0.107
Obesity	3.94 (2.04–7.64)	**<0.001**	2.79 (1.66–4.69)	**<0.001**	2.01 (1.40–2.89)	**<0.001**
Current smoking			1.48 (0.85–2.56)	0.164		

LV left ventricular, *LA* left atrial, *OD* organ damage, *OR* odds ratio, *CI* confidence interval, *BP* blood pressure

*Male sex

†Female sex

Bold values represent statistically significant results ($p < 0.05$)

Table 4 Covariates of cardiac organ damage in patients; multivariable logistic regression analyses

Variable	Abnormal LV geometry (n=52)		LA enlargement (n=123)	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Presence of PFO	0.55 (0.28–1.07)	0.077		
Sex	2.56 (1.24–5.30)*	**0.011**	1.75 (1.11–2.75)†	**0.016**
Age (years)	1.03 (0.98–1.08)	0.227	1.02 (0.99–1.05)	0.114
Systolic BP (mmHg)	1.04 (1.01–1.06)	**< 0.001**	1.01 (1.00–1.03)	0.066
Obesity	2.46 (1.28–4.72)	**0.007**	2.36 (1.47–3.78)	**<0.001**

LV left ventricular, *LA* left atrium, *OD* organ damage, *OR* odds ratio, *CI* confidence interval, *PFO* patent foramen ovale, *BP* blood pressure

*Male sex

†Female sex

Bold values represent statistically significant results ($p < 0.05$)

separately in patients. In all analyses a two-tailed *p* value of <0.05 was considered statistically significant.

3 Results

3.1 Clinical Characteristics

The study participants were on average 39.3 ±7.9 years old and included 44% women. In the total study cohort, obesity was present in 23%, and hypertension in 33% of the participants. Among participants with hypertension, 29% used antihypertensive drug treatment. BMI (27.4 kg/m^2 vs. 26.6 kg/m^2) and proportion of obesity (27% vs. 19%) were higher in patients than in controls (both $p < 0.05$) (Table 1). Tobacco smoking was twice as frequent in patients compared to controls (31% vs. 15%, $p < 0.001$). Known DM was present in 2% of both groups, and hypercholesterolaemia in 3% in patients and 5% of controls ($p = 0.077$) at the initial assessment. A new diagnosis of DM was found in 1% of patients and hypercholesterolaemia in 3% of patients at the incident hospitalisation.

3.2 Echocardiographic Findings

The prevalence of LVH was twice as high in patients compared to controls (7% vs. 3%, $p = 0.015$), and more prevalent in male than female patients (11% vs. 3%, $p = 0.003$). The prevalences of concentric LV remodelling did not differ between patients and controls (5% vs. 3%, p=0.26). Abnormal LV geometry (combined LVH and concentric LV remodelling) was more prevalent in patients compared to controls (12% vs. 7%, $p < 0.01$) (Fig. 1).

The presence of abnormal LV geometry was particularly common in individuals with combined hypertension and obesity (Fig. 2). LAE was the most common type of cardiac organ damage but did not differ between patients and controls (29% of patients and 31% of controls, $p = 0.66$) (Fig. 1). LAE was particularly prevalent among participants with obesity (Fig. 2).

Presence of PFO was twice as prevalent in patients compared to controls (52% vs. 25%, $p < 0.001$) (Table 2). Presence of cardiac organ damage did not differ between groups of patients with and without PFO.

3.3 Covariates of Cardiac Organ Damage in the Total Study Cohort

Univariable covariates of individual types of cardiac organ damage in the total study cohort are shown in Table S1. In multivariable analyses, having CIS status was significantly associated with presence of LVH and abnormal LV geometry, but not with LAE (Table 3). Other independent covariates or cardiac organ damage included obesity which was significantly associated with presence of LV hypertrophy, abnormal LV geometry and LAE (all $p < 0.001$), and higher

systolic BP which was associated with presence of LVH and abnormal LV geometry (both $p < 0.01$) (Table 3). Male sex was associated with presence of LVH and abnormal LV geometry, while female sex and older age were both significantly associated with LAE (all $p < 0.05$) (Table 3). When we replaced obesity with increased waist circumference in the models, increased waist circumference was independently associated with presence of LV hypertrophy, abnormal LV geometry, and LAE (all $p < 0.05$), and results for other covariates remained unchanged (Table S2).

3.4 Covariates of Cardiac Organ Damage in Patients

Univariable covariates of individual types of cardiac organ damage in patients are detailed in Table S1. In multivariable analyses in patients, obesity remained significantly associated with both abnormal LV geometry and with LAE (both $p < 0.01$), and higher systolic BP with presence of abnormal LV geometry ($p < 0.001$) (Table 4). Male sex was associated with presence of abnormal LV geometry and female sex with presence of LAE (both $p < 0.05$). There was no significant multivariable association between presence of PFO and cardiac organ damage neither in the patient group nor in the total study cohort. When we replaced obesity with increased waist circumference the statistical models, increased waist circumference was independently associated with presence of abnormal LV geometry and LAE (both $p < 0.05$) (Table S2).

4 Discussion

This study expands the current knowledge on cardiac organ damage in young patients with CIS by demonstrating that abnormal LV geometry was more prevalent compared to age- and sex-matched stroke free controls. Notably, obesity emerged as a key risk factor associated with both LV and left atrial organ damage independent of systolic BP.

The prevalence of abnormal LV geometry in patients in the present study was lower than reported in previous studies of patients with ischaemic stroke, probably due to the focus on CIS in this study, while other studies included older patients with diverse causes of ischaemic stroke [19, 28, 29] or focused on older patients with lacunar stroke [30]. These cohorts also had a notably higher proportion of hypertensive patients. In the Norwegian Stroke in the Young study (NORSYS), including on average 10 years older patients with ischaemic stroke, abnormal LV geometry was found in 37% of patients, and significantly higher in those with hypertension [28]. In the Secondary prevention of Small Subcortical Strokes (SPS3) trial in patients with lacunar infarction and a mean age of 63 years, abnormal LV geometry was found in 77%, and particularly common among those with hypertension or diabetes mellitus [30]. In the present study, higher systolic BP was independently associated with abnormal LV geometry, but not with LAE. It is known from non-stroke cohorts that high BP and hypertension is a major driver of abnormal LV geometry, and treatment with an angiotensin II receptor blocker was associated with a more favourable normalisation of cardiac organ damage in The Losartan Intervention For Endpoint reduction in Hypertension study [31]. However, in the current study details regarding types of antihypertensive treatment were not available.

Adding to previous knowledge, the present study identified obesity as an important contributor to organ damage both in the left ventricle and the left atrium, independent of significant associations with higher systolic BP. Furthermore, abnormal LV geometry was most prevalent among participants with combined obesity and hypertension. These findings expand to a previous report from the SECRETO study showing that obesity was associated with increased left atrial stiffness and impaired left atrial mechanics assessed by speckle tracking echocardiography in patients with CIS [32]. A meta-analysis found overweight and obesity in young adults to increase the risk of ischaemic stroke later in life by 40% and 78% [33]. A large nationwide population-based Israeli study later found an association between overweight and obesity in adolescence with stroke in young adulthood [34]. Abdominal obesity was a significant ischaemic stroke risk factor for young females aged 18-45 years in the INTERSTROKE study, as also previously reported from the SECRETO study [35, 36]. In the current analysis, obesity (based on BMI) and increased waist circumference were interchangeable in the statistical analyses. Taken together, the present results suggest obesity as a major risk factor for cardiac organ damage in young patients with CIS, independent of increased systolic BP. The findings are also in keeping with results from non-stroke cohorts, demonstrating associations between central obesity and abnormal LV geometry, and between overweight in early-life and abnormal LV geometry in midlife [37, 38].

Although presence of PFO was twice as prevalent in patients compared to controls, presence of any cardiac organ damage did not differ between groups of patients with and without PFO. Of note, patients recruited in the SECRETO study all had CIS—which would oversample the prevalence of PFO compared to a general ischemic stroke population.

4.1 Strengths and Limitations

The main strengths of the study include centralised blinded reading of all the echocardiograms, the use of guideline-recommended sex-specific threshold values for diagnosis of cardiac organ damage, the large sample of young adults

with CIS and inclusion of a non-stroke control group. The SECRETO study cohort consisted of 97% white Europeans, similar in patients and controls. Generalisation of findings in this study to other stroke aetiologies, age ranges or ethnicities should be done with caution. Twenty-four-hour ambulatory BP recording was not part of the study protocol, and the associations of masked hypertension and non-dipping BP pattern with cardiac organ damage could therefore not be assessed. Detailed information of antihypertensive therapy and duration of hypertension were not available in the study. Potential secondary causes of hypertension were not systematically explored within the study protocol. Biochemical tests of lipids and HbA_{1c} were only performed in patients. Thus, prevalences of hypercholesterolemia and diabetes mellitus may have been underestimated in controls since they were based on self-reported medical history. Furthermore, causality cannot be determined based on the cross-sectional study design.

5 Conclusions

In young patients with CIS participating in the SECRETO study, presence of abnormal LV geometry was more common compared to age- and sex-matched controls. Hypertension and obesity emerged as major independent risk factors associated with presence of cardiac organ damage, pointing to the importance of combined BP and weight control in CIS to prevent progression of cardiac organ damage and recurrent cardiovascular events.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40292-026-00789-2.

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Author Contributions All authors reviewed and edited the manuscript and approved the final version of the manuscript. JP, NMM, PJ, JS, JH, MH, ACF, UWA and EG contributed towards conceptualisation, protocol development, or design of the study. All authors participated in participant recruitment or data collection. JP, NMM, JS, RKE, RBS, DC, UWA, HM, and EG participated in statistical analysis and interpretation.

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Data Availability Data are available upon reasonable request.

Declarations

Conflict of interest The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article. EG Speaker's fee from Boehringer Ingelheim, Amgen, Menarini Foundation, OMRON. EG is a nucleus member of the European Society of Cardiology Council on hypertension. HM received speaker fees from Boehringer Ingelheim, Pfizer and Bayer. AS received consultancy or lecture fees from Abbott, Astra Zeneca, BMS, Novo Nordic and Pfizer. The other authors did not report any potential conflicts of interest.

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