Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study

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Summary

Background A third of transient ischaemic attacks (TIAs) and ischaemic strokes are of undetermined cause (ie, cryptogenic), potentially undermining secondary prevention. If these events are due to occult atheroma, the risk-factor profile and coronary prognosis should resemble that of overt large artery events. If they have a cardioembolic cause, the risk of future cardioembolic events should be increased. We aimed to assess the burden, outcome, risk factors, and long-term prognosis of cryptogenic TIA and stroke.

Methods In a population-based study in Oxfordshire, UK, among patients with a first TIA or ischaemic stroke from April 1, 2002, to March 31, 2014, we compared cryptogenic events versus other causative subtypes according to the TOAST classification. We compared markers of atherosclerosis (ie, risk factors, coronary and peripheral arterial disease, asymptomatic carotid stenosis, and 10-year risk of acute coronary events) and of cardioembolism (ie, risk of cardioembolic stroke, systemic emboli, and new atrial fibrillation [AF] during follow-up, and minor-risk echocardiographic abnormalities and subclinical paroxysmal AF at baseline in patients with index events between 2010 and 2014).

Findings Among 2555 patients, 812 (32%) had cryptogenic events (incidence of cryptogenic stroke 0·36 per 1000 population per year, 95% CI 0·23–0·49). Death or dependency at 6 months was similar after cryptogenic stroke compared with non-cardioembolic stroke (23% *vs* 27% for large artery and small vessel subtypes combined; p=0·26) as was the 10-year risk of recurrence (32% *vs* 27%; p=0·91). However, the cryptogenic group had fewer atherosclerotic risk factors than the large artery disease (p<0·0001), small vessel disease (p=0·001), and cardioembolic (p=0·008) groups. Compared with patients with large artery events, those with cryptogenic events had less hypertension (adjusted odds ratio [OR] 0·41, 95% CI 0·30–0·56; p<0·0001), diabetes (0·62, 0·43–0·90; p=0·01), peripheral vascular disease (0·27, 0·17–0·45; p<0·0001), hypercholesterolaemia (0·53, 0·40–0·70; p<0·0001), and history of smoking (0·68, 0·51–0·92; p=0·01), and compared with small vessel and cardioembolic subtypes, they had no excess risk of asymptomatic carotid disease (adjusted OR 0·64, 95% CI 0·37–1·11; p=0·11) or acute coronary events (adjusted hazard ratio [HR] 0·76, 95% CI 0·49–1·18; p=0·22) during follow-up. Compared with large artery and small vessel subtypes combined, patients with cryptogenic events also had no excess of minor-risk echocardiographic abnormalities (cryptogenic 37% *vs* 45%; p=0·18) or paroxysmal AF (6% *vs* 10%; p=0·17) at baseline or of new AF (adjusted HR 1·23, 0·78–1·95; p=0·37) or presumed cardioembolic events (1·16, 0·62–2·17; p=0·64) during follow-up.

Interpretation The clinical burden of cryptogenic TIA and stroke is substantial. Although stroke recurrence rates are comparable with other subtypes, cryptogenic events have the fewest atherosclerotic markers and no excess of cardioembolic markers.

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Introduction

By contrast with coronary and peripheral vascular events, up to a third of transient ischaemic attacks (TIAs) or ischaemic strokes—about 400 000 cases annually in western Europe—are of undetermined cause (ie, cryptogenic).[1] In young patients, half of strokes are cryptogenic.[1] Yet, recurrence rates after cryptogenic TIA and ischaemic stroke are close to those of large artery and cardioembolic causes.[2] The Cryptogenic Stroke/ESUS International Working Group proposed that cryptogenic events might often be caused by occult arterial sources of thromboembolism, paroxysmal atrial fibrillation (AF), patent foramen ovale (PFO), or minor-risk cardiac structural abnormalities.[3–5]

However, even with detailed investigation, only a third of patients with cryptogenic stroke have aortic atheroma or potentially unstable plaques in other vessels, some of which are probably coincidental.[3,6] Similarly, although long-term monitoring of heart rhythm identifies paroxysmal AF in up to a third of patients with cryptogenic events,[7,8] the relevance of these mostly short episodes of AF for cryptogenic stroke is uncertain.

Research in context

Evidence before this study

We searched PubMed for articles on cryptogenic transient ischaemic attack (TIA) or cryptogenic stroke published between Jan 1, 1993, and Feb 1, 2015, with the search terms "cryptogenic stroke", "undetermined stroke", "stroke of undetermined aetiology", and "embolic strokes of undetermined source". We also identified all hospital-based and population-based stroke studies that reported data on the frequency of vascular risk factors or prognosis according to the Trial of Org 10172 in Acute Stroke Treatment classification, or similar, with the search terms "stroke and incidence", "stroke and population-based study", "stroke and hospital-based study", "stroke and community-based study", "stroke and risk factors", "stroke subtype", and " stroke classification". Others have suggested that cryptogenic TIA or stroke might often be caused by occult cardiac or arterial sources of thromboembolism. However, most previous studies of risk factors or prognosis of cryptogenic stroke were hospital based, did not separate cryptogenic cases with detailed diagnostic work-up from cases with more than one cause or cases with unknown cause because of incomplete investigation, and rarely compared cryptogenic stroke with other subtypes, and no study reported the long-term coronary prognosis or risk of cardioembolic events by causative subtypes.

Added value of this study

In this large population-based study of TIA and ischaemic stroke with long-term follow-up, we confirmed that the incidence of cryptogenic events was high and the risk of recurrent stroke was substantial. However, patients with cryptogenic events had the lowest prevalence of risk factors for atherosclerosis, the lowest frequency of comorbid atherosclerotic disease, and the lowest risk of acute coronary events compared with patients with events of known cause. Similarly, patients with cryptogenic events had low long-term risk of new atrial fibrillation (AF), low risk of recurrent cardioembolic stroke or systemic embolism, and no excess prevalence of paroxysmal AF or minor-risk cardiac abnormalities on baseline investigation.

Implications of all the available evidence

In view of the large burden of cryptogenic TIA and ischaemic stroke, further research on potential causes and treatments is needed. More research on detection of aortic plaque and other non-stenosing atherosclerosis and on intensive cardiac rhythm monitoring and detection of patent foramen ovale in older patients may be informative, but possible causal links with cryptogenic stroke should be interpreted with caution. However, in view of the high rate of recurrent cryptogenic stroke, randomised trials of available preventive treatments, such as new anticoagulants, are justified despite uncertainty about cause.

Findings from the INTERSTROKE study[9] suggested that traditional risk factors account for 90% of the risk of all stroke, but the investigators did not differentiate between stroke subtypes, and risk-factor profiles seem to differ across ischaemic stroke subtypes.[10,11] Since atheroma is a systemic disease with known risk factors, if occult or non-stenotic atheroma was the underlying cause of cryptogenic events, the atherosclerotic risk-factor profile and the extent of atherosclerosis in other vascular beds should be closer to that of overt large artery TIA or stroke and the risk of coronary events during follow-up should be high, particularly because plaque instability is also a systemic phenomenon.[12] Similarly, if paroxysmal AF was the underlying cause of cryptogenic events, the long-term risk of new AF would be increased, and if covert cardioembolism from other sources was responsible, the risk of future overtly embolic events (ie, with an identified embolic source) would be increased.[13,14]

Most previous studies of risk factors or prognosis of cryptogenic stroke were hospital based (appendix p 2), did not separate cryptogenic cases from cases with more than one cause or from cases with unknown cause because of incomplete investigation (appendix p 4), and rarely compared cryptogenic stroke specifically with other stroke subtypes.[15,16] Also, no study has reported the coronary prognosis or risk of cardioembolic events by subtypes, and no study has included a follow-up of 10 years to detect any late increase in new AF or cardioembolism. Therefore, we assessed the risk-factor profile, prevalence of atherosclerotic and cardioembolic markers, outcome, and long-term prognosis of ischaemic stroke subtypes in a large population-based study of TIA and stroke.

See Online for appendix

Methods

Study design and participants

The Oxford Vascular Study (OXVASC) is an ongoing population-based study of the incidence and outcome of all acute vascular events.[17] The study population comprises all 92728 individuals, irrespective of age, who are registered with 100 general practitioners in nine general practices in Oxfordshire, UK. The analysis reported herein includes consecutive cases with a first TIA or ischaemic stroke from April 1, 2002, to March 31, 2014, with follow-up until Sept 30, 2014.

The OXVASC study design has been described in detail elsewhere.[17] Briefly, several overlapping methods of hot and cold pursuit were used to achieve near-complete ascertainment of all individuals with TIA or stroke.[17,18] These included (1) a daily, rapid-access TIA and stroke clinic to which participating general practitioners and the local emergency department team referred individuals with suspected TIA or minor stroke; (2) daily searches of admissions to medical, stroke, neurology, and other relevant wards; (3) daily searches of the local emergency department attendance

register; (4) daily searches of in-hospital death records via the bereavement office; (5) monthly searches of all death certificates and coroner's reports for out-of-hospital deaths; (6) monthly searches of general practitioner diagnostic coding and hospital discharge codes; and (7) monthly searches of all brain and vascular imaging referrals.

Patients gave written informed consent after an event or assent was obtained from a relative for patients who were unable to provide consent. OXVASC was approved by the local research ethics committee.

Procedures

We collected demographic data, atherosclerotic risk factors (ie, male sex, previous hypertension, previous diabetes, history of smoking, and previous hypercholesterolaemia), and history of coronary or peripheral vascular disease during face-to-face interviews and cross-referenced these data with primary care records. For patient data ascertained after death, medical records were used. Patients routinely had 12-lead electrocardiography (ECG) and routine bloods (ie, full blood count, clotting, C-reactive protein, erythrocyte sedimentation rate, liver function, renal function, thyroid function, electrolytes, and lipid profile) after the event. Thrombophilia screening, vasculitis screening, and genetic tests, where appropriate, were done for patients with cryptogenic TIA or stroke or those younger than 55 years. During the 12-year study period of OXVASC, different imaging protocols were used in two different time periods. From April 1, 2002, to March 31, 2010 (phase 1), CT brain and carotid doppler were the first-line imaging methods, with MRI or magnetic resonance angiography done in selected patients when clinically indicated. Echocardiography, 24-h ECG (Holter monitor), and 5-day ambulatory home ECG monitoring (R test) were also done when clinically indicated. From April 1, 2010, to March 31, 2014 (phase 2), brain MRI and magnetic resonance angiography of extracranial and intracranial vessels became the first-line imaging methods, and all clinic patients had R tests and transthoracic echocardiography. We also referred patients for screening for PFO to the Department of Cardiology at John Radcliffe Hospital (Oxford, UK) when clinically indicated (ie, patients aged <55 years, those with concomitant venous thrombosis, those who went on a long-haul flight preceding the cerebrovascular event, or those with clinical or imaging evidence of multi-territory events with undetermined cause).

All cases were reviewed by a senior neurologist (PMR) and the cause of stroke was classified according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (appendix p 5).[19] In view of the potential for bias, risk factors such as hypertension and diabetes were not included in the criteria.[20] We classified patients in phase 1 as cryptogenic only if the diagnostic work-up included at least brain imaging, ECG, and extracranial imaging, and no clear cause was found. We classified patients with missing investigation as having unknown events, whereas events with more than one cause were classified separately. In phase 2, we extended the diagnostic work-up to include intracranial vascular imaging, R test, and echocardiography and used these additional results as indications for classification as listed in the appendix (p 5). We further classified all cryptogenic TIAs or strokes according to the embolic strokes of undetermined source (ESUS) criteria (appendix p 6).[3]

Patients were followed up face to face at 1, 6, 12, 60, and 120 months by a study nurse or physician to identify recurrent strokes; acute coronary events and sudden cardiac deaths; any new AF; acute cardioembolic events, including recurrent cardioembolic stroke, acute embolic limb ischaemia, and visceral embolisation; and disability (modified Rankin Scale >2). Patients who had moved out of the study area were followed up via telephone at the same timepoints as face-to-face follow-up. We recorded all deaths during follow-up and their causes. All recurrent strokes and cardiac and peripheral vascular events that occurred during follow-up would also be identified by our ongoing daily case ascertainment. If a recurrent vascular event was suspected, the patient was reassessed and investigated by a study physician.

Statistical analysis

We calculated sex-specific rates (per 1000 population per year) of incident stroke of cryptogenic cause in 10-year age bands and estimated 95% CIs assuming a Poisson distribution, standardised to the 2012 population of England and Wales. Recurrent strokes that were cryptogenic in patients with a previous non-cryptogenic stroke were not included in our analyses of incident stroke.

We compared the frequency of atherosclerotic risk factors and of comorbid atherosclerotic disease (ie, history of coronary disease, peripheral vascular disease, and asymptomatic carotid stenosis) in each stroke subtype using the χ^2 test and logistic regression analysis adjusted for age and sex. We also did sensitivity analyses excluding all TIA events. At baseline, we compared the frequency of minor-risk echocardiographic abnormalities and subclinical paroxysmal AF on R test in cryptogenic cases versus large artery and small vessel subtypes in patients from phase 2 of the study using the χ^2 test.

We used Kaplan-Meier survival analysis to calculate the 1-year, 5-year, and 10-year actuarial risks of events during follow-up, censored at death or Sept 30, 2014, for each subtype and compared risks by Cox regression analysis adjusted for age and sex. We studied the following outcomes during follow-up: death, vascular death, first recurrent stroke, first recurrent ischaemic stroke, first acute coronary event, first cardioembolic event, and any new AF.

Because of the potential effect of the change of investigation protocol in OXVASC in 2010 on the classification of cryptogenic TIA and stroke, we stratified

	Cryptogenic (n=812)	Cardioembolic (n=668)	Large artery disease (n=280)	Small vessel disease (n=317)	Unknown cause (n=331)	More than one cause (n=90)	Other causes (n=57)	Total (n=2555)	p value*
Baseline characteristics									
Age (years)	70·4 (12·8)	77·9 (11·9)	73·3 (10·3)	69·7 (12·6)	81·2 (10·4)	77·2 (10·5)	56·7 (17·7)	73·9 (13·0)	<0·0001
Sex									
Male	402 (50%)	306 (46%)	172 (61%)	182 (57%)	112 (34%)	56 (62%)	32 (56%)	1262 (49%)	<0·0001
Female	410 (50%)	362 (54%)	108 (39%)	135 (43%)	219 (66%)	34 (38%)	25 (44%)	1293 (51%)	..
Hypertension	432 (53%)	477 (71%)	208 (74%)	188 (59%)	203 (61%)	66 (73%)	26 (46%)	1600 (63%)	<0·0001
Diabetes	99 (12%)	81 (12%)	52 (19%)	51 (16%)	55 (17%)	17 (19%)	2 (4%)	357 (14%)	0·004
Myocardial infarction	67 (8%)	117 (18%)	39 (14%)	16 (5%)	34 (10%)	18 (20%)	5 (9%)	296 (12%)	<0·0001
Peripheral vascular disease†	31 (4%)	58 (9%)	40 (14%)	15 (5%)	27 (8%)	16 (18%)	3 (5%)	190 (7%)	<0·0001
Hypercholesterolaemia	265 (33%)	240 (36%)	137 (49%)	105 (33%)	100 (30%)	37 (41%)	18 (32%)	902 (35%)	<0·0001
Smoking status									
Present‡	127 (16%)	45 (7%)	54 (19%)	77 (24%)	30 (9%)	17 (19%)	11 (19%)	361 (14%)	<0·0001
Past§	317 (39%)	302 (45%)	129 (46%)	120 (38%)	120 (37%)	42 (47%)	25 (44%)	1055 (41%)	0·02
Secondary prevention during follow-up									
On antiplatelets									
At 1 month¶	764/809 (94%)	331/555 (60%)	258/273 (95%)	306/317 (97%)	196/244 (80%)	59/86 (69%)	47/55 (86%)	1961/2339 (84%)	<0·0001
At 1 year‖	711/766 (93%)	186/435 (43%)	228/247 (92%)	290/310 (94%)	110/151 (73%)	38/76 (50%)	40/46 (87%)	1603/2031 (79%)	<0·0001
On anticoagulants									
At 1 month¶	9/809 (1%)	221/555 (40%)	12/273 (4%)	2/317 (1%)	19/244 (8%)	27/86 (31%)	8/55 (15%)	298/2339 (13%)	<0·0001
At 1 year‖	11/766 (1%)	239/435 (55%)	11/247 (4%)	2/310 (1%)	2/151 (1%)	36/76 (47%)	4/46 (9%)	305/2031 (15%)	<0·0001
On a statin									
At 1 month¶	650/809 (80%)	379/555 (68%)	232/273 (85%)	266/317 (84%)	132/244 (54%)	65/86 (76%)	31/55 (56%)	1755/2339 (75%)	<0·0001
At 1 year‖	627/766 (82%)	315/435 (72%)	221/247 (89%)	256/310 (83%)	80/151 (53%)	61/76 (80%)	29/46 (63%)	1589/2031 (78%)	<0·0001
On one or more antihypertensives									
At 1 month¶	590/809 (73%)	445/555 (80%)	224/273 (82%)	258/317 (81%)	150/244 (61%)	72/86 (84%)	32/55 (58%)	1771/2339 (76%)	<0·0001
At 1 year‖	574/766 (75%)	358/435 (82%)	213/247 (86%)	246/310 (79%)	89/151 (59%)	65/76 (86%)	27/46 (59%)	1572/2031 (77%)	<0·0001

Data are mean (SD), number (%), or n/N (%). *For heterogeneity among all subtypes (χ^2 test for categorical variables and one-way ANOVA test for continuous variables). †Data missing for one patient with event of unknown cause. ‡Data missing for eight patients: four with cardioembolic events, three with events of unknown cause, and one with a cryptogenic event. §Data missing for nine patients: four with cardioembolic events, three with events of unknown cause, and two with cryptogenic events. ¶Data available for 2339 patients; 216 died before 1 month of follow-up. ||Data available for 2031 patients: 470 died before 1 year of follow-up, 45 have not reached 1-year follow-up, and nine had missing data.

Table 1: **Baseline characteristics and secondary prevention during follow-up among transient ischaemic attack or ischaemic stroke subtypes**

	Cryptogenic (n=812)	LAD (n=280)	Cryptogenic *vs* LAD				Non-LAD (n=985)	Cryptogenic *vs* non-LAD			
			Crude OR (95% CI)	p value	Age and sex adjusted OR (95%CI)	p value		Crude OR (95% CI)	p value	Age and sex adjusted OR (95% CI)	p value
Age (years)	70·4 (12·8)	73·3 (10·3)	0·98 (0·97–0·99)	0·001	0·98 (0·97–0·99)	0·0001	75·3 (12·7)	0·97 (0·96–0·98)	<0·0001	0·97 (0·96–0·98)	<0·0001
Male	402 (50%)	172 (61%)	0·62 (0·47–0·81)	0·001	0·57 (0·43–0·75)	0·0001	488 (50%)	1·00 (0·83–1·20)	0·99	0·85 (0·70–1·03)	0·09
Hypertension	432 (53%)	208 (74%)	0·39 (0·29–0·53)	<0·0001	0·41 (0·30–0·56)	<0·0001	665 (68%)	0·55 (0·45–0·66)	<0·0001	0·64 (0·53–0·79)	<0·0001
Diabetes	99 (12%)	52 (19%)	0·61 (0·42–0·88)	0·008	0·62 (0·43–0·90)	0·01	132 (13%)	0·90 (0·68–1·19)	0·45	0·89 (0·67–1·18)	0·40
Hypercholesterolaemia	265 (33%)	137 (49%)	0·51 (0·38–0·67)	<0·0001	0·53 (0·40–0·70)	<0·0001	345 (35%)	0·90 (0·74–1·09)	0·29	0·91 (0·74–1·10)	0·34
Past or present smoker*	444 (55%)	183 (65%)	0·64 (0·49–0·85)	0·002	0·68 (0·51–0·92)	0·01	544 (55%)	0·98 (0·81–1·18)	0·79	0·92 (0·76–1·13)	0·43

Data are mean (SD) or number (%), unless otherwise specified. LAD=large artery disease. Non-LAD=small vessel disease and cardioembolic events combined. OR=odds ratio. *Data missing for four patients with cardioembolic events and two with cryptogenic events.

Table 2: **Prevalence of different risk factors in cryptogenic versus other transient ischaemic attack and ischaemic stroke subtypes**

analyses by phase (phase 1 *vs* phase 2). We also did a sensitivity analysis confined to an ideal cryptogenic group using the ESUS definition; this group included all patients with cryptogenic events who had brain imaging, intracranial and extracranial vascular imaging, prolonged cardiac monitoring (5 days), and echocardiography. All analyses were done using SPSS version 20.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

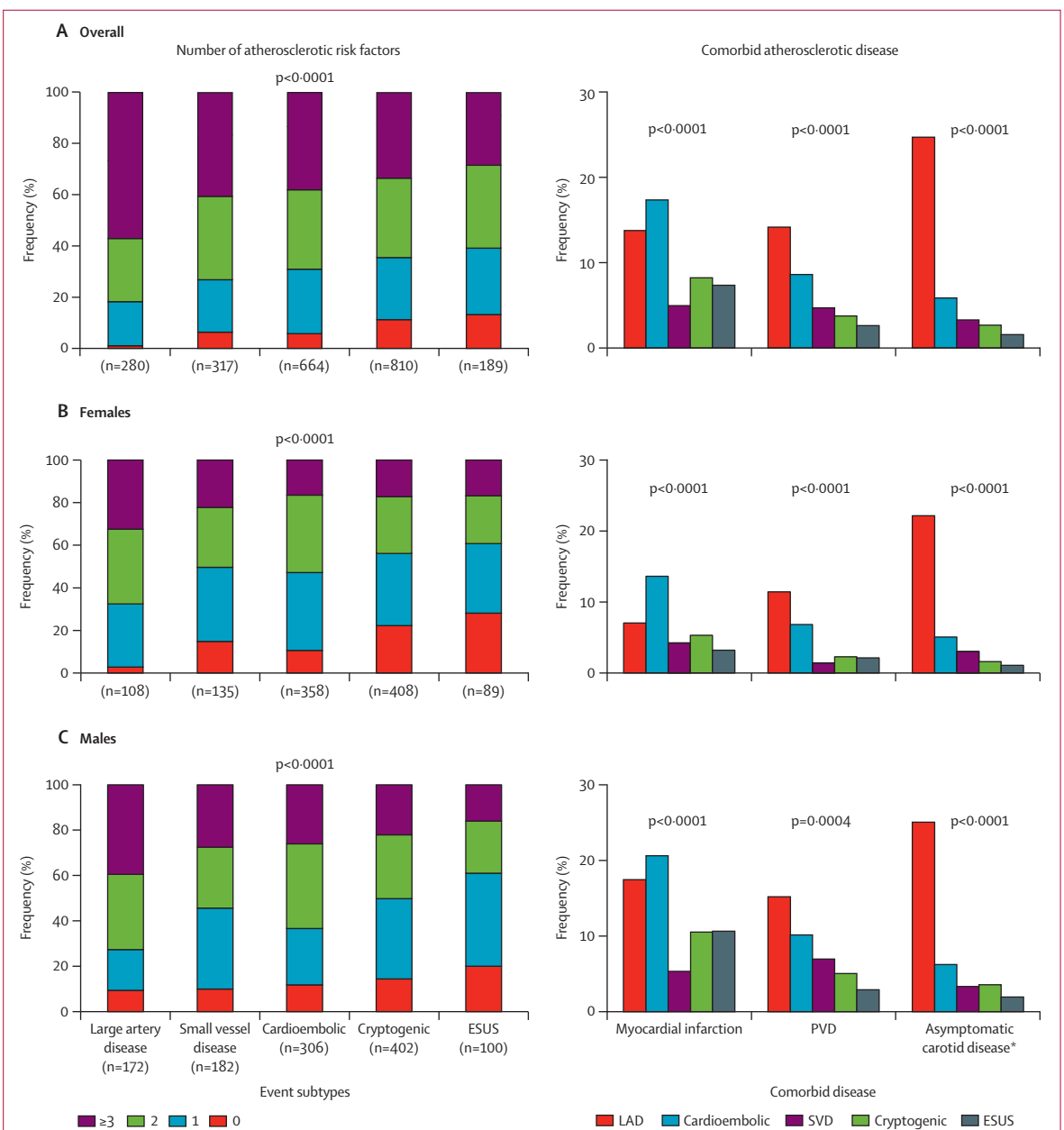

Figure 1: **Number of atherosclerotic risk factors and frequency of comorbid atherosclerotic disease in different transient ischaemic attack and ischaemic stroke subtypes**

Frequencies of risk factors and comorbid disease are shown (A) overall and for (B) females and (C) males. Data on smoking status were missing in four patients with cardioembolic events and two patients with cryptogenic events. Risk factors were male sex, hypertension, diabetes, hypercholesterolaemia, and history of smoking. Male sex was not taken into account in the stratification analysis by sex (ie, B and C). p values are for heterogeneity among all subtypes using the χ^2 test. ESUS=embolic strokes of undetermined source. LAD=large artery disease. PVD=peripheral vascular disease. SVD=small vessel disease. *Asymptomatic carotid stenosis ≥50% at bifurcation.

Results

Of 2555 patients with a first ischaemic event (1607 stroke and 948 TIA), 812 (32%) were classified as cryptogenic, 668 (26%) cardioembolic, 280 (11%) large artery disease, 317 (12%) small vessel disease, 331 (13%) unknown cause, 90 (4%) with more than one cause, and 57 (2%) as other causes. These proportions were in line with data from other published population-based studies in predominantly white populations (appendix p 7). Among the 226 patients aged younger than 55 years, 108 (48%) had cryptogenic events. Incidence of cryptogenic stroke was 0·36 per 1000 population per year (95% CI 0·23–0·49) and seemed to be higher in men than women, particularly at younger ages (ie, <55 years; appendix p 8).

Table 1 lists the baseline characteristics of all patients. Among 2441 patients who presented with cerebral events (ie, excluding ocular ischaemic events), 2315 (95%) had brain imaging or autopsy for the index event. The appendix (p 9) details the diagnostic work-up in patients classified as having cryptogenic events. All patients were prescribed standard treatment after the event, and secondary prevention during follow-up was broadly similar between patients with cryptogenic events and those with events of known cause (table 1).

Patients with cryptogenic events had the lowest prevalence of risk factors for atherosclerosis (table 2). Compared with patients with large artery TIA or stroke, they had less hypertension (age-adjusted and sex-adjusted odds ratio [OR] 0·41, 0·30–0·56; p<0·0001), diabetes (0·62, 0·43–0·90; p=0·01), hypercholesterolaemia (0·53, 0·40–0·70; p<0·0001), and history of smoking (0·68, 0·51–0·92; p=0·01). Moreover, no individual risk factor was proportionally more prevalent in the cryptogenic than in the non-large artery disease groups (ie, cardioembolic and small vessel disease; table 2) and the cryptogenic group had fewer risk factors overall (figure 1) than the large artery disease (p<0·0001), small vessel disease (p=0·001), and cardioembolic (p=0·008) groups, with similar findings for the ESUS-defined cryptogenic group (p<0·0001, p=0·0003, and p=0·001, respectively; figure 1). The results were broadly similar for men and women (figure 1), analyses that excluded TIA (appendix p 10), OXVASC phase 1 and phase 2 (appendix p 11), analyses that included only patients with MRI or only patients with acute infarct on imaging (appendix p 12), and ESUS versus large artery disease subtype and ESUS versus non-large artery disease subtypes (appendix p 13).

Compared with large artery and cardioembolic events, patients with cryptogenic events had the lowest prevalence of previous myocardial infarction and peripheral vascular disease (figure 1). Compared with patients with large artery TIA or stroke, they had less peripheral vascular disease (40 [14%] *vs* 31 [4%]; adjusted OR 0·27, 0·17–0·45; p<0·0001), and weak evidence of less myocardial infarction (39 [14%] *vs* 67 [8%]; 0·68, 0·44–1·04; p=0·08). Compared with patients with non-large artery subtypes, those with cryptogenic events had less peripheral vascular disease (73 [7%] *vs* 31 [4%]; adjusted OR 0·56, 95% CI 0·36–0·87; p=0·01) and less myocardial infarction (133 [14%] *vs* 67 [8%]; 0·68, 0·49–0·93; p=0·02).

The cryptogenic group also had the least stenosis at the asymptomatic carotid bifurcation (figure 2). They had no excess risk compared with small vessel and cardioembolic subtypes combined (adjusted OR 0·64, 95% CI 0·37–1·11; p=0·11). 22 (3%) of 812 patients in the cryptogenic group had at least 50% asymptomatic stenosis, compared with 69 (25%) of 277 in the large artery disease group (adjusted OR 0·09, 95% CI 0·06–0·16; p<0·0001), 23 (6%) of 390 in the cardioembolic group (0·58, 0·32–1·06; p=0·08), and ten (3%) of 302 in the small vessel disease group (0·82, 0·38–1·76; p=0·61). Results were similar in sensitivity analyses that excluded patients with TIA (appendix p 10), that were stratified by different study phases (appendix p 11), that included only cases with MRI (appendix p 12), and that compared the ESUS group with other subtypes (appendix p 13).

The cryptogenic group excluded all patients who were known to have or found to be in AF at initial assessment or during routine inpatient investigation. In phase 2 of the study, patients with TIA and non-disabling stroke had ambulatory home cardiac monitoring. The cause was changed to cardioembolic from cryptogenic or to more than one cause from large artery or small vessel subtypes if paroxysmal AF longer than 30 s was detected on ambulatory monitoring. Among the 322 (80%) of 401 phase 2 patients with TIA or non-disabling stroke who had ambulatory monitoring—all of whom also had echocardiography—11 (6%) of 197 patients with cryptogenic events had paroxysmal AF longer than 30 s compared with 12 (10%) of 125 patients with other non-cardioembolic events (ie, large artery disease and small vessel disease combined; p=0·17). The proportion of patients with minor-risk potential cardioembolic sources on echocardiography was 74 (37%) of 198 after cryptogenic

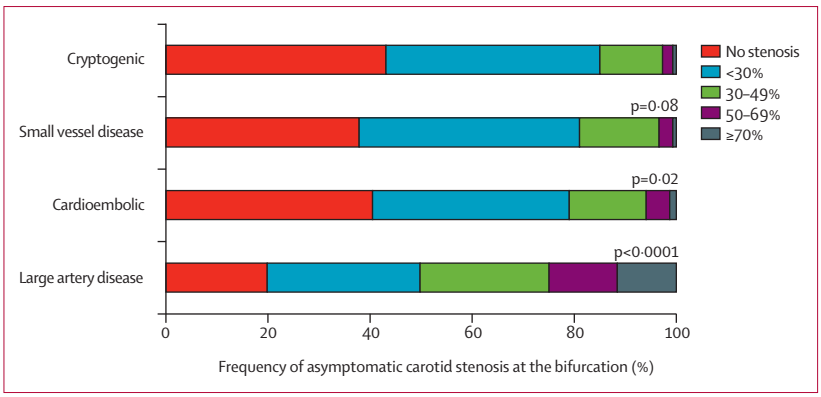

Figure 2: **Severity of stenosis at the asymptomatic carotid bifurcation in different transient ischaemic attack and ischaemic stroke subtypes**

Carotid events were calculated as carotid stenosis (%) at the asymptomatic side; posterior circulation events were calculated as mean carotid stenosis (%) of both carotid arteries at the bifurcation. p values are for the difference of stenosis distribution between cryptogenic and other subtypes.

events and 57 (45%) of 127 after non-cardioembolic events (p=0·18).

During 10 698 patient-years of follow-up, 1101 deaths, 412 recurrent ischaemic strokes, 143 acute coronary events, and 26 acute peripheral events of presumed cardioembolic cause occurred. Among the 438 recurrent ischaemic strokes and acute peripheral vascular events, 189 were presumed cardioembolic, of which 173 were AF related, with AF newly diagnosed during follow-up in 39 of these patients. A further 53 patients also developed new AF during follow-up, but had no embolic event.

Compared with patients with non-cardioembolic ischaemic stroke (ie, small vessel disease and large artery disease stroke), a similar proportion of those with cryptogenic stroke died or were dependent (modified Rankin Scale >2) at 6 months (cryptogenic 23% *vs* 27%; p=0·26). Moreover, between cryptogenic stroke and non-cardioembolic ischaemic stroke, the 10-year risks of death (46% *vs* 49%; p=0·63), vascular death (15% *vs* 15%; p=0·68), or any recurrent stroke (32% *vs* 27%; p=0·91) were also comparable (table 3). Risks of recurrent ischaemic stroke did not differ significantly between stroke subtypes (table 3; figure 3). However, when index TIAs were included in the analysis, cryptogenic cases had a lower risk of recurrent ischaemic stroke than did cases with cardioembolic cause (age-adjusted and sex-adjusted hazard ratio [HR] 0·66, 95% CI 0·51–0·87; p=0·003), large artery disease (0·67, 0·48–0·92; p=0·02), and small vessel disease (0·67, 0·49–0·91; p=0·01); however, this difference between cryptogenic cases and cases with known cause was mainly due to lower early risks (<90 days) of recurrent ischaemic stroke after cryptogenic events than after events of known cause (adjusted HR 0·47, 95% CI 0·32–0·70; p=0·0001). The risks of ischaemic stroke after 90 days were not significantly lower after cryptogenic events than after cases of known cause (adjusted HR 0·80, 95% CI 0·60–1·06; p=0·12). 70 (63%) of 112 recurrent strokes after cryptogenic events remained cryptogenic after further investigation (table 4).

	Cryptogenic (n=392)		Small vessel disease (n=220)		Large artery disease (n=158)		Cardioembolic (n=472)		p value
	Number	% (95% CI)*	Number	% (95% CI)*	Number	% (95% CI)*	Number	% (95% CI)*	
Disability (mRS >2)									
Premorbid†	58	15%‡	18	8%‡	17	11%‡	146	32%‡	p<0·0001§
6 months¶	89	23%‡	50	23%‡	51	32%‡	305	66%‡	p<0·0001§
Mortality									
1 year	23	6·0% (3·6–8·4)	2	0·9% (0·0–2·1)	23	14·7% (9·2–20·2)	196	41·7% (37·2–46·2)	p<0·0001
5 years	80	24·9% (20·0–29·8)	37	19·8% (13·9–25·7)	42	30·9% (22·9–38·9)	280	64·6% (59·9–69·3)	p<0·0001
10 years	114	45·5% (38·4–52·6)	64	44·9% (35·9–53·9)	56	54·9% (42·6–67·2)	317	83·3% (78·2–88·4)	p<0·0001
Vascular death									
1 year	11	2·8% (1·2–4·4)	2	0·9% (0·0–2·1)	12	7·8% (3·5–12·1)	155	34·0% (29·7–38·3)	p<0·0001
5 years	32	10·0% (6·7–13·3)	12	6·4% (2·9–9·9)	14	9·9% (4·8–15·0)	183	43·5% (38·6–48·4)	p<0·0001
10 years	39	15·4% (10·3–20·5)	17	12·2% (6·1–18·3)	18	21·7% (8·6–34·8)	195	53·4% (46·5–60·3)	p<0·0001
Any recurrent stroke									
1 year	35	9·1% (6·2–12·0)	27	12·3% (8·0–16·6)	21	14·0% (8·5–19·5)	54	15·1% (11·4–18·8)	0·11
5 years	76	24·0% (19·1–28·9)	41	20·5% (14·8–26·2)	31	24·1% (16·3–31·9)	79	27·8% (21·9–33·7)	0·25
10 years	85	31·9% (25·2–38·6)	47	26·9% (19·5–34·3)	32	26·9% (17·7–36·1)	87	40·0% (30·6–49·4)	0·13
Any recurrent ischaemic stroke									
1 year	34	8·8% (6·1–11·5)	27	12·3% (8·0–16·6)	20	13·4% (7·9–18·9)	50	14·0% (10·3–17·7)	0·19
5 years	73	23·2% (18·3–28·1)	40	20·0% (14·3–25·7)	30	23·4% (15·8–31·0)	72	25·3% (19·6–31·0)	0·49
10 years	79	28·6% (22·3–34·9)	46	26·4% (19·1–33·7)	31	26·2% (17·0–35·4)	79	36·3% (26·9–45·7)	0·32
Any acute coronary syndrome									
1 year	5	1·3% (0·1–2·5)	0	..	6	4·1% (1·0–7·2)	12	3·3% (1·3–5·3)	0·008
5 years	14	4·2% (2·0–6·4)	9	4·6% (1·7–7·5)	11	9·5% (4·0–15·0)	20	8·2% (4·5–11·9)	0·10
10 years	18	8·7% (3·6–13·8)	11	7·3% (2·6–12·0)	17	22·2% (11·2–33·2)	23	11·8% (6·3–17·3)	0·005
Any recurrent cardioembolic event									
1 year	2	0·5% (0·0–1·3)	0	..	2	1·3% (0·0–3·1)	53	14·5% (10·8–18·2)	p<0·0001
5 years	14	5·1% (2·4–7·8)	4	2·3% (0·0–4·7)	3	2·2% (0·0–4·7)	74	25·0% (19·5–30·5)	p<0·0001
10 years	18	9·2% (4·3–14·1)	5	4·3% (0·0–8·8)	4	6·3% (0·0–14·5)	79	31·3% (23·9–38·7)	p<0·0001

p values are log-rank p, unless otherwise specified. mRS=modified Rankin Scale. *Represents absolute risk, unless otherwise specified. †Data missing for 22 patients: 15 for cardioembolic, three for large artery disease, and four for cryptogenic stroke. ‡Outcome of the index event reported as percentage of total. §χ^2 test. ¶Data missing for 20 patients: ten for cardioembolic, one for large artery disease, and nine for cryptogenic stroke.

Table 3: **Outcome and prognosis of cryptogenic stroke and ischaemic stroke of known cause**

Patients with cryptogenic events had a significantly lower risk of acute coronary events than did those with large artery disease events (adjusted HR 0·40, 95% CI 0·24–0·66; p=0·0003) and a similar risk to those with non-large artery disease events (0·76, 0·49–1·18; p=0·22; figure 3). Patients with cryptogenic events also had a low risk of presumed cardioembolic events (26 events, 10-year risk 6·4%, 95% CI 3·6–9·1), which was similar to that in patients with large artery disease and small vessel disease events combined (adjusted HR 1·16, 95% CI 0·62–2·17; p=0·64; figure 3). No patient with cryptogenic events presented with any recurrent cardioembolic event within 90 days of the index event. Of all 85 recurrent strokes of cryptogenic or unknown cause after an index cryptogenic

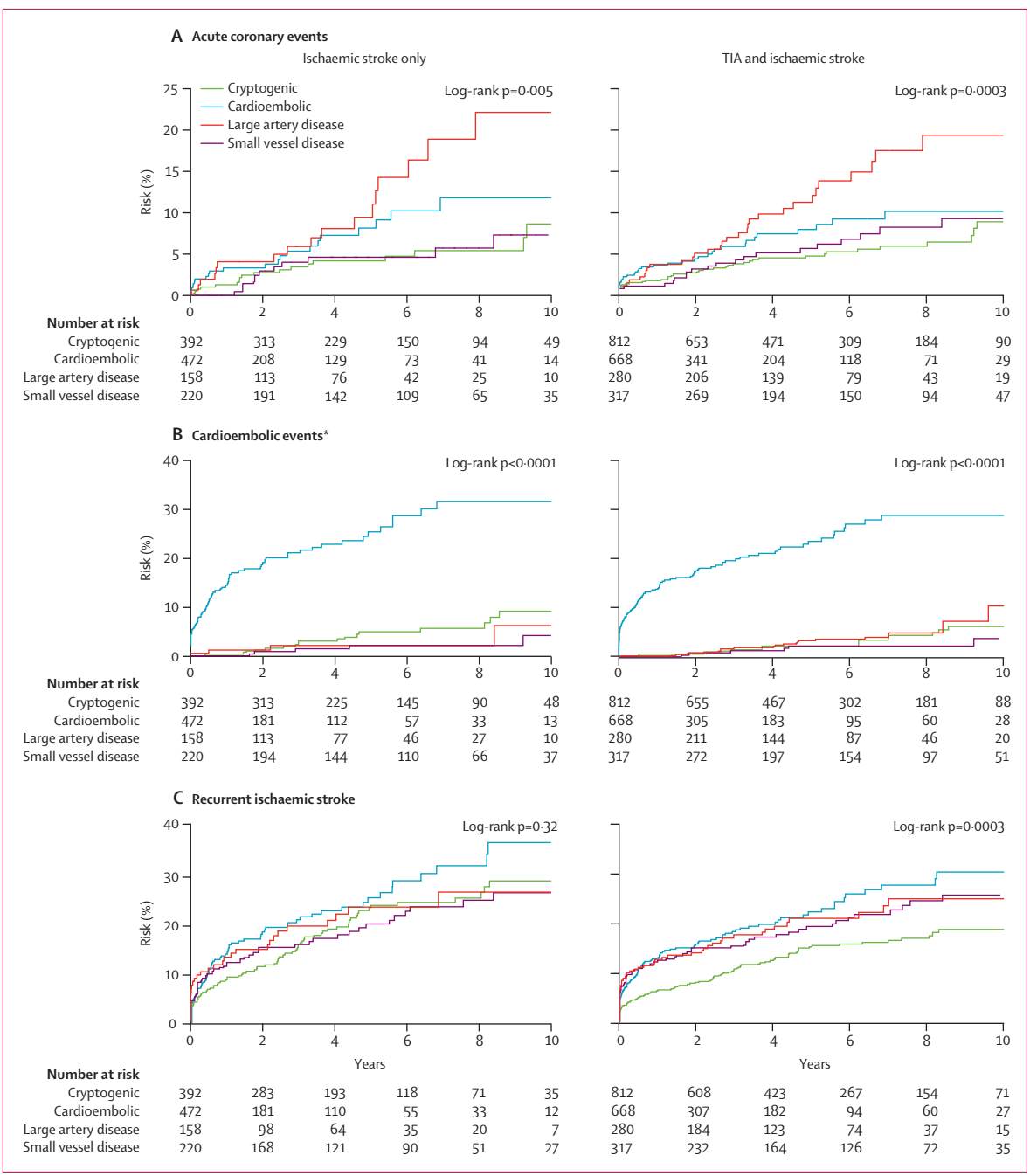

Figure 3: **10-year absolute risks of acute coronary events, cardioembolic events, and recurrent ischaemic stroke**
TIA=transient ischaemic attack. *Consisted of recurrent cardioembolic stroke, acute embolic limb ischaemia, and acute embolic visceral embolisation caused by presumed cardioembolism.

	First recurrent ischaemic stroke								Presumed PVE				New AF-related ischaemic stroke or PVE
	Cardioembolic	Large artery disease	Small vessel disease	Cryptogenic	Unknown cause	More than one cause	Other causes	Total	New AF	Known AF	No AF	Total	
Cardioembolic	101 (89%)*	2	0	0	5	3	2	113	0	10	1	11	1
Large artery disease	4	41 (76%)*	2	1	4	0	2	54	2	0	1	3	7
Small vessel disease	4	3	37 (58%)*	15	5	0	0	64	0	0	2	2	5
Cryptogenic	17	4	5	70 (63%)*	15	1	0	112	1	0	5	6	21
Unknown cause	5	0	1	1	36 (82%)*	0	1	44	1	0	1	2	5
More than one cause	7	1	0	0	0	9 (53%)*	0	17	0	1	0	1	0
Other causes	1	0	0	0	0	1	6 (75%)*	8	0	0	1	1	0
Total	139†	51	45	87	65	14	11	412	4	11	11	26	39

Data are number of patients or number of patients with recurrent events. AF=atrial fibrillation. PVE=peripheral vascular embolism. *Percentages are shown for the recurrent events that had the same cause as the index event. †134 (96%) were AF related. Three acute-myocardial-infarction-related recurrent strokes occurred after index cardioembolic, unknown cause, and large artery disease events, one recurrent stroke due to severe cardiac failure occurred after an index event of other cause, and one recurrent stroke with patent foramen ovale and concomitant pulmonary embolism occurred after an index event of unknown cause.

Table 4: **Subtypes of first recurrent ischaemic stroke or presumed embolic peripheral vascular events by index event subtype**

event, 82 were of a single vascular territory and three presented with acute infarcts in several vascular territories. Five peripheral vascular events with presumed embolic cause occurred with no proven embolic source after cryptogenic events versus two after small vessel disease and one after large artery disease events (table 4). The risk of any new AF during follow-up did not differ significantly between patients with cryptogenic events versus those with large artery disease and small vessel disease events combined (10-year risks 13·0% *vs* 9·3%; adjusted HR 1·23, 95% CI 0·78–1·95; p=0·37), and the risks of new AF-related cardioembolic events were also similar (5·4% *vs* 5·4%; 1·22, 0·60–2·50; p=0·58). The relative risks of cardioembolic events or new AF in patients with cryptogenic events versus large artery disease and small vessel disease events combined were consistent in phase 1 and phase 2 (appendix p 14). Sensitivity analyses excluding patients with TIA and comparing TOAST-defined non-ESUS cryptogenic cases and ESUS cases also showed consistent results (figure 3; appendix pp 15–16).

Discussion

In this population-based study, the burden of cryptogenic events was high, particularly in young patients. We did not screen for aortic atheroma, but patients with cryptogenic events had the lowest prevalence of risk factors for atherosclerosis, the lowest frequency of comorbid atherosclerotic disease, and the lowest risk of acute coronary events compared with patients with events of known cause. Similarly, patients with cryptogenic events had no excess of long-term risks of new AF or recurrent cardioembolic stroke or systemic embolism compared with large artery disease and small vessel disease subtypes. We did not routinely screen for PFO, but we found no increased prevalence of paroxysmal AF or minor-risk cardiac abnormalities on imaging in patients with cryptogenic events in phase 2 of OXVASC.

Only two previous retrospective hospital-based studies specifically aimed to establish the risk-factor profile of cryptogenic stroke: one study of anterior circulation stroke[15] that showed that cryptogenic stroke had similar prevalence of vascular risk factors to large artery disease and small vessel disease, and one small case-control study[16] of patients aged younger than 60 years that showed that hypertension and present smoking were independently associated with cryptogenic stroke. Previous studies of prognosis of cryptogenic stroke had mostly only short-term follow-up, and many did not separate cryptogenic stroke from ischaemic stroke of several or unknown causes (appendix p 4). We found little evidence to support the suggestion that cryptogenic stroke might often be caused by occult arterial sources of thromboembolism.[3] Although complex proximal aortic atheroma has been incorporated in the newly published ischaemic stroke classification systems,[5,21] the number of strokes caused by such plaques remains controversial. Findings from case-control and hospital-based cohort studies showed a strong association between complex aortic atheroma and ischaemic stroke.[22,23] However, population-based cohort studies have so far not confirmed this finding.[24–26] In studies confined to cryptogenic stroke, results have also been conflicting.[3,27] However, the aortic arch is not the only potential site of occult atherosclerosis, and to what extent non-stenosing atherosclerosis not visible on lumen imaging studies might still lead to thromboembolism is also uncertain. We therefore used several potential surrogate markers of the likely overall burden of occult atherosclerosis: the frequency of traditional atherosclerotic risk factors, the prevalence of

symptomatic atherosclerosis in coronary and peripheral arterial territories, and the severity of any asymptomatic carotid stenosis. Although none of these surrogates is ideal, we found no evidence of any excess of atherosclerotic potential in patients with cryptogenic events. Findings from a 2012 study[28] that used a similar surrogate approach involving genetic markers of atherosclerotic potential also showed a low proportion of cryptogenic strokes that were probably arterial in nature.[28]

We also found little evidence to support the suggestion that cryptogenic stroke might often be caused by subclinical paroxysmal AF.[7,8] Findings from recent studies of prolonged cardiac monitoring using 30-day recording or implantable devices have shown rates of paroxysmal AF of up to 16% up to 6 months after cryptogenic stroke,[7,8] with higher rates on longer-term recording.[7] However, we do not know in how many cases these generally short runs of paroxysmal AF are causally related to stroke. In ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial),[29] few patients who had stroke during follow-up had paroxysmal AF detected on implanted pacemakers in the month before their event, and in many cases AF was detected only after an embolic event despite no record on prolonged monitoring beforehand. In phase 1 of our study, few patients with cryptogenic TIA or ischaemic stroke underwent ambulatory home cardiac monitoring, such that the rate of recurrent stroke caused by unrecognised paroxysmal AF in patients treated only with antiplatelet drugs should have been high. We found that the long-term risk of cardioembolic events was low and was no greater than after large artery disease or small vessel disease events. The same was true for the risk of all new AF on follow-up. In phase 2, when 5-day ambulatory cardiac monitoring was routine, the rate of paroxysmal AF lasting for longer than 30 s did not differ between otherwise cryptogenic, large artery disease, or small vessel disease events.

We found no excess of minor-risk cardiac abnormalities on echocardiography. However, since we did not screen routinely for PFO, we were not able to compare the prevalence of PFO in cryptogenic cases versus cases of known cause. Associations between PFO and cryptogenic stroke in young patients have been suggested by findings from case-control studies.[3] However, the relation had been inconsistent in older patients.[30,31] In view of evidence that the diameter of PFO and the prevalence of venous thrombosis increased with age,[31] older patients might be more susceptible to paradoxical embolism associated with PFO. More research into the possible association between PFO and cryptogenic TIA and stroke at older ages is needed.

Although we consider our conclusions to be valid, our study has limitations. First, although intracranial vascular imaging was routine in phase 2 of our study, some patients with intracranial stenosis in phase 1 would have been misclassified as having cryptogenic events. However, this misclassification should have biased our analysis to finding more atherosclerotic markers in the cryptogenic group. Moreover, our analyses confined to the cryptogenic group in phase 2 showed results consistent with phase 1. Second, because brain MRI was routinely done only in phase 2, we might have misclassified some small vessel disease cases with non-lacunar syndrome and normal CT brain imaging as cryptogenic events or vice versa. However, our sensitivity analysis including only patients who underwent MRI showed consistent results. Third, echocardiography and prolonged ambulatory cardiac monitoring were similarly only done routinely in phase 2. However, we found no excess of paroxysmal AF or minor-risk cardiac abnormalities in patients with cryptogenic events in phase 2, suggesting that misclassification in phase 1 is unlikely to have biased our results substantially. Fourth, since transoesophageal echocardiography or bubble saline contrast echocardiography were not done in all patients overall, we might have underestimated the burden of some minor-risk cardiac abnormalities, although undertaking transoesophageal echocardiography in all patients in a large population-based study is not feasible and is not required for the ESUS definition.[3] Similarly, since we did not screen routinely for PFO in either phase, we were not able to address the potential association between PFO and cryptogenic events. Fifth, AF was ascertained during follow-up on a clinical basis, and we did not repeat ambulatory monitoring. However, since the causative relevance of short runs of paroxysmal AF detected shortly after the index events is still debatable, the results of regular intensive cardiac monitoring during long-term follow-up would be difficult to interpret. Sixth, although we used several overlapping methods (ie, interviews, ongoing daily ascertainment, primary diagnostic coding, death certificates, and national hospital coding) to achieve near complete follow-up, a small proportion of patients (<1%) who emigrated might not have been followed up. Finally, our results apply only to a predominantly white population in the UK.

Our findings have implications for research and practice. In view of the large burden of cryptogenic events in OXVASC and in previous population-based studies, further research on potential causes and treatments in fully investigated cohorts is needed. Future studies should report results separately for cryptogenic events rather than combining them with strokes of unknown cause because of incomplete investigation or those with several potential pathological abnormalities. More research on detection of aortic plaque, other non-stenosing atherosclerosis, intensive cardiac rhythm monitoring, PFO, and minor-risk cardiac abnormalities, particularly in the elderly, is still necessary. However, in view of the high rate of recurrent cryptogenic stroke, randomised trials of available preventive treatments, such as the ongoing trials of new anticoagulants,[32,33] are justified

despite uncertainty about cause and might also cast light on the cause and pathogenesis of cryptogenic events.

Contributors

LL collected data, did the statistical analysis and interpretation, and wrote and revised the manuscript. GSY, OCG, UGS, and WK acquired data and revised the manuscript. ZM did the statistical analysis. PMR conceived and designed the study, provided study supervision and funding, analysed and interpreted data, and wrote and revised the manuscript.

Declaration of interests

We declare no competing interests.

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References

1 Amarenco P. Cryptogenic stroke, aortic arch atheroma, patent foramen ovale, and the risk of stroke. *Cerebrovasc Dis* 2005; **20** (suppl 2): 68–74.

2 Bang OY, Lee PH, Joo SY, Lee JS, Joo IS, Huh K. Frequency and mechanisms of stroke recurrence after cryptogenic stroke. *Ann Neurol* 2003; **54:** 227–34.

3 Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014; **13:** 429–38.

4 Ntaios G, Papavasileiou V, Milionis H, et al. Embolic strokes of undetermined source in the athens stroke registry: a descriptive analysis. *Stroke* 2015; **46:** 176–81.

5 Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. New approach to stroke subtyping: the A-S-C-O (phenotypic) classification of stroke. *Cerebrovasc Dis* 2009; **27:** 502–08.

6 Gu X, He Y, Li Z, et al. Comparison of frequencies of patent foramen ovale and thoracic aortic atherosclerosis in patients with cryptogenic ischemic stroke undergoing transesophageal echocardiography. *Am J Cardiol* 2011; **108:** 1815–19.

7 Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014; **370:** 2478–86.

8 Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014; **370:** 2467–77.

9 O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010; **376:** 112–23.

10 Schulz UG, Rothwell PM. Differences in vascular risk factors between etiological subtypes of ischemic stroke: importance of population-based studies. *Stroke* 2003; **34:** 2050–59.

11 Song YM, Kwon SU, Sung J, et al. Different risk factor profiles between subtypes of ischemic stroke. A case-control study in Korean men. *Eur J Epidemiol* 2005; **20:** 605–12.

12 Rothwell PM, Villagra R, Gibson R, Donders RC, Warlow CP. Evidence of a chronic systemic cause of instability of atherosclerotic plaques. *Lancet* 2000; **355:** 19–24.

13 Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998; **82:** 2N–9N.

14 Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006; **367:** 1903–12.

15 Bang OY, Lee PH, Yeo SH, Kim JW, Joo IS, Huh K. Non-cardioembolic mechanisms in cryptogenic stroke: clinical and diffusion-weighted imaging features. *J Clin Neurol* 2005; **1:** 50–58.

16 Karttunen V, Alfthan G, Hiltunen L, et al. Risk factors for cryptogenic ischaemic stroke. *Eur J Neurol* 2002; **9:** 625–32.

17 Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet* 2004; **363:** 1925–33.

18 Feigin V, Hoorn SV. How to study stroke incidence. *Lancet* 2004; **363:** 1920.

19 Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; **24:** 35–41.

20 Jackson C, Sudlow C. Are lacunar strokes really different? A systematic review of differences in risk factor profiles between lacunar and nonlacunar infarcts. *Stroke* 2005; **36:** 891–901.

21 Ay H, Benner T, Arsava EM, et al. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. *Stroke* 2007; **38:** 2979–84.

22 Amarenco P, Cohen A, Tzourio C, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med* 1994; **331:** 1474–79.

23 The French Study of Aortic Plaques in Stroke Group. Atherosclerotic disease of the aortic arch as a risk factor for recurrent ischemic stroke. *N Engl J Med* 1996; **334:** 1216–21.

24 Meissner I, Khandheria BK, Sheps SG, et al. Atherosclerosis of the aorta: risk factor, risk marker, or innocent bystander? A prospective population-based transesophageal echocardiography study. *J Am Coll Cardiol* 2004; **44:** 1018–24.

25 Russo C, Jin Z, Rundek T, Homma S, Sacco RL, Di Tullio MR. Atherosclerotic disease of the proximal aorta and the risk of vascular events in a population-based cohort: the Aortic Plaques and Risk of Ischemic Stroke (APRIS) study. *Stroke* 2009; **40:** 2313–18.

26 Agmon Y, Khandheria BK, Meissner I, et al. Relation of coronary artery disease and cerebrovascular disease with atherosclerosis of the thoracic aorta in the general population. *Am J Cardiol* 2002; **89:** 262–67.

27 Katsanos AH, Giannopoulos S, Kosmidou M, et al. Complex atheromatous plaques in the descending aorta and the risk of stroke: a systematic review and meta-analysis. *Stroke* 2014; **45:** 1764–70.

28 Jickling GC, Stamova B, Ander BP, et al. Prediction of cardioembolic, arterial, and lacunar causes of cryptogenic stroke by gene expression and infarct location. *Stroke* 2012; **43:** 2036–41.

29 Brambatti M, Connolly SJ, Gold MR, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation* 2014; **129:** 2094–99.

30 Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke. A meta-analysis of case-control studies. *Neurology* 2000; **55:** 1172–79.

31 Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med* 2007; **357:** 2262–68.

32 Diener HC, Connolly S, Easton J, Smith J, Duffy C, Bruckmann M. Rationale, objectives and design of a secondary stroke prevention study of dabigatran etexilate versus acetylsalicylic acid in patients with embolic stroke of undetermined source (RE-SPECT-ESUS). *Cerebrovasc Dis* 2014; **37:** 261.

33 The NAVIGATE ESUS trial. Population Health Research Institute. http://www.phri.ca/research/stroke-cognition/navigate-esus/ (accessed Feb 8, 2015).