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Prevalence, predictors and prognosis of symptomatic intracranial stenosis in patients with TIA or minor stroke: population-based cohort study

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On behalf of the Oxford Vascular Study phenotyped cohort

Abstract

Background—Symptomatic intracranial stenosis (ICS) was perceived to convey a high risk of recurrent stroke but trials (*Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis* (SAMMPRIS) and *Vitesse Intracranial Stent Study for Ischemic Stroke Therapy* (VISSIT)) failed to show superiority of ICS stenting over intensive medical management alone, partly due to a lower than expected risk of recurrent stroke without stenting, possibly reflecting the young age of recruits (median age <60 years), and raising questions about generalisability to routine clinical practice. We therefore studied the age-specific prevalence, predictors and prognosis of symptomatic ICS in a population-based cohort of patients with transient ischaemic attack (TIA) and minor stroke on intensive medical management.

Methods—The Oxford Vascular Study (OXVASC) is a prospective incidence study of all vascular events in a population of 92,728 people residing in Oxfordshire, UK. All patients, irrespective of age, with TIA and minor ischaemic stroke occurring between 1st March 2011 and 1st March 2018 (follow-up to 28th September 2018) were ascertained with multiple methods, including assessment in a dedicated daily emergency clinic and daily review of all hospital admissions. Imaging was by magnetic resonance angiography (MRA) of the intracranial and cervicocranial arteries, by computed tomography angiography (CTA) if MRA was contraindicated, and by carotid/transcranial Doppler ultrasound if CTA was contraindicated. We determined the age-specific prevalence of 50-99% ICS and the associated stroke risk of 50-99% and 70-99% stenosis (adjusted for age and vascular risk factors) by face-to-face follow-up to 2019 on intensive medical treatment without stenting.

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Dr. Lau reports grants, personal fees and non-financial support from Boehringer Ingelheim, grants and non-financial support from Pfizer, grants from Sanofi, grants from Eisai, outside the submitted work.

Contributions of the authors
Robert Hurford was responsible for acquisition of data, analysis and interpretation and drafting of the manuscript. Wilhelm Küker was responsible for imaging analysis. Peter M Rothwell was responsible for study conception, design, supervision, funding, analysis and interpretation of data and drafting of the manuscript. Other authors were responsible for acquisition of data and for revision of the manuscript.

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Findings—Of 1368 eligible patients with intracranial vascular imaging, 241 (17.6%) had a total of 385 50-99% symptomatic or asymptomatic ICS. The prevalence of symptomatic 50-99% ICS increased from 29/596 (4.9%) at age <70 to 10/51 (19.6%) at age ≥90 years (p_{trend} <0.0001). Of 94 patients with 50-99% symptomatic ICS, 14 had recurrent strokes (12 ischaemic; 2 haemorrhages) during median follow-up of 2.8 years (interquartile range= 3.1). Although symptomatic ICS conveyed an increased risk of ischaemic stroke compared to no ICS (adjusted hazard ratio= 1.43, 1.04-1.96), the risks of same-territory ischaemic stroke in patients with 70-99% symptomatic ICS tended to be less than those reported in the non-stenting arms of the trials (1-year risk – 5.6%, 0.0-13.0 vs 9.4%, 3.1-20.7 in VISSIT; 2-year risk – 5.6%, 0.0-13.0 vs 14.1%, 10.1-19.4 in SAMMPRIS).

Interpretation—The prevalence of 50-99% symptomatic ICS increases steeply with age in predominantly Caucasian patients with TIA and minor stroke. However, the risk of recurrent stroke on intensive medical treatment of symptomatic ICS is consistent with randomised trials in younger cohorts, supporting their generalisability to routine practice.

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Introduction

Intracranial atherosclerotic stenosis (ICS) of the major cerebral arteries is an important cause of ischaemic stroke.[1,2] ICS is particularly prevalent in Asians[3–6] but is under-investigated in population-based studies of non-Asians (Supplementary Material pages 1-3, Table 1a) Although patients with ICS have long been considered to be at high risk of recurrent stroke (Supplementary Material pages 4-6, Table 1b), and percutaneous stenting was therefore developed and widely used in some countries, two recent randomised controlled trials failed to show superiority of percutaneous stenting over intensive medical management in patients with recently symptomatic ICS: Stenting *Versus Aggressive Medical Management Therapy for Intracranial Arterial Stenosis* (SAMMPRIS)[7] and *Vitesse Intracranial Stent Study for Ischemic Stroke Therapy* (VISSIT).[8] Both trials were stopped early partly due to lower than expected recurrent stroke rates in the medical management groups; SAMMPRIS reported a 2-year risk of death or stroke in the ICS territory of 14.1% (95% CI 10.1-19.4) and VISSIT reported a 1-year risk of stroke or TIA in the ICS territory of 15.1% (6.7-27.6).[8,9]

Although recent guidelines have reflected the results of SAMMPRIS and VISSIT,[10,11] there is evidence of ongoing angioplasty or stenting for symptomatic ICS in some healthcare systems,[12,13] and the generalisability of the results of the trials has been questioned.[14,15] Two particular non-technical criticisms of the trials have been raised. Firstly, the better than expected prognosis on medical treatment alone in these trials might reflect the exclusion of elderly patients from both, with a median age at recruitment of less than 60 years, such that generalisability of the trial results to older patients is uncertain. Secondly, the particularly intensive medical treatment may have been responsible for the low stroke risks in the medical treatment only arms compared with previous studies.[16,17]

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To understand the external validity of the findings in the recent trials of stenting versus medical treatment only for recently symptomatic ICS in relation to age and intensive medical treatment, we aimed to determine the age-specific prognosis of symptomatic ICS in a population-based cohort of patients with transient ischaemic attack (TIA) and minor stroke (to replicate trial eligibility) recruited irrespective of age and followed-up on intensive medical treatment.

Methods

Study background

The Oxford Vascular Study (OXVASC) is a longitudinal population-based incidence cohort of all acute vascular events in a defined population of 92 728, covered by around 100 primary care physicians in nine primary care practices in Oxfordshire, UK. An estimated 97% of the true study residential population is registered with a primary care practice; most unregistered people are young students. The study area contains a mix of urban and rural populations. The OXVASC population is 94% Caucasian, 3% Asian, 2% Chinese, and 1% Afro-Caribbean.[18]

Written informed consent or assent from relatives was obtained in all participants for study interview and follow-up, including ongoing review of primary care and hospital records and death certificate data. OXVASC was approved by the Oxfordshire research ethics committee (OREC A: 05/Q1604/70).

Procedures

We studied consecutive patients referred to OXVASC between 1st March 2011 and 1st March 2018 with TIA or minor ischaemic stroke (defined as National Institute of Health Stroke Scale (NIHSS) ≤3) and consenting to investigation. Patients with intracranial vascular imaging were included in the analyses. Only TIA or minor ischaemic stroke patients were included in this study in order to reflect the eligibility criteria for SAMMPRIS and VISSIT, both of which excluded major disabling strokes.

Multiple overlapping methods were used for ascertainment of all individuals with TIA and stroke, approaching 100% of events reaching medical attention. These include the following: (1) a daily, rapid access clinic to which participating general practitioners and the local emergency department refer individuals with suspected TIA or minor stroke; (2) daily searches of admissions to the 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.[20,21]

Demographic data and stroke risk factors were collected from face-to-face interview by study physicians as soon as possible after referral or hospital admission and cross-referenced with primary care records. Detailed clinical history was recorded in all patients and assessments were made for stroke severity using the NIHSS as recorded on assessment.

Cause of ischaemic events was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[22] Stroke and TIA were defined according to World Health Organisation (WHO) criteria (acute onset of neurological deficit, persisting for >24 hours in case of a stroke, or for <24 hours in case of a TIA),[23] with review of all cases as soon as possible after presentation by the same senior neurologist (PMR) throughout the study.

Patients were followed up face to face at 1, 6, 12, 24, 60, and 120 months by a study nurse or physician to identify any recurrent stroke (supplemented by review of primary care records) and to ensure medication compliance and adequate blood pressure control. Patients who had moved out of the study area (or were unwilling/ unable to have face-to-face follow-up) were followed up via telephone at the same time-points. All recurrent events that occurred during follow-up would also be identified by the ongoing daily case ascertainment. We recorded all deaths during follow-up with the underlying causes by direct follow-up, via primary care records, and by centralised registration with Office for National Statistics (ONS).

Patients received intensive medical management, including dual anti-platelet therapy (Aspirin and Clopidogrel) for the first month with Aspirin or Clopidogrel monotherapy thereafter, high-dose statin and treatment of hypertension to guideline targets (<130/ 80 mmHg). Patients were also provided smoking cessation and dietary advice.

Intracranial vascular imaging done routinely in all patients in OXVASC from 2011 onwards. We attempted to obtain as high an imaging rate as possible by using magnetic resonance angiography (MRA) as first choice, computed tomography angiography (CTA; Toshiba, Aquilion 64, 64-slice scanner) if MRI was contraindicated (e.g. implantable devices or claustrophobia), and transcranial Doppler (TCD; Doppler Box; Compumedics DWL, Singen, Germany) and carotid ultrasound if CTA was also contraindicated (e.g. low estimated glomerular filtration rate).

The MRI scanners and protocols used in OXVASC have been described elsewhere,[25] but sequences included diffusion weighted imaging (DWI), time of flight (TOF) angiography of the intracranial arteries and gadolinium contrast enhanced angiography (CE-MRA) of the intracranial and cervicocranial arteries including the aortic arch. Patients were scanned at the Acute Vascular Imaging Centre (AVIC), John Radcliffe Hospital, in a 3.0 Tesla Siemens Verio scanner; a neurovascular coil was used (CE-MRA sequence: 15 ml ProHance® followed by 40 ml NaCl, flow rate 2 ml/s, TR 22 ms, TE 3.6 ms, Flip angle 18°, slice thickness 0.5 mm).

Reconstructed TOF and CE-MRA sequences were used to assess intracranial and extracranial stenosis, respectively. Both sequences were used for assessment of potential artefact. In the case of CTA use, unreconstructed CTA images were analysed.

Significant stenoses were defined as 50-99% of the luminal diameter, measured using the *Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis* (WASID) method[26] (between the narrowest point and compared with the normal luminal size prior to the stenosis) or using *Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis* (SONIA) criteria with TCD[24]. Symptomatic ICS detected by MRA or CTA

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were sub-classified into 70-99% stenosis also using the WASID method.[26] Trained assessors (RMH and FJW) independently evaluated the images for vascular stenosis, blinded to the clinical details and consultant neuroradiologist report (WK). In situations of disagreement, a third assessor adjudicated (LL). Arteries assessed include – extracranial: subclavian, common carotid, proximal internal carotid and vertebral (V1, V2, V3) and intracranial: distal internal carotid, middle cerebral (M1 and M2), anterior cerebral, posterior cerebral (P1 and P2), basilar, posterior communicating and vertebral (V4). Supplementary Table 2 (Supplementary Material page 7) outlines the standard anatomical landmarks used. All significant stenoses were classified as symptomatic or asymptomatic in relation to the most recent clinical presentation and results of parenchymal brain imaging.

Statistical analysis

Analyses included all eligible patients with intracranial vascular imaging. Interobserver agreement for 50-99% stenosis was assessed using Cohen's kappa.

Baseline characteristics were compared between patients with 50-99% ICS vs no ICS using Chi squared or Student's t-test as appropriate. The characteristics of patients with 50-99% and 70-99% symptomatic ICS were also compared with those in the non-stenting arms of the SAMMPRIS and VISSIT trials.

We calculated the age-specific prevalence of 50-99% symptomatic and asymptomatic ICS and occlusions in 10-year bands in OXVASC and compared rates with those for extracranial stenosis. We also determined any other predictors of any 50-99% symptomatic or asymptomatic ICS with univariate, age-adjusted and multivariate regression analyses.

We used Kaplan-Meier survival analysis to determine risk of recurrent ischaemic stroke during follow-up after the index event, stratified by 50-99% symptomatic ICS and no ICS, including and excluding patients with atrial fibrillation. Analyses were censored at recurrent event, death or the end of follow-up (28th September 2018). We used Cox regression analysis to compare risks of recurrent ischaemic stroke, ischaemic vascular events (ischaemic stroke, myocardial infarction or peripheral vascular disease) and death during follow-up in patients with 50-99% symptomatic ICS vs no ICS and 50-99% asymptomatic ICS vs no ICS, with adjustment for baseline characteristics that were independent predictors of the presence of ICS.

We also used Cox regression analysis to compare risks of outcomes reported in the non-stenting arms of SAMMPRIS and VISSIT trials with comparable outcomes in the OXVASC cohort. Only patients fulfilling the trial inclusion criteria were included for this analysis, i.e. patients with 70-99% symptomatic ICS and without tandem stenoses, bilateral intracranial vertebral artery stenoses, intracranial arterial occlusion, atrial fibrillation/ cardioembolic aetiology or had undergone ICS stenting/ angioplasty.

All statistical analyses were performed with IBM SPSS Version 25.0®.

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Data availability statement

Requests for access to the data reported in this paper will be considered by the corresponding author.

Role of the funding source

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

Results

Of 1579 eligible patients (1000/63.4% TIA; 579/36.7% minor stroke) 1368 (86.6%) underwent intracranial vascular imaging (1034/65.5% MRA; 253/16.0% CTA; 81/5.2% TCD only), whereas 154 (9.8%) had only carotid bifurcation ultrasound imaging (often due to contraindications to MRA and CTA) and 57 (3.6%) did not undergo any vascular imaging (Supplementary Material page 8, Table 3). Patients who did not receive intracranial vascular imaging were older with a higher burden of vascular risk factors (Supplementary Material page 9, Table 4).

Of the 1368 patients with intracranial vascular imaging, 385 50-99% ICS were identified in 241 (17.6%) patients (Table 1). There was good agreement for the presence of intracranial, extracranial, and no stenosis (Cohen's kappa 0.82, 0.79 and 0.84, respectively; n=50). Of 241 patients with any (symptomatic or asymptomatic) 50-99% ICS, 188 (78.0%) received MRA, 49 (20.3%) CTA and 4 (1.7%) TCD. Prevalence of any 50-99% ICS in imaged patients (n=1368) was similar in the intracranial segment of the internal carotid artery (84/3.4% of vessels), the posterior cerebral artery (93/3.6%) and the middle cerebral artery (98/3.8%). The basilar artery was the least affected with 13 (1.0%) stenoses (Supplementary Material page 10, Table 5). The vertebral arteries (V1-3) and proximal ICA were the most common sites of extracranial stenosis, with 236 (9.6%) and 273 (9.5%) vessels affected, respectively.

Patients with ICS were older than those without and had a higher burden of hypertension, diabetes mellitus, hyperlipidaemia, atrial fibrillation, previous stroke, peripheral vascular disease and ischaemic heart disease (all $p \leq 0.0010$) (Table 1). ICS was considered symptomatic in relation to the most recent clinical presentation in 94 (6.9%) patients.

The prevalence of any 50-99% ICS increased with age from 9/ 129 (7.0%) at <50 years to 23/ 51 (45.1%) at ≥90 years (Figure 1a), and from 6/ 129 (4.7%) to 10/ 51 (19.6%) for 50-99% symptomatic ICS. At age <80 years the prevalence of ICS was similar to that of stenosis of the proximal ICA and to that of extracranial vertebral stenosis (Figure 1b), but ICS predominated at older ages.

The independent baseline predictors of any 50-99% ICS (Table 2) were age (OR= 1.60, 95% CI 1.39-1.83), minor stroke (vs TIA) (1.37, 1.01-1.87), peripheral vascular disease (1.64, 1.13-2.38) and prior ischaemic stroke/TIA (1.94, 1.09-3.45). The presence of proximal

internal carotid artery (ICA) stenosis was also predictive of any 50-99% ICS, independently of age (Supplementary Material page 11, Table 6).

All patients had at least six months of follow-up. Stroke risk differed between patients with symptomatic 50-99% ICS and no ICS (Figure 2). Of 94 patients with symptomatic 50-99% ICS, 12 had recurrent ischaemic and 2 had intracerebral haemorrhages during median follow-up of 2.8 years (interquartile range= 3.1). Of the 12 patients with recurrent ischaemic stroke, four patients had minor (NIHSS ≤3) and eight had major recurrent ischaemic strokes. On Cox regression there was no difference between patients with asymptomatic ICS versus no ICS in risk of recurrent ischaemic stroke, but risk was increased in patients with symptomatic ICS (Supplementary Material page 12, Table 7). This increased risk remained after adjustment for age, event type and prior ischaemic vascular events (HR= 1.43, 95% CI 1.04-1.96) and risks of any ischaemic vascular event and all-cause death were also increased (Supplementary Material page 12, Table 7).

Characteristics of the 36 patients in OXVASC fulfilling the trial inclusion criteria differed (all $p<0.05$) from those in the SAMMPRIS trial non-stenting arm (Supplementary Material page 13, Table 8) in relation to age, ethnicity and vascular risk factors (hypertension, diabetes, hyperlipidaemia, current smoking), with similar trends also evident in comparison with VISSIT.

The 2-year risk of any recurrent ischaemic stroke in patients with symptomatic 70-99% ICS in our cohort was 10.4% (95% CI 1.8-19.0). The absolute risk of same-territory ischaemic stroke during all follow-up was higher in patients with 70-99% compared to 50-69% symptomatic ICS [22.9%, 95% CI 6.0-39.8 vs 4.8%, 0.0-11.3].

In relation to the outcome definitions and follow-up durations reported in the trials (Table 3), the 2-year risk of any stroke or death in OXVASC (22.7%, 95% CI 8.8-36.6) was similar to that in SAMMPRIS (19.8%, 15.1-25.6) and the 1-year risk of same territory ischaemic stroke or TIA in OXVASC (13.9%, 2.5-25.3) was comparable with that in VISSIT (15.1%, 6.7-27.6). The long-term (beyond one year) rates of same territory recurrent ischaemic stroke were similar in OXVASC and SAMMPRIS (1.4 and 1.0 events per 100 patient years, respectively). The risk of any recurrent ischaemic stroke in all patients (as reported in some previous studies) is higher than risk of any same-territory recurrent ischaemic stroke in patients with 50-99% and 70-99% symptomatic ICS (Supplementary Material page 18, Figure 2).

Of the 74 patients without atrial fibrillation and 50-99% symptomatic ICS, there was a high rate of compliance with antiplatelet and statin therapy up to 5 years follow-up (Supplementary Material page 14, Table 9). At baseline, 45/ 74 (60.8%) patients were on ≥2 antihypertensives, increasing to 18/ 26 (69.2%) patients at 5 years follow-up (Supplementary Material page 14, Table 9). Of all 94 patients with 50-99% symptomatic ICS, patients with recurrent stroke or died during follow-up were older, had a higher burden of diabetes mellitus and ICS and higher 1 month systolic blood pressures than those without (Supplementary Material page 15, Table 10).

Discussion

To our knowledge, this is the first population-based study of predominantly Caucasian patients with minor stroke/TIA and a high rate of intracranial imaging. We have found symptomatic or asymptomatic 50-99% ICS in 241 (17.6%) patients in our population, with highest rates at older ages. Previous hospital-based studies performed in predominantly Caucasian patients with TIA or stroke have reported a wide range of prevalence of symptomatic ICS, with rates varying from 0.04% to 36.4%, probably reflecting in part differences in the definition of ICS, imaging technique, inclusion criteria and completeness of ascertainment (Supplementary Material pages 1-3, Table 1a).

The presence of symptomatic 50-99% ICS was independently associated with an increased risk of recurrent ischaemic stroke which was higher for the 70-99% ICS subgroup. The 2-year risk of any recurrent ischaemic stroke in patients during with symptomatic 70-99% ICS in our cohort was 10.4% (95% CI 1.8-19.0). Importantly, this risk was lower than that reported in earlier studies,[16,27] and prognosis was comparable to that in the medical treatment arms of the SAMMPRIS and VISSIT trials. Furthermore, the long-term (beyond one year) rates of same territory recurrent ischaemic stroke were similar in OXVASC and SAMMPRIS. The risk of recurrent stroke in OXVASC was also dependent on the definition of the outcome (Supplementary Material page 18, Figure 2), which might explain some of the heterogeneity in risks reported in previous studies (Supplementary Material pages 4-6, Table 1b).

The impact of randomised controlled trials and systematic reviews depends on the external validity (or generalisability), that is the extent to which the results apply to a definable group of patients in a particular setting[28]. Both SAMMPRIS and VISSIT had young cohorts, due to the exclusion of elderly patients, and reported a lower than expected recurrent event rates on medical treatment alone. Our findings in a population-based cohort, including many older patients, nevertheless supports the external validity of the trials.

It has been suggested that the low risk of stroke on medical treatment alone in SAMMPRIS was due to the intensity of risk factor management.[17,29] The patients in OXVASC also received intensive medical management, similar to that of both SAMMPRIS and VISSIT. This consisted of dual anti-platelet therapy (Aspirin and Clopidogrel) for the first month with Clopidogrel or Aspirin monotherapy thereafter, high-intensity statin and ambulatory monitoring of blood pressure (target of <130/ 80 mmHg). Patients were also given advice on smoking cessation, exercise and diet, and were regularly followed up by study research nurses to ensure medication compliance and adequate blood pressure control. For example, in patients with 50-99% symptomatic ICS, SBP was reduced by about 20mmHg between baseline and one-month follow-up.

Routine screening for extracranial ICA stenosis in secondary prevention of stroke is supported by international guidelines,[10,30] but there is no consensus on the utility of routine screening for ICS. Although the increased use of intracranial vascular imaging in the treatment of major acute stroke sometimes identifies patients with ICS, patients with TIA or minor stroke are often not screened. Our results show that although stroke risk is similar to

that in SAMMPRIS and VISSIT, patients with symptomatic ICS are nevertheless a high-risk subgroup even when treated according to current guidelines. While trials provided no evidence to support a role for percutaneous stenting for symptomatic ICS, the high stroke risk might justify routine screening to tailor risk factor management. For example, as intensive lipid-lowering with monoclonal antibodies becomes available, the high costs are likely to limit treatment to subgroups of patients with higher-risk atherosclerotic disease. There is also some evidence that combinations of antithrombotic agents might also be effective in reducing stroke risk in patients with higher-risk atherosclerotic disease.[31] Moreover, recruitment into future trials in patients with ICS will be difficult if potentially eligible patients are not identified. Finally, in patients with otherwise apparently cryptogenic TIA or stroke, knowledge of a symptomatic ICS is likely to motivate both patient and physician to comply with intensive medical treatment, particularly given the resistance on the part of some patients to take statins,[32,33] and on the part of some clinicians to prescribe lipid-lowering drugs in the very elderly, in whom we found high rates of ICS.

The strengths of our study include its large, population-based nature with high rates of ascertainment, a long period of follow-up, intensive medical management and investigation; nearly 90% of eligible patients underwent intracranial vascular imaging of some kind, the majority receiving MRA. We chose the most commonly used definition of ICS (50-99% luminal stenosis, further subcategorised to 70-99% for trial comparison) and demonstrated good inter-rater reliability. However, our study also had some limitations. Firstly, our findings do not apply to patients with major stroke. However, 90% of all recurrent strokes occur after a TIA/ minor stroke[34] and the previous trials[1,2] of stenting for ICS also recruited predominantly TIA/minor stroke. Second, although our patients were followed up regularly by study nurses and clinicians offering similar lifestyle advice and risk factor management to that is in the previous trials,[1,2] rates of medication compliance and risk factor control are likely to have been higher than in some other settings. Thirdly, although two-thirds of patients in our study received our first preference of MRI/MRA brain, other imaging modalities had to be used when MRA was contraindicated, principally CTA, which has different sensitivity and specificity for detecting ICS. Although we did find differences in the detection rates between MRA and CTA (Supplementary Material page 10, Table 5), CTA was used in an older subgroup of patients with contraindications to MRI (such as pacemakers) and with a higher burden of vascular risk factors. Fourthly, time-of-flight (ToF) MRA is prone to artefact because of flow abnormalities – low flow may mimic stenosis and high flow through stenosis may underestimate its degree[35]. However, we used a combination of contrast enhanced and ToF MRA to improve the specificity of ICS detection and MRA is commonly used clinically to detect ICS due to the unacceptable risks of catheter angiography for screening. The previous trials only included patients with high-grade 70-99% symptomatic ICS as determined by catheter angiography.[1,2] Although this is more accurate in grading ICS than non-invasive angiography there are associated risks and it cannot now be used for routine screening or for research. Non-invasive angiography was therefore the only suitable method of answering the study questions and the increased risk of same-territory recurrent stroke seen in those with higher grade ICS supports the accuracy of non-invasive angiography. Finally, although the OXVASC cohort was older, there were fewer vascular comorbidities than in the SAMMPRIS population. This is likely due to

differing patient selection: SAMMPRIS required at least one vascular risk factor in patients below the age of 50 years. Moreover, both SAMMPRIS and VISSIT had upper age limits for eligibility and younger-onset vascular disease tends to be associated with more vascular risk factors.

In conclusion, ICS is prevalent in elderly Caucasian patients with minor stroke/TIA and the risk of recurrent stroke following symptomatic ICS was consistent with randomised trials in younger cohorts. Given the consequent likely generalisability of the trials results to the broader patient population, routine screening for ICS would not be justified to identify candidates for stenting, but ICS does identify a higher-risk atherosclerotic disease subgroup of patients who may require tailored risk factor management and recruitment to future clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

We did two systematic reviews, one on the prevalence and one on the prognosis of ICS in population and hospital-based cohorts of patients with transient ischaemic attack (TIA) and stroke. We searched Embase and Medline databases for articles published in English up to November 1, 2019 with the search terms [prevalence] OR [prognosis] AND [intracranial stenosis] (for full details see Supplementary Material pages 16-17, Figures 1a and b). Studies were chosen if they had been performed in mostly Caucasian TIA/stroke patients (or in European centres if ethnicity not specified) receiving medical treatment only. Fifty studies, including 25 prognostic studies, were identified.

Multiple imaging modalities for screening for intracranial stenosis (ICS) were used in 21 studies, 15 of which included transcranial Doppler (TCD), TCD only was used in 11 studies, computed tomography angiography (CTA) or magnetic resonance angiography (MRA) in seven and catheter angiography in 11. ICS definition included a 50% reduction of the luminal diameter (usually by the *Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis* (WASID) method) in 28 studies, by TCD flow criteria in 11 studies, other percentage reductions in six studies, any reduction in four studies, and was not described in one study. The mean age of participants in all studies was 64 years (standard deviation (SD) 6.3). The mean pooled prevalence of any ICS was 16.5% (SD 11.7) and of symptomatic ICS 10.1% (9.9). However, there is significant heterogeneity in the reported risk estimates following symptomatic ICS (ranging from 4.6%-45.7%) due to a mixture definitions, case ascertainment and length of follow-up.

Added value of this study

We performed a large, prospective population-based longitudinal cohort study of all acute cerebrovascular events, irrespective of age, with near-complete ascertainment and a high rate of intracranial vascular imaging. The prevalence of ICS in elderly patients with TIA/minor stroke was high in Caucasians, but the absolute risk of recurrent ischaemic events was low on intensive medical management. Our findings also validate the risk estimates from previous randomised controlled trials in a population-based setting and support the role for intensive medical management over stenting, irrespective of age.

Implications of all the available evidence

Estimates of stroke risk distal to symptomatic ICS from previous older studies are heterogeneous, but imaging methods and outcome definitions differed and intensity of medical treatment and compliance during follow-up were uncertain, such that meta-analysis would be difficult to interpret. Our findings provide risk estimates in an up-to-date population-based setting with standard non-invasive imaging and high rates of guideline-based medical treatment and support the role for conservative management of symptomatic ICS over routine stenting, irrespective of age.

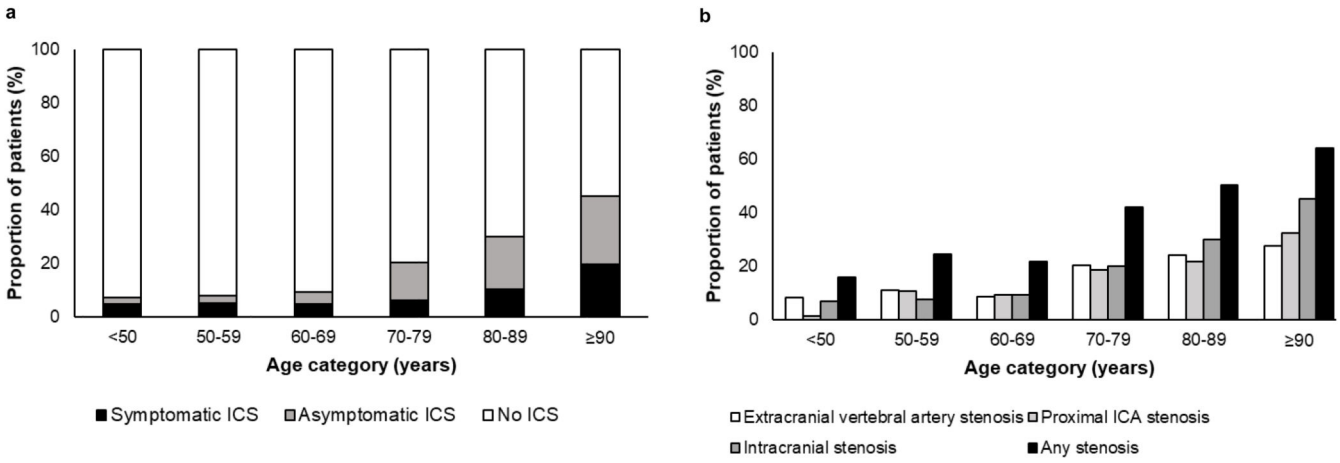

Figure 1.

Age-specific prevalence of **a)** 50-99% symptomatic, asymptomatic and no intracranial stenosis (ICS), and **b)** proximal extracranial internal carotid artery (ICA) stenosis, extracranial vertebral artery stenosis, 50-99% intracranial stenosis (ICS) and any stenosis (extra- or intracranial).

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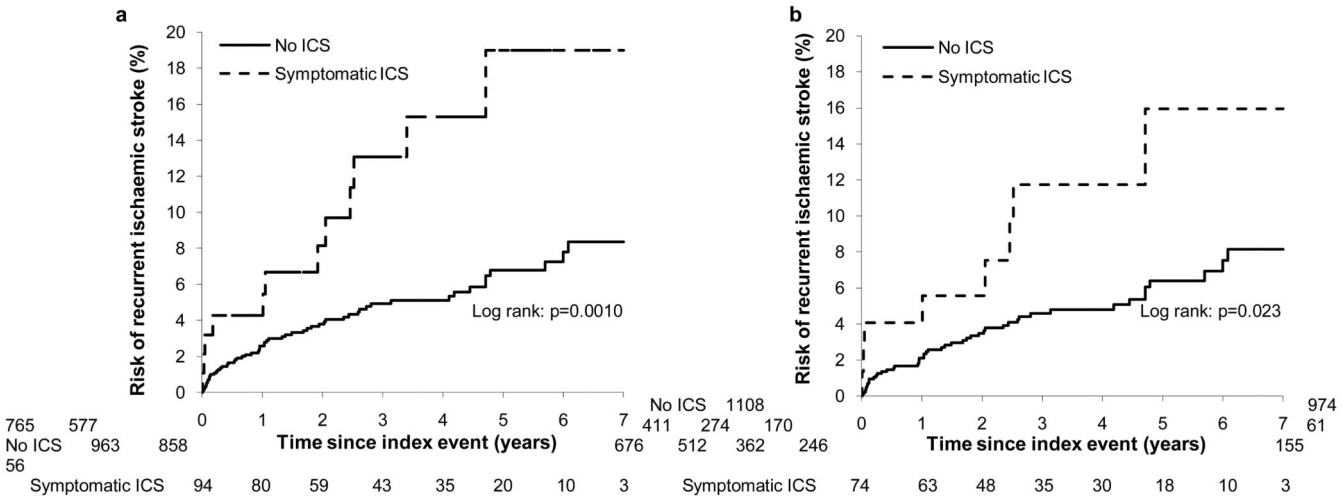

Figure 2.

Kaplan-Meier graphs showing the 7-year risk of recurrent ischemic stroke in patients with 50-99% symptomatic intracranial stenosis (ICS) and no ICS in **a)** all patients and **b)** excluding those with atrial fibrillation or cardioembolic aetiology.

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Table 1

Baseline characteristics of the OXVASC cohort stratified according to the presence of any symptomatic or asymptomatic 50-99% intracranial stenosis.

Characteristic	Patients with intracranial vascular imaging* (N= 1368)		p-value
	Intracranial stenosis (N= 241)¶	*No intracranial stenosis (N= 1108)*	
Mean age (SD)	76.0 (11.9)	67.7 (13.8)	<0.0001
Male sex (%)	127 (52.7)	558 (50.4)	0.40
Female sex (%)	114 (47.3)	550 (69.6)	
Caucasian (%)	229 (95.0)	1045 (94.3)	0.56
Hypertension (%)	168 (69.7)	572 (51.6)	<0.0001
Diabetes mellitus (%)	42 (17.4)	134 (12.1)	<0.0001
Hyperlipidaemia (%)	103 (42.7)	355 (32.0)	<0.0001
Current smoker (%)	26 (10.8)	165 (14.9)	0.090
Atrial fibrillation (%)	52 (21.6)	145 (13.1)	0.0010
Any vascular disease§ (%)	105 (43.6)	259 (23.4)	<0.0001
History of stroke or TIA (%)	58 (24.1)	143 (12.9)	<0.0001
PVD (%)	24 (10.0)	36 (3.2)	<0.0001
IHD (%)	54 (22.4)	120 (10.8)	<0.0001
Event type			
TIA (%)	146 (60.6)	735 (66.3)	0.22
Minor stroke (%)	95 (39.4)	373 (33.7)	
TOAST classification			
Cardioembolic (%)	35 (14.5)	172 (15.5)	
Atherosclerotic (%)	95 (39.4)	78 (7.0)	
Undetermined (%)	47 (19.5)	494 (44.6)	<0.0001
Lacunar (%)	11 (4.6)	120 (10.8)	
Multiple/unknown/other (%)	53 (22.0)	244 (22.1)	
Vascular territory			
Carotid (%)	129 (53.5)	580 (52.4)	0.12
Vertebrobasilar (%)	94 (39.0)	408 (36.8)	
Uncertain/ both (%)	18 (7.5)	120 (10.8)	
Imaging modality			
MRA	188 (78.0)	829 (74.8)	0.039
CTA	49 (20.3)	202 (18.2)	
TCD	4 (1.7)	77 (7.0)	

PVD= peripheral vascular disease, IHD= ischaemic heart disease, MRA= magnetic resonance angiography, CTA= computed tomography angiography, TCD= transcranial Doppler.

*Including: MRA, CTA or TCD.

¶Excluding patients with intracranial vessel occlusion (n=19).

§Vascular disease= ischaemic stroke/ TIA, PVD or IHD.

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Table 2

Predictors of any symptomatic or asymptomatic 50-99% intracranial stenosis in the OXVASC cohort.

	Unadjusted risk indicators OR (95% CI)	p-value	Age-adjusted risk indicators OR (95% CI)	p-value	Multivariable risk indicators OR (95% CI)	p-value
Age (per 10 years)	1.71 (1.51- 1.94)	<0.0001	-		**1.60 (1.39- 1.83)**	**<0.0001**
Male sex	1.10 (0.83-1.45)	0.51	1.31 (0.98-1.76)	0.066	1.17 (0.87-1.58)	0.31
Hypertension	2.16 (1.60-2.91)	<0.0001	1.58 (1.15-2.15)	0.0040	1.34 (0.96-1.87)	0.081
Diabetes mellitus	1.53 (1.05-2.24)	0.027	1.48 (1.00-2.18)	0.050	1.19 (0.79-1.81)	0.41
Hyperlipidaemia	1.58 (1.19-2.11)	0.0020	1.39 (1.03-1.86)	0.029	1.04 (0.76-1.44)	0.79
Atrial fibrillation	1.87 (1.32-2.66)	<0.0001	1.34 (0.93-1.93)	0.12	1.18 (0.81-1.71)	0.39
Any prior vascular disease *	2.53 (1.89- 3.38)	<0.0001	1.83 (1.35- 2.49)	<0.0001	-	
Prior stroke/ TIA	2.14 (1.52-3.02)	<0.0001	1.72 (1.21-2.46)	0.0030	**1.64 (1.13-2.38)**	**0.0090**
PVD	3.29 (1.93-5.63)	<0.0001	2.49 (1.43-4.33)	0.0010	**1.94 (1.09-3.45)**	**0.024**
IHD	2.38 (1.66-3.40)	<0.0001	1.68 (1.16-2.44)	0.0060	1.34 (0.90-1.99)	0.18
Event type						
TIA	1.0		1.0		1.0	
Minor stroke	1.28 (0.96-1.71)	0.089	1.40 (1.04-1.88)	0.027	**1.37 (1.01-1.87)**	**0.040**

PVD= peripheral vascular disease; IHD= ischaemic heart disease.

* vascular disease = ischaemic stroke/ TIA, PVD or IHD

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Table 3

Comparison of the outcomes reported in the non-stenting medical treatment only arms of the SAMMPRIS and VISSIT trials with comparable outcomes in OXVASC cohort categorised by 50-99% and 70-99% symptomatic intracranial stenosis (ICS).

	SAMMPRIS 2-year outcomes*						**VISSIT 1-year outcomes**					
	Any stroke/ death <30d and same territory IS >30d		**Any stroke or death**		**Any stroke**		**Same territory IS or hard TIA (>2d)**		**Same territory IS**		**Any territory hard TIA (>2d)**	
	Events	**Risk (95% CI)**	**Events**	**Cum. risk (95% CI)**	**Events**	**Cum. risk (95% CI)**	**Events**	**Cum. risk (95% CI)**	**Events**	**Cum. risk (95% CI)**	**Events**	**Cum. risk (95% CI)**
SAMMPRIS (n= 227)	34	14.1 % (10.1-19.4)	51	19.8% (15.1-25.6)	13	17.2% (12.9-22.9)				-		
VISSIT (n= 53)				-			8	15.1% (6.7-27.6)	5	9.4% (3.1-20.7)	3	5.7% (1.2-15.7)
OXVASC (1) (n= 94)	8	9.0% (2.9-15.1)	21	23.4% (14.6-32.2)	9	10.8% (3.9-17.7)	11	12.0% (5.3-18.7)	5	5.5% (0.8-10.2)	7	7.6% (2.1-13.1)
OXVASC (2) (n= 74)	6	8.2% (1.9-14.5)	16	22.6% (12.8-32.4)	6	8.9% (2.0-15.8)	8	11.1% (3.9-18.4)	4	5.6% (0.3-11.1)	5	6.9% (1.0-12.8)
OXVASC (3) (n= 36)	2	5.6% (0.0-13.0)	8	22.7% (8.8-36.6)	3	9.2% (0.0-19.2)	5	13.9% (2.5-25.3)	2	5.6% (0.0-13.0)	3	8.3% (0.0-17.3)

(1) All OXVASC 50-99% symptomatic ICS

(2) OXVASC 50-99% symptomatic ICS excluding atrial fibrillation

(3) OXVASC 70-99% symptomatic ICS fulfilling trial criteria

*Any stroke= ischaemic stroke (IS), intracerebral haemorrhage or subarachnoid haemorrhage