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Original article

The prevalence of carotid stenosis in patients presenting with ischaemic stroke: a one-year prospective observational study

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Figures ~~1~~2, Tables 2.

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Background: Carotid stenosis is regarded as a common cause of ischaemic stroke and transient ischaemic attack (TIA). Despite a rising recognition and centralisation of stroke services there has been a decline in interventions for carotid stenosis in recent years. The aim of this study is to determine the current prevalence and management of carotid stenosis in the United Kingdom.

Methods: A one-year prospective observational study was performed on consecutive patients presenting with ischaemic stroke, TIA or ischaemic retinal artery occlusion to a central London hyper-acute stroke unit. Patients with Ssignificant carotid stenosis, ~~was~~ defined as atherosclerotic narrowing ≥50%, ~~. All patients were followed and~~ underwent multidisciplinary team (MDT) discussion to determine cause of stroke and ~~define~~ carotid stenosis as symptomatic or 'incidental'. ~~Patient demographics and subsequent management were documented.~~

Results: ~~A total of~~In total 2726 patients were seen, half had an ischaemic event and the majority had carotid imaging (1252/1444); ~~, of whom~~ 238 had carotid stenosis ≥50% (prevalence 19·0%; 95% CI 16·6–21·4). ~~Patients with significant carotid stenosis~~and ~~were more likely to have~~more likely had hypertension, hypercholesterolaemia, diabetes, and ischaemic heart disease. Carotid stenosis was symptomatic in 99 ~~patients~~ (7·9%; 95% CI 6·3–9·5). Of these, 17 had carotid occlusion, ~~,~~ 17 were ~~too~~ unfit for surgery~~, and 3 were lost to follow up. A total of~~ and 58 patients ~~were~~ referred for carotid intervention. In 139 with asymptomatic stenosis, 75 had carotid stenosis ipsilateral to the stroke but following MDT causality was deemed; 32 atrial fibrillation, 15 small vessel disease, 5 other determined causes and 23 undetermined due to atypical imaging or clinical presentation. ~~ipsilateral~~

stenosis to the stroke and were nonetheless deemed to be asymptomatic after MDT discussion and identification of an alternative cause. Patients with significant carotid stenosis were more likely to have hypertension, hypercholesterolaemia, diabetes, and ischaemic heart disease.

Conclusion: Atherosclerotic carotidCarotid stenosis is common in 1 in 5 patients presenting with stroke., However, carotid stenosis was responsible for 7·9% of the events of whom half underwent intervention.Careful MDT discussion may avoid unnecessary intervention and should be standard of care.

Introduction

Stroke is the third most common cause of death worldwide after ischaemic heart disease (IHD) and all types of cancer combined.[1] Carotid artery disease due to atherosclerotic narrowing can lead to thrombosis, embolism or reduced blood supply to the brain. Early intervention by carotid endarterectomy or stenting is recommended to reduce the risk of major stroke and disability.[2]

The last decade, the United Kingdom has seen significant changes in the reorganisation of acute stroke service provision. In London, eight Hyper-Acute Stroke Units (HASU) assess, manage and admit all adult patients referred for a suspected stroke. Integrated pathways are provided by multidisciplinary teams that exclusively manage patients with stroke. HASU's are associated with better quality, reduced death and dependency, and reduced length of hospital stay.[3] Diagnosis of stroke has increased, from 73,422 patients diagnosed with stroke in 2013-2014 to 81,978 patients in 2016-2017.[4]

The reported prevalence of carotid artery stenosis varies from 5% up to 30%, depending on the population sample and exact criteria used for diagnosis.[5] However, the UK National

Vascular Registry has reported a steady decline in carotid endarterectomy over the last five years, from 5,543 in 2012 to 4,330 in 2017.[6,7]

The reasons for this are not clear and with current proposals for further reorganisation of the UK vascular service and the 'Get It Right First Time' initiative there is a need to better understand the current prevalence of carotid artery disease, patient population, demographics diagnostic and management pathways to better inform service structure (or restructure).[8,9] The aim of this study was to assess the prevalence, diagnosis and management of extracranial atherosclerotic carotid stenosis in patients with acute ischaemic stroke or TIA presenting to a central London HASU and TIA clinic.

Methods

Clinical Pathways

All patients presenting to the HASU and TIA clinic at University College London Hospitals were consecutively included from the period of 1 July 2014 to 30 June 2015. All patients above 17 years with suspected stroke across North Central London present to this unit and receive clinical assessment with rapid Computed Tomography Angiography (CTA) if there are no contra-indications. Additional investigations for patients with carotid stenosis include Magnetic Resonance Angiography (MRA) and/or duplex ultrasound. All cases with carotid stenosis ≥50% were discussed at a twice-weekly multidisciplinary team (MDT) meeting, attended by neuro-radiologists, stroke physicians, and vascular surgeons, allowing all carotid patients to be discussed on the mechanism of stroke based on the clinical presentation and review of imaging. This carotid pathway was set up in 2013 which supports the HASU and TIA clinic to represent a comprehensive adult population to accurately assess the prevalence, management and intervention of ischaemic stroke patients with carotid stenosis.

Carotid stenosis identified on CTA (routine protocols included from aortic arch to cranium), MRA or duplex ultrasound were defined by North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria,[10,11] as mild (<50%), moderate (50-70%), severe (>70%), or occlusion. Symptomatic carotid stenosis was defined at discussion at the MDT with; the presence of ipsilateral carotid stenosis ≥50% with agreement of clinical and radiological features. Where appropriate, patients were considered for urgent carotid endarterectomy. Exclusions for carotid intervention included; occluded carotid artery, severe residual disability or severe comorbidities.

The Second European Carotid Surgery Trial (ECST-2, see www.ECST-2.com) assesses patients with low risk of future ipsilateral stroke, randomising patients to best medical treatment versus best medical treatment and carotid endarterectomy. The patient risk is assessed by the Carotid Artery Risk (CAR) score (available for download at: https://itunes.apple.com/gb/app/ecst-2-car-score/id986827121?mt=8 or https://play.google.com/store/apps/details?id=com.sealedenvelope.carscore), which estimates the 5-year risk of ipsilateral stroke based on the patient's risk factors, degree of stenosis and presenting event. This model was derived from the results of a Cox regression model from patients treated in European Carotid Surgery Trial (ECST) and NASCET.[12-14] Patients with symptomatic carotid stenosis but at low risk of future ipsilateral stroke (delayed or equivocal diagnosis, minor event, comorbidities) and who were referred for ECST-2 were, for the purpose of this audit, recorded as having undergone intervention. All patients who had significant carotid stenosis and fit enough for surgery (modified Rankin score of <3), but were not deemed to be symptomatic, were also considered for the trial.

Data collection

Data were collected prospectively on patient demographics and vascular risk factors including; hypertension, diabetes mellitus, hypercholesterolemia, previous stroke or TIA, previous myocardial infarction (MI) or IHD, atrial fibrillation, and smoking habits. Hypercholesterolaemia was defined as; total cholesterol level >5·0 mmol/l or LDL levels of >3·0 mmol/l, a history of hypercholesterolaemia, or taking lipid-lowering medication pre-admission. Medications documented at admission included; antiplatelets, anticoagulants, lipid-lowering medication and antihypertensives.

The aetiology of ischaemic stroke, TIA, amaurosis fugax, or ischaemic retinal artery occlusion, was classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.[15] Patients were classed as having an unknown aetiology if no TOAST defined cause of stroke was found during their stay at the stroke unit. Patients with an alternative or uncertain diagnosis and patients who did not have carotid imaging were excluded. Severity of the neurological deficit was evaluated by using the National Institutes of Health Stroke Scale (NIHSS) at presentation. Patients seen or admitted more than once were included only at first presentation.

The audit was registered with University College London Hospitals audit department for stroke research as part of an audit of process. No intervention or measurement was undertaken on patients outside normal clinical care.

Statistical analysis

The prevalence of symptomatic carotid stenosis was calculated using the normal approximation to calculate the standard error. The chi-square test, Fisher's exact test or Mann-Whitney U test was used to identify the statistical significance of the differences between the group with and without carotid stenosis ≥50%. P values <0·05 were considered statistically significant for all

analyses. Statistical analysis was performed on STATA version 15 (http://www.stata.com/company/).

Results

In one year, 2726 patients were seen at the HASU and TIA clinic, of whom 1444 patients ~~had~~ were diagnosed with ischaemic stroke, TIA, amaurosis fugax, or an ischaemic retinal artery event, arising from any cerebral arterial territory. Intracerebral haemorrhage was diagnosed in a further 126 patients. Carotid imaging was not undertaken in 192 of cases, predominantly due to poor immediate prognosis. In total, 1252 cases with carotid imaging were included for analysis (Figure 1). Overall, mean age was 71·4±14·5 years (median of 74 years, interquartile range 62-82), 677 (54·1%) were male, and 71·2% of the patients were taking secondary preventive medication for cardiovascular diseases prior to admission (either antiplatelet therapy, warfarin, antihypertensives, or statins) (Table 1). In total 980 had a known ethnicity, 725 (74·0%) were white, 63 (6·4%) Asian, 78 Black (8·0%), and 114 other ethnicities including mixed ethnicities, Hispanic, and Latino.

All patients with significant carotid stenosis were reviewed at the MDT with a median of 3 days from presentation (interquartile range = 2 to 5 days). Atrial fibrillation was the cause of stroke in 252 patients (20·1%; 95% CI 18·0–22·4) and small vessel disease in 193 of the patients (15·4%, 95% CI 13·5–17·5). In more than half of the patients the aetiology of stroke was unclear (52·4%, 95% CI 49·6–55·1).

Carotid stenosis

Overall, carotid stenosis ≥50% was present in 238 patients (19·0%; 95% CI 16·6–21·4), 162 patients had unilateral and 76 had bilateral carotid stenosis. Carotid stenosis was defined as cause of the stroke (symptomatic carotid stenosis) in 99 patients (7·9%; 95% CI 6·3–9·5) of whom 15 were also found to have atrial fibrillation (15·2%; 95% CI 9·4–23·5). Of the 139 patients (11·0%, 95% CI 9·5–13·0) defined as having an incidental asymptomatic carotid stenosis; 38 had the stenosis on the contralateral side of the stroke, and 26 had a posterior circulation infarct (Figure 2). The other 75 patients were diagnosed with a different cause of stroke after MDT discussion, of which atrial fibrillation and small vessel disease were most common (32 and 15 patients, respectively). The cause of stroke was deemed unclear after MDT discussion in 23 patients who also had carotid stenosis (stenosis being borderline significant, an atypical clinical presentation or a combination thereof with normal cerebral imaging). All patients with asymptomatic carotid stenosis were considered for ECST-2.

Of the 99 symptomatic carotid patients, 17 had carotid occlusion and 17 ~~were deemed~~remained too unwell for any surgical intervention after follow up (concomitant illness or disability modified Rankin score >3). A total of 58 patients were referred to intervention; 41 had carotid endarterectomy, 3 underwent carotid stenting, 5 declined surgery and 9 patients were offered ECST-2. Seven patients agreed to participate in ECST-2 of which 4 were randomised for carotid endarterectomy, and 3 randomised to best medical therapy. The two

patients who declined ECST-2 were managed conservatively. The remaining patients not referred for intervention included four patients considered as low risk and were managed conservatively and 3 patients who were lost to follow up.

Discussion

This observational study shows that carotid stenosis ≥50% was causal to ischaemic stroke, TIA, or retinal artery occlusion in 7·9% of the 1252 patients presenting to a regional stroke service. Atrial fibrillation accounted for 20·1%, small vessel disease in 15·4%, and half of the patients had no clearly defined causality. Whilst carotid stenosis was found in 19·0% of all patients, this was often incidental, with 11·0% defined as asymptomatic carotid stenosis. Of those with symptomatic carotid stenosis over half were referred for intervention (58 patients, 4·6%).

There are a few possible reasons for lower than expected rates of symptomatic carotid stenosis in this population. The last decades the population has seen a significant rise in the

medical therapy. Data in stroke related to carotid stenosis used in previous studies reported before the era of commonly used antiplatelet therapy, lipid-lowering medication, and/or blood pressure lowering medication as secondary prevention for cardiovascular and cerebrovascular diseases.[16,17] It has been suggested from prospective studies of asymptomatic carotid stenosis that modern medical therapy, especially statin therapy, has reduced the incidence of stroke associated with carotid stenosis.[18,19] A large proportion of patients (71·2%) in our population were taking at least one secondary preventive medication (either antiplatelet, anticoagulant, statin, or antihypertensives) for ischaemic stroke prior to admission.

A second reason for lower stenosis rates might be the role of the MDT. A MDT approach is well known to be of great benefit to the patient, and is most recognised in cancer surgery.[20] Before the advent of a MDT and multiple imaging modalities in the setting of stroke, 'asymptomatic stenosis' may have been classified as symptomatic. This is the first study robustly assessing the prevalence and diagnosis of carotid stenosis with detailed carotid and cerebral imaging on stroke patients combined with MDT discussion on the mechanism of stroke. We acknowledge that a MDT pathway may be more accurate to diagnose symptomatic carotid stenosis as specifically, cases with ambiguity were resolved by discussion with multiple physicians based on the patient's clinical details and imaging studies. We also acknowledge that a MDT has limitations. There were 75 patients with ipsilateral carotid stenosis ≥50% that were deemed 'asymptomatic' as inferred by the MDT discussion as 32 were also found to have atrial fibrillation, in 15 there was also presence of significant small vessel disease and in 23 patients it was felt that the cause could not be confidently deemed to be the carotid disease. Whilst in these cases the MDT felt there was no proof of the carotid stenosis causing the stroke or TIA or ambiguity, it does not necessarily exclude that the carotid artery stenosis may have been causal to the event in some.

~~In addition~~However, all patients with suspected stroke in one predefined area in London were referred to a centralised HASU and TIA clinic, and it is therefore thought this service would accurately assess the prevalence of carotid stenosis in patients with ischaemic stroke. Diagnostic strategies have also improved with rapid access CT scanning in most patients and the use of MRI to aid causal differentiation. A large number of patients was diagnosed with a stroke with unclear aetiology in our population (52·4%). This is due to the hyper-acute setting of the stroke unit, where patients are repatriated to their local stroke unit as early as possible when the patient is stable, for early rehabilitation and further follow up investigations. We acknowledge that diagnosis of unknown cause for stroke may be impacted by the early repatriation of patients from HASU to local hospitals, before they had all their investigations completed. Unfortunately, it was not possible to examine the records from the repatriation hospitals. The majority of these patients were either those that still needed 24/72-hour electrocardiogram tapes to search for atrial fibrillation, or patients who did not have obvious small vessel disease on CT brain but did not have an MRI before discharge. In this sense, the prevalence of cardio-embolism is most likely to be under diagnosed in our population.

Patient risk factors for atherosclerotic disease of hypertension, diabetes, hypercholesterolaemia, and smoking were higher in carotid stenosis as seen with other studies.[21] This finding suggests that these factors are more likely leading to atherosclerotic stroke and TIA than contributing to other pathological mechanisms for stroke. Smoking has been noted as one of the risk factors with most impact on the presence of carotid stenosis in some studies.[22] We confirmed that increasing age and IHD are independent predictors for the presence of carotid stenosis.[23] This is probably because IHD and carotid stenosis share an atherosclerotic pathogenesis, while increasing age is likely to be associated with an increasing prevalence of carotid stenosis.[24] We compared our patient population with data from other

stroke units nationally by the Sentinel Stroke National Audit Programme (SSNAP) database from April 2014 to March 2015.[25] The sex distribution and age are comparable (51.2% male vs 50% male nationally, median age 76 vs 77 years nationally). The prevalence of hypertension, diabetes and stroke or TIA prior to the stroke was 62.6% vs 54.3%, 22.3% vs 20.4% and 24.6% vs 27% (University College London Hospitals HASU vs national data), respectively. Due to the SSNAP database including patients with intracerebral haemorrhage and unknown type of stroke, and we have included patients from the TIA clinic, we did not compare our figures with the SSNAP database. However, looking at the SSNAP data alone, there were no large differences found in the given demographics between our patient population and data nationally. The prevalence of hypertension does seem to be larger in our population and could possibly be explained by a generally more stressful lifestyle in the city centre of London. Unfortunately, there is no national data available on the ethnic background in SSNAP. In our population, 980 patients (78%) had a known ethnicity with 255 patients classified as either Asian, Black, or mixed ethnicities. This is of importance due to

~~T~~ the ethnicity ~~is~~ known to be associated with the aetiology of ischaemic stroke and it is often thought that White people present with large-artery atherosclerosis subtype of stroke, Black people with small vessel disease, whilst Asians often present with intracranial stenosis.[~~25,26~~26,27] More recently however, it was shown that the most common subtype of ischaemic stroke in Whites was cardio-embolism and large-artery atherosclerosis in Asians.[~~27~~ 28] In our population, most patients were White (74·0%) and only 6·4% were Asian. Atrial fibrillation was the most common cause of stroke (in 20·1% of the strokes) followed by small vessel disease (15·4%). This is fairly consistent with recent findings in the literature.[~~27~~ 28] ~~A large number of patients was diagnosed with a stroke with unclear aetiology in our population (52·4%). This is due to the hyper-acute setting of the stroke unit, where patients are repatriated to their local stroke unit as early as possible when the patient is stable, for early rehabilitation~~

~~and further follow-up investigations. In this sense, the prevalence of cardio-embolism is most likely to be under-diagnosed in our population.~~

Carotid imaging was performed in the majority of cases (86·7%) with only 192 of the 1444 patients who did not, often in the frail or those with a poor prognosis. Due to this, it is likely that we have missed patients with carotid stenosis who had a more severe stroke. However, the rate of carotid imaging in our study is higher than other population-based studies.[29,30] A small number of patients with stroke or TIA were not seen by our service, e.g. because the stroke was not recognised, or because the stroke occurred after major surgery or as a terminal event. However, it is unlikely that this selection-bias had a significant influence on our findings.

Current management of carotid stenosis is based on the original studies of the NASCET and the ECST.[31,32] These large trials were however conducted more than 20 years ago and it is thought that the medical therapy has improved ever since. ~~Consequently, the adage of symptom plus stenosis follows operation may not be as accurate. New~~More recent trials ~~rising~~ suggest ~~are suggesting~~ that aggressive medical treatment for carotid stenosis is beneficial for prevention of stroke recurrence.[33,34] Along with the improvement of medical therapy, this suggests more evidence is needed in the management of patients with carotid stenosis, in particular the ones with low risk of recurrent ipsilateral stroke. Consequently, it may be inaccurate to assume that the presence of stroke symptoms plus carotid stenosis requires operation.

Conclusion

Carotid artery stenosis was symptomatic in 7·9% of the patients with ischaemic stroke or TIA and only 5·4% of the patients ~~are~~ were indicated to have surgical intervention on their carotid to reduce the risk of future stroke. In the majority of patients with significant carotid stenosis, the stenosis was deemed to be asymptomatic after MDT discussion and identification of an alternative cause. MDT discussion should therefore be considered as a standard of care in patients with carotid stenosis to avoid unnecessary surgery.

Disclosures

The authors declare no conflicts of interest.

Figure and table legends

Figure	Description
1	Flowchart of patients from, Hyper-Acute Stroke Unit (HASU) or transient ischaemic attack (TIA) service seen with stroke, TIA or ischaemic ocular event over a one-year period.
2	Flowchart of patients with significant stenosis ≥50%. * Carotid intervention includes 41 patients for carotid endarterectomy and 3 for carotid artery stenting, excludes those for intervention in ECST-2. † Other includes 5 patients who declined surgery, 4 managed conservatively and 3 lost to follow up.
Table	**Description**
1	Patient demographics.
2	Presence of vascular risk factors between patients with and without significant carotid stenosis.

Table 1. Patient demographics.

	No of patients (n = 1252), n (%)	
Mean age* (years)	71·4 ± 14·5	
Sex		
Female	575	(45·9)
Male	677	(54·1)
Hypertension	793	(63·3)
Hypercholesterolemia	689	(55·0)
Diabetes mellitus	302	(24·1)
Previous stroke / TIA	296	(23·6)
Previous MI/IHD	180	(14·4)
Atrial fibrillation	252	(20·1)
History of smoking	438	(35·0)
Antiplatelet use prior admission		
Aspirin	274	(21·9)
Clopidogrel	121	(9·7)
Dual therapy	34	(2·7)
Warfarin use prior admission	86	(6·9)
Antihypertensive use prior admission	699	(55·8)
Statin use prior admission	546	(43·6)
NIHSS*	5·04 ± 6·12	

Abbreviations: TIA, transient ischaemic attack; MI, myocardial infarction; IHD, Ischaemic Heart Disease; and NIHSS, National Institutes of Health Stroke Scale.

*Age and NIHSS are expressed as mean±SD; other values are expressed as n (%).

Table 2. Presence of vascular risk factors between patients with and without significant carotid stenosis.

	No significant stenosis (<50%) (n = 1014), n (%)	Significant stenosis (≥50%) (n = 238), n (%)	P value	95% CI
Characteristics				
Mean age* (years)	70·6 ± 14·8	74·6 ± 12·4	**<0·001**	1·96, 6·04
Sex (male)	529 (52·5)	148 (62·2)	**0·005**	1·13, 2·01
Hypertension	629 (62·0)	164 (68·9)	**0·048**	1·00, 1·86
Hypercholesterolemia	533 (52·6)	156 (65·5)	**<0·001**	1·28, 2·31
Diabetes mellitus	223 (22·0)	79 (33·2)	**0·001**	1·23, 2·30
Previous stroke / TIA	232 (22·9)	64 (26·9)	0·190	0·90, 1·71
Previous MI/IHD	134 (13·2)	46 (19·3)	**0·016**	1·09, 2·28
Atrial fibrillation	203 (20·0)	49 (20·6)	0·844	0·73, 1·47
History of smoking	337 (33·2)	101 (42·4)	**0·007**	1·11, 1·98
NIHSS*	4·74 ± 5·89	6·35 ± 6·87	**0·006**	0·64, 2·58

Abbreviations: TIA, transient ischaemic attack; MI, myocardial infarction; IHD, ischaemic heart disease; and NIHSS, National Institutes of Health Stroke Scale.

*Age and NIHSS are expressed as mean±SD; other values are expressed as n (%).

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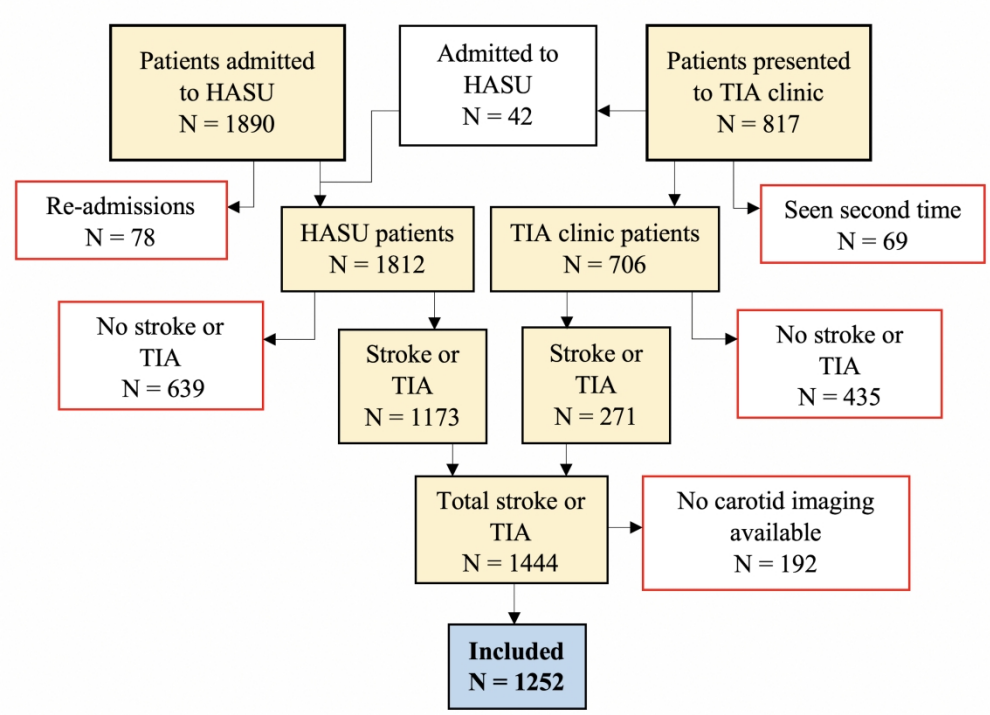

Figure 1. Flowchart of patients from, Hyper-Acute Stroke Unit (HASU) or transient ischaemic attack (TIA) service seen with stroke, TIA or ischaemic ocular event over a one-year period.

468x337mm (300 x 300 DPI)

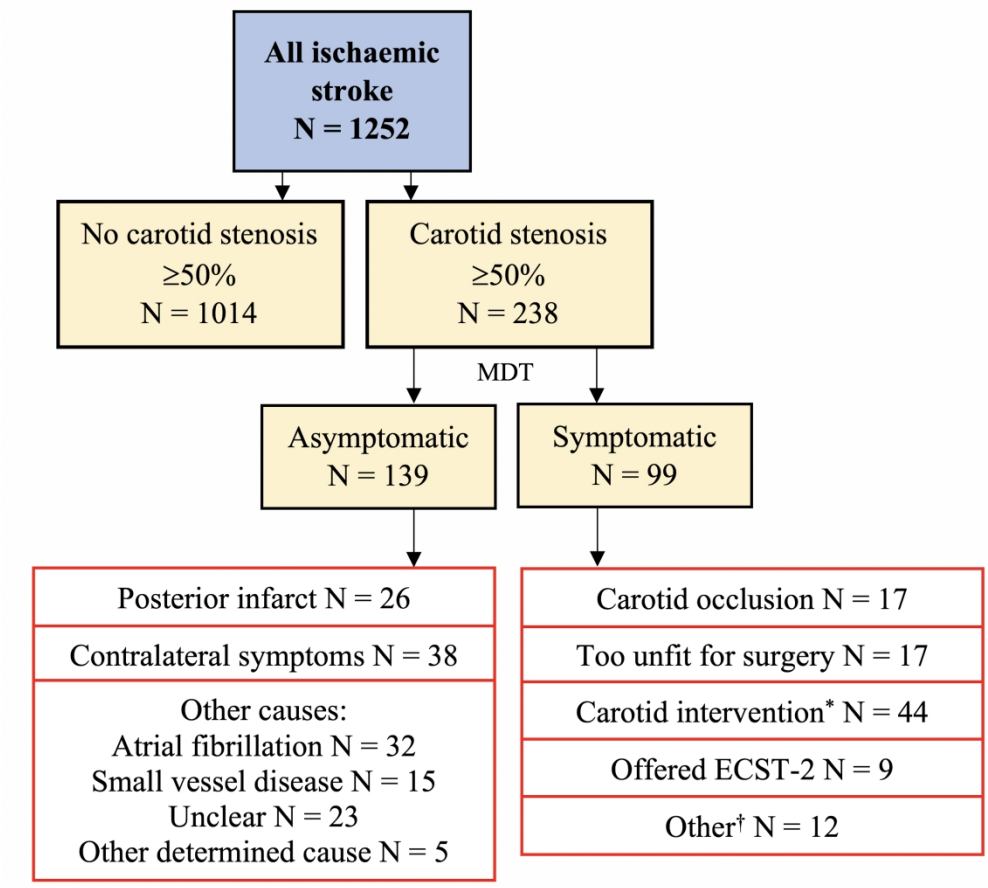

Figure 2. Flowchart of patients with significant stenosis ≥50%.
* Carotid intervention includes 41 patients for carotid endarterectomy and 3 for carotid artery stenting, excludes those for intervention in ECST-2.
† Other includes 5 patients who declined surgery, 4 managed conservatively and 3 lost to follow up.

480x432mm (300 x 300 DPI)