EMERGING AREAS IN EXTRACRANIAL CAROTID STENOSIS EVALUATION AND MANAGEMENT

EDITED BY: Seemant Chaturvedi, Christopher Bladin, Hege Ihle-Hansen and Peter Kelly

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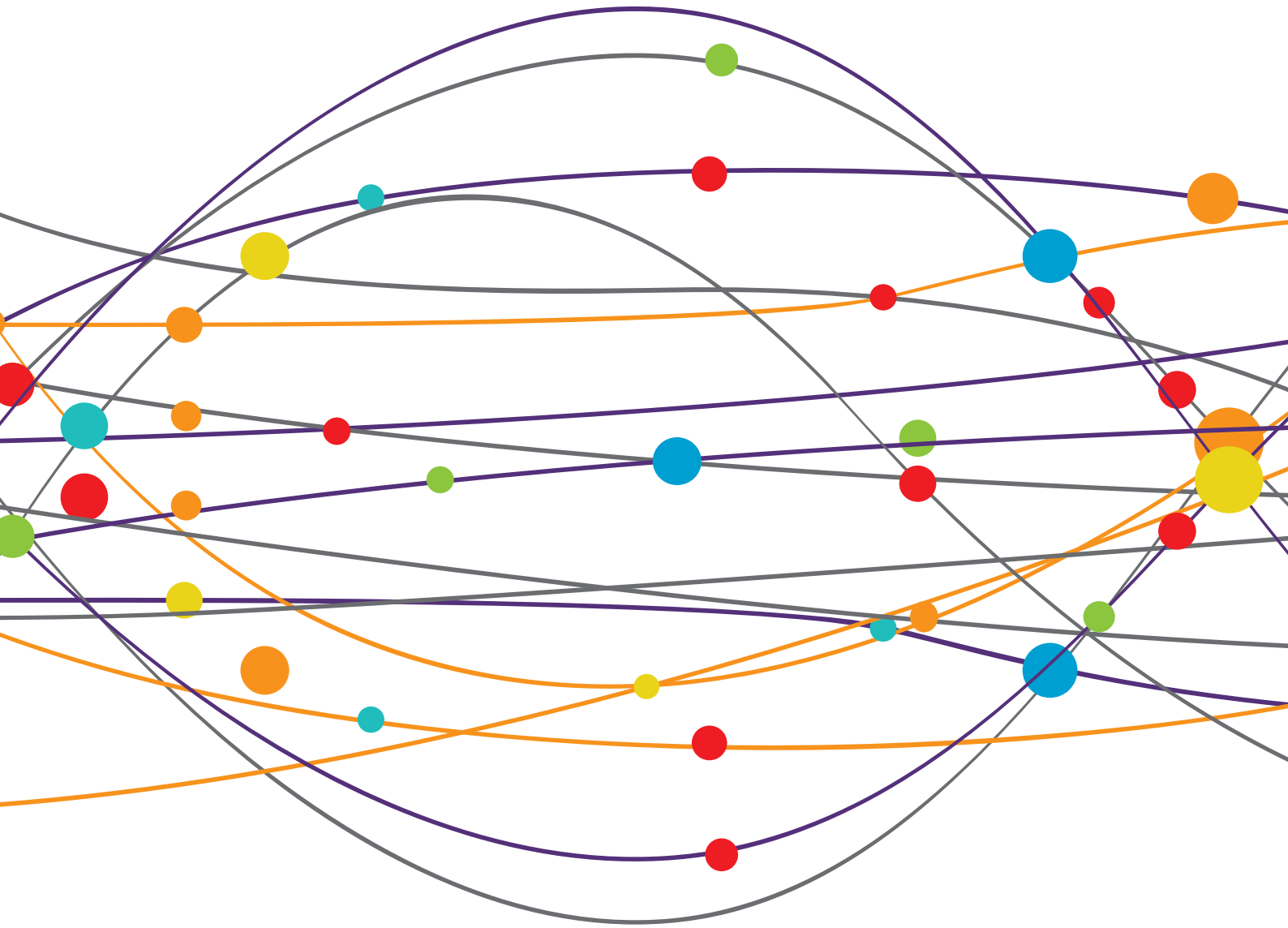

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EMERGING AREAS IN EXTRACRANIAL CAROTID STENOSIS EVALUATION AND MANAGEMENT

Topic Editors:
Seemant Chaturvedi, University of Maryland, United States
Christopher Bladin, Monash University, Australia
Hege Ihle-Hansen, Oslo University Hospital, Norway
Peter Kelly, University College Dublin, Ireland

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EDITORIAL
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Editorial: Emerging Areas in Extracranial Carotid Stenosis Evaluation and Management

Hege Ihle-Hansen[1]*, *Peter Kelly*[2,3], *Christopher Bladin*[4] and *Seemant Chaturvedi*[5]

[1] Stroke Unit, Department of Neurology, Oslo University Hospital, Oslo, Norway, [2] HRB Stroke Clinical Trials Network Ireland, University College Dublin, Dublin, Ireland, [3] Stroke Service, Mater Misericordiae University Hospital, Dublin, Ireland, [4] Department of Neurosciences, Monash University, Melbourne, VIC, Australia, [5] School of Medicine, University of Maryland, Baltimore, MD, United States

Keywords: extracranial carotid stenosis, atherosclerosis, ischemic stroke, secondary prevention, atheroinflammation, plaque, cognition

Editorial on the Research Topic

Emerging Areas in Extracranial Carotid Stenosis Evaluation and Management

Extracranial internal carotid artery stenosis is a leading cause of ischemic stroke. Patients can reduce their risk of future stroke with treatment with intensive medical therapy. In addition, selected patients can benefit from revascularization with carotid endarterectomy (CEA) or carotid stenting. Imaging methods for carotid stenosis evaluation have evolved considerably since the original randomized trials evaluating CEA that started more than three decades ago. These developments offer the prospect for more refined individual decision making for patients with carotid stenosis.

Today, stroke physicians on call assess and identify internal carotid artery stenosis on duplex ultrasound or CT angiography as part of the acute diagnostic work up and decision making regarding the potential cause and most beneficial intervention in the acute phase (1, 2). Measures of vascular burden and atherosclerosis as a subclinical disease can be included in optimizing primary and secondary prevention of vascular disease. Evaluation of extracranial vessels represents an important strategy to guide treatment decision making to improve outcome after stroke.

In this Research Topic, the editors aimed to summarize selected advances in carotid stenosis, including medical and surgical treatments. In line with the rapid development of new diagnostic and therapeutic approaches in stroke treatment, we aimed to explore the different new approaches for evaluation and management of extracranial carotid stenosis. Ten different publications report on novel aspects of risk factors, treatment, inflammation and use of advanced imaging modalities for plaque and stenosis, and extra cranial carotid stenosis as a cause of stroke, in prediction of prognosis and relation to cognition.

In the paper "*In Asymptomatic Carotid Disease and Cognitive Impairment: What Is the Evidence?*" Baradaran et al. review the current evidence on the relation between different manifestations of carotid disease and cognitive dysfunction, requesting longitudinal studies and streamlined diagnostic criteria regarding cognitive impairment. Like Ihle-Hansen et al. in "*Subclinical Carotid Artery Atherosclerosis and Cognitive Function: A Mini-Review,*" they report a significant association of carotid atherosclerosis and cognitive decline, and propose screening of carotid artery atherosclerosis to identify people at increased risk of cognitive impairment and to guide optimal risk factor management. Nuotio et al. report an association between long-term warfarin anticoagulation with increased calcification of carotid atherosclerotic plaques in the paper "*Warfarin Treatment Is Linked to Increased Internal carotid Artery Calcification.*" In "*Vascular Diameters as Predictive Factors of Recanalization Surgery Outcomes in Internal Carotid Artery Occlusion,*" Yan et al. introduced a risk stratification model to predict success

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Edited and reviewed by:
Jean-Claude Baron,
University of Cambridge,
United Kingdom

***Correspondence:**
Hege Ihle-Hansen
hmihle@ous-hf.no

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rate of revascularization surgery. Further, in "*Nonstenotic Carotid Plaques In Embolic Stroke of Unknown Source,*" Kamtchum-Tatuene et al. discuss current knowledge regarding the association between embolic stroke of undetermined source (ESUS) and ipsilateral non-stenotic carotid plaque. Evans et al. demonstrate an independent association between atheroinflammation within carotid atherosclerosis and the severity of small vessel disease in "*Carotid Atheroinflammation Is Associated With Cerebral Small Vessel Disease Severity*," indicating a future anti-inflammatory therapeutic approach to reduce the burden of chronic small vessel disease. Giannotti et al. combined PET and MRI markers of inflammation and of plaque stability to assess plaque vulnerability in "*Association Between 18-FDG Positron Emission Tomography and MRI biomarkers of Plaque Vulnerability in Patients With Symptomatic Carotid Stenosis.*" In addition, Nies et al. propose the inclusion of MRI biomarkers to assess plaque vulnerability in prediction models for stroke recurrence in "*Emerging Role of Carotid MRI for Personalized Ischemic Stroke Risk Prediction in Patients With Carotid Artery Stenosis.*" Finally, Lui et al. presented an uncommon etiology of stroke in the young; "*Hyoid Elongation May Be a Rare Cause of Recurrent Stroke in Youth-A Case Report and Literature Review*" Liu et al.

Still, to be able to compare results from different studies and to further explore the effect of interventions and the potential for including measures of plaques and stenosis in prediction models, we need standardization of methods to assess, define and report pathologies. The medical community also needs modern randomized trials to compare revascularization vs. intensive medical therapy (3), including long-term follow-up. It would be ideal to include cognitive outcomes as part of these trials.

Through these publications, our contributors have moved our knowledge a further step forward. Characterizing the nature and severity of extracranial carotid stenosis as part of regular stroke care may lead to improvements in outcomes that are meaningful to both patients and clinicians.

AUTHOR CONTRIBUTIONS

Guest editors, HI-H drafted the first version of the editorial. All authors contributed and approved the final version.

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ORIGINAL RESEARCH
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Warfarin Treatment Is Associated to Increased Internal Carotid Artery Calcification

Krista Nuotio[1,2], Suvi M. Koskinen[2,3], Laura Mäkitie[1,2], Jarno Tuimala[4], Petra Ijäs[1,2], Hanna M. Heikkilä[2], Jani Saksi[2], Pirkka Vikatmaa[5], Pia Sorto[2], Sonja Kasari[2], Ilari Paakkari[6], Heli Silvennoinen[3], Leena Valanne[3], Mikko I. Mäyränpää[7], Lauri Soinne[1,2], Petri T. Kovanen[8] and Perttu J. Lindsberg[1,2]*

[1] Neurology, Neurocenter, Helsinki University Hospital, Helsinki, Finland, [2] Clinical Neurosciences, Clinicum, University of Helsinki, Helsinki, Finland, [3] Medical Imaging Center, Radiology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [4] Independent Researcher, Helsinki, Finland, [5] Abdominal Center, Vascular Surgery, Helsinki University Hospital, Helsinki, Finland, [6] Pharmacology, Faculty of Medicine, University of Helsinki, Helsinki, Finland, [7] Pathology, Helsinki University and Helsinki University Hospital, Helsinki, Finland, [8] Wihuri Research Institute, Biomedicum Helsinki 1, Helsinki, Finland

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Edited by:
Hege Ihle-Hansen, Oslo University Hospital, Norway

Reviewed by:
Ryoma Morigaki, Tokushima University, Japan
Anita Ante Arsovska, Saints Cyril and Methodius University of Skopje, North Macedonia

***Correspondence:**
Krista Nuotio
krista.nuotio@hus.fi

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Background: Long-term treatment with the vitamin K antagonist warfarin is widely used for the prevention of venous thrombosis and thromboembolism. However, vitamin K antagonists may promote arterial calcification, a phenomenon that has been previously studied in coronary and peripheral arteries, but not in extracranial carotid arteries. In this observational cohort study, we investigated whether warfarin treatment is associated with calcification of atherosclerotic carotid arteries.

Methods: Overall, 500 consecutive patients underwent carotid endarterectomy, 82 of whom had received long-term warfarin therapy. The extent of calcification was assessed with preoperative computed tomography angiography, and both macroscopic morphological grading and microscopic histological examination of each excised carotid plaque were performed after carotid endarterectomy.

Results: Compared with non-users, warfarin users had significantly more computed tomography angiography-detectable vascular calcification in the common carotid arteries (odds ratio 2.64, 95% confidence interval 1.51–4.63, $P < 0.001$) and even more calcification in the internal carotid arteries near the bifurcation (odds ratio 18.27, 95% confidence interval 2.53–2323, $P < 0.001$). Histological analysis revealed that the intramural calcified area in plaques from warfarin users was significantly larger than in plaques from non-users (95% confidence interval 3.36–13.56, $P = 0.0018$).

Conclusions: Long-lasting warfarin anticoagulation associated with increased calcification of carotid atherosclerotic plaques, particularly in locations known to be the predilection sites of stroke-causing plaques. The clinical significance of this novel finding warrants further investigations.

Keywords: carotid artery, warfarin, computed tomography angiography, histology, vascular calcification, calcification

INTRODUCTION

An atherosclerotic lesion in the internal carotid artery is a major cause of cerebral ischemic stroke. Although many elements of the underlying pathological processes of atherosclerosis, e.g., lipid accumulation and the inflammatory component, have been well-characterized in developing atherosclerotic lesions (1), the multifaceted roles of calcification in atherosclerotic lesions are still debated and under investigation (2–5).

Atrial fibrillation (AF), the most common sustained arrhythmia (6) poses a significant risk for cerebral embolism, which is most effectively prevented by anticoagulants (7–9). Both warfarin and modern oral anticoagulants are available and neurologists are frequently deciding on anticoagulation on patients with AF, often with simultaneous large artery atherosclerosis.

Warfarin has been claimed to have harmful effects on the arterial wall. Evidence from experimental animals has demonstrated that treatment with warfarin is linked to vascular calcification (10, 11), with similar findings from preliminary human studies (12–14). Human studies have suggested that exposure to warfarin may increase calcification in coronary arteries (15, 16), peripheral arteries (17), aorta (18), and aortic valve leaflets (19).

However, there are only a few studies that have investigated the association of warfarin and vascular calcification in carotid arteries (20, 21), and none of them has studied vascular calcification in extracranial carotid arteries. Hence, the present clinical investigation was undertaken to evaluate the hypothesis that chronic warfarin use is associated with vascular calcification in atherosclerotic carotid artery disease. We examined the preoperative computed tomography angiography (CTA) results, macroscopic calcification of the dissected carotid specimens, and histopathology of the plaques to determine the potential presence of calcification, and the extent of different types of calcification. The results obtained in users and non-users of warfarin therapy were compared.

MATERIALS AND METHODS

This observational study was conducted at Helsinki University Hospital (HUS) in Finland in collaboration with the departments of neurology, vascular surgery, radiology, and pathology. Patients were referred for CEA from the Hospital District of Helsinki and Uusimaa (the total patient population in this district is ∼1.5 million) due to a moderate- or high-grade of carotid artery stenosis, and the decision to perform CEA was based in each case on the guidelines of the European Stroke Organization (22). Between October 2012 and September 2015, we recruited 500 consecutive patients who were due to undergo CEA because of advanced atherosclerotic carotid stenosis, either symptomatic (typically following carotid territory neurological symptoms) or asymptomatic (typically following carotid Doppler ultrasound findings after non-specific cerebral symptoms). Patients were recruited consecutively either by a research assistant (S.K.) or a neurologist (P.I., K.N., L.S.). Exclusion criteria were severe aphasia or inability to give informed consent. All consenting eligible CEA patients, except for those undergoing CEA during holiday periods, were recruited. There was no randomization, and no study-related interventions were performed. All patients were interviewed and examined before CEA, except those patients who had emergency surgery, who were interviewed postoperatively. Carotid plaques (CPs) were collected immediately after CEA. Full methodological details about the morphological and histological investigation of CPs in these patients have been published previously (23). The study was approved by the local medical ethics committee and all study patients gave written informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

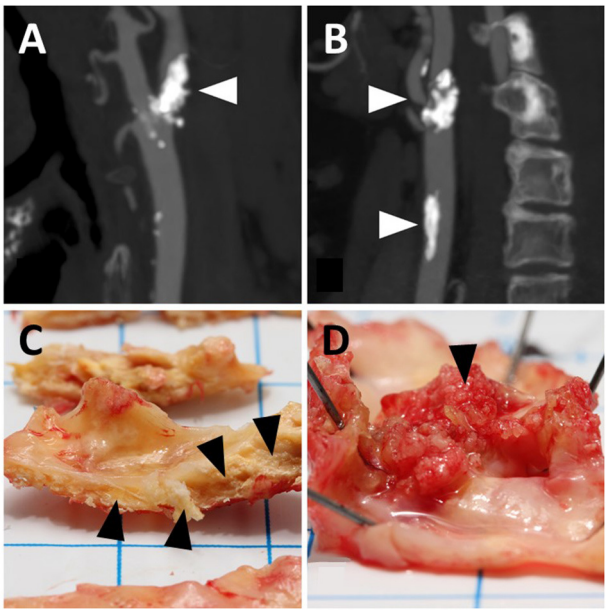

FIGURE 1 | Representative illustrations of calcification in angiograms **(A,B)** and carotid endarterectomy samples for macroscopic observation **(C,D)**. **(A)** Shows calcification of the internal carotid artery (arrowhead); **(B)** shows that calcification is present in the internal (upper arrowhead) as well as the common carotid artery (lower arrowhead). **(C)** shows intramural calcification (arrowheads); **(D)** shows luminal calcification (arrowhead). the angiograms and endarterectomy samples do not refer to the same patients.

Imaging Protocol

Before recruitment, most patients ($n = 477$) underwent multi-detector carotid artery CTA. If a patient had contraindications for CTA, magnetic resonance angiography (MRA) of the carotid arteries was performed instead. The Meilahti HUS CTA protocol has been described in detail previously (24). Representative CTA images of the internal carotid artery (ICA) and the common carotid artery (CCA) calcification are shown in **Figures 1A,B**.

Imaging data were analyzed more extensively than required by standard clinicoradiological evaluation guidelines. Carotid CTAs were primarily analyzed at a 3D reformatting station (Advantage Workstation, AW 4.4; GE Medical Systems) by two experienced neuroradiologists (L.V., H.S.) together with a radiology resident

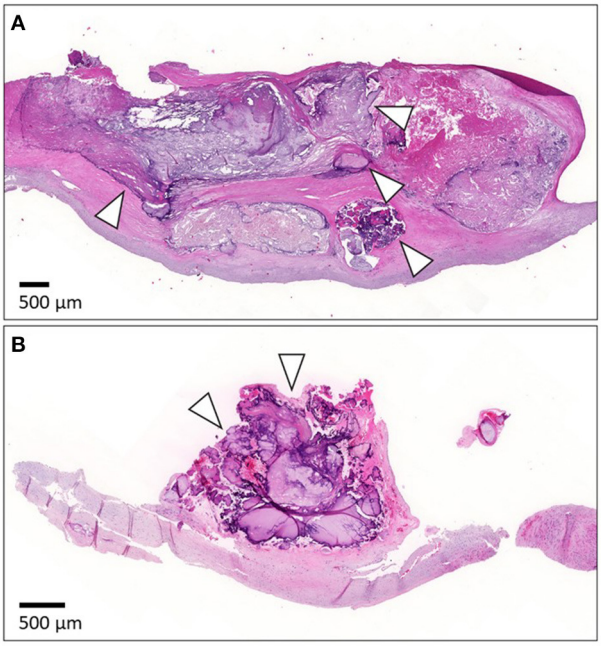

FIGURE 2 | Representative images of calcification in histological samples. **(A)** Shows histology of the intramural calcification and arrowheads point to areas of calcification. **(B)** Presents the histology of luminal calcification (arrowheads). For histology, the specimen was cut longitudinally. The luminal side is upward. The scale bar is 500 µm.

TABLE 1 | Characteristics of study patients.

	Warfarin users ($n = 82$)	Warfarin non-users ($n = 418$)	$P^{\dagger}$
Gender (male/female)	60/22	278/140	0.249
Age (median, years)	74.5	69.0	<0.0001*
Smoking	10 (12%)	147 (35%)	<0.0001*
Symptomatic carotid plaque	31 (38%)	293 (70%)	<0.0001*
Comorbidities			
Atrial fibrillation	67 (82%)	19 (5%)	<0.0001*
Hypertension	64 (78%)	343 (82%)	0.035*
Diabetes	30 (37%)	137 (33%)	0.634
Hyperlipidemia	74 (90%)	381 (91%)	0.933
Coronary artery disease	47 (57%)	137 (33%)	0.025*
ASO	16 (20%)	70 (17%)	0.430
Medication			
DM with medication	26 (32%)	131 (31%)	1.000
Dyslipidemia medication	80 (98%)	395 (95%)	0.403
ATR blocker	30 (37%)	152 (36%)	1.000
ACE inhibitor	29 (35%)	155 (37%)	0.900
Beta blocker	70 (85%)	207 (50%)	<0.0001*
Calcium channel blocker	23 (28%)	159 (38%)	0.103

† Fisher's exact test was used in all comparisons except for age, which was analyzed using t-test.
Statin medication in all patients, expect for six who had only ezetimibe; of the patients treated with ezetimibe, one also received warfarin and five were warfarin non-users.
ASO, peripheral arterial disease; DM, diabetes mellitus; ATR, angiotensin receptor; ACE, angiotensin converting enzyme.
**Indicates statistically significant ($p < 0.05$).*

(S.M.K.) specifically trained to analyze carotid CTAs; all were blinded to warfarin treatment. Carotid MRAs were excluded from the calcification analysis because of the high specificity of CTA in visualizing calcified carotid artery structures. Thus, our analysis focused on the visual grading of the amount of carotid artery calcification.

Radiological Classification of Carotid Calcification

The final classification of the carotid CTA calcification was performed using the Impax workstation (AGFA Impax version 6.6.1.5003) from high-resolution calibrated medical monitors. CCA and ICA were visualized from thin axial source images, as well as from sagittal and coronal reformations. The CCA was evaluated throughout its length, i.e., from the aortic arch to the bifurcation level. However, the bifurcation area of the CCA was included in the ICA grading. While the entire length of the CCA was classified for calcification, the classification of ICA calcification was limited to the length encompassed by the typical operative extent of CEA.

CCA calcification (**Figure 1B**) was graded as Class 0 if no significant calcification was seen along its course (one small spot-like calcification with an estimated diameter of 0.5 mm or less was allowed) and as Class 1 if several small spot-like calcifications or one larger calcification was detected. ICA calcification was graded as Class 0 if the stenosing plaque did not contain any calcification, and thus the domains predominantly contained lipid-like components. As for the CCA, one or two small spot-like calcifications in the plaque area were also allowed with a limit of up to 0.5 mm. The ICA calcification (**Figure 1A**) was graded as Class 1 if numerous small calcifications were detected in the plaque area; however, the presence of lipid-like components was not excluded from Class 1, even as a dominant feature (heterogeneous plaque structure). In addition, this ICA Class included calcifications observed as ring-like structures, surrounding a lipid-containing stenotic plaque. Fully calcified stenotic plaques with a uniform bulky calculus as the clear dominant plaque feature were graded as Class 2.

Macroscopic Evaluation of Calcification

The carotid CEA specimens were photographed and macroscopically evaluated based on their visual and morphological characteristics, as previously described (23). The macroscopic evaluations of the calcification revealed that in a fraction of the specimens the entire calcification was located intramurally, i.e., within the vessel wall, while in another fraction of the specimens the calcification had broken the luminal surface of the specimen and extended into the lumen. Accordingly, two forms of CP calcification could be distinguished: purely intramural calcification (**Figure 1C**) and calcification extending into the lumen referred to as "luminal calcification" (**Figure 1D**). Regarding the purely intramural location, the calcification was graded into three categories: 0 = no calcified areas, 1 = small

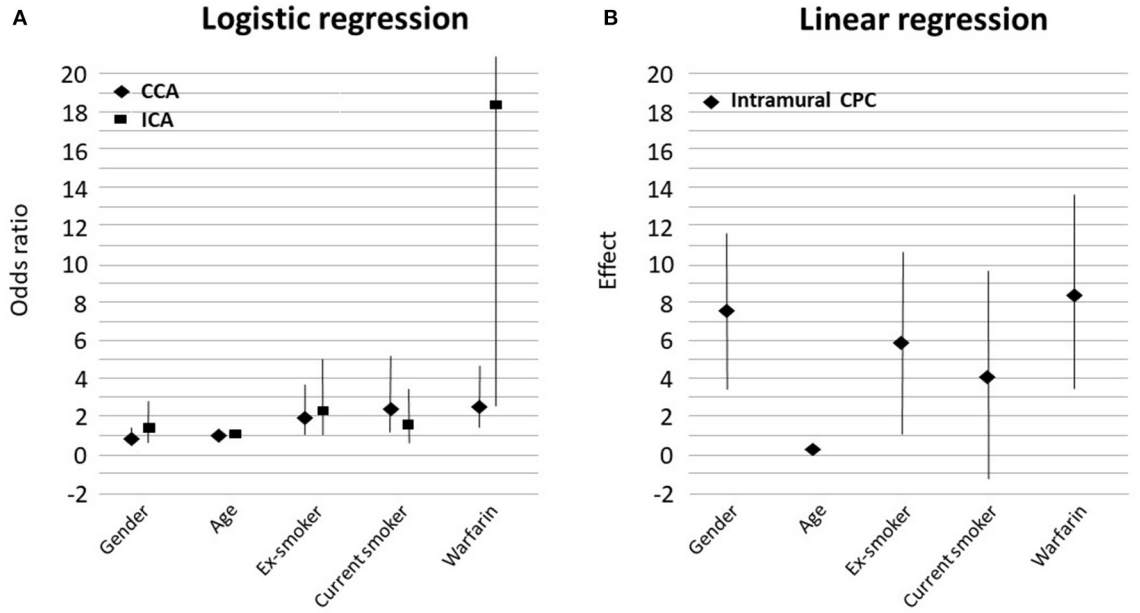

FIGURE 3 | Graphs showing the strength of association between variables in the multivariable model and the radiological evidence of calcification **(A)** and linear regression results for the histological evidence of calcification **(B)**. Female gender favored intramural calcification. CCA, common carotid artery; ICA, internal carotid artery; CPC, carotid plaque calcification.

calcified areas, and 2 = large heavily calcified areas. The luminal calcifications had broken the surface of the carotid plaque, and they differed macroscopically from the purely intramural calcifications in that they resembled coral reefs, as has also been observed in calcified aortic walls (25). The coral-like projections were graded dichotomously: 0 = no luminal calcification and 1 = luminal calcification.

Histopathology

Histopathological evaluation was carried out using one representative longitudinal slice with two histological stains: Hematoxylin and eosin (HE) and Masson's trichrome (MT). Slices were fixed in 10% formalin for 2–4 days, decalcified in EDTA-decalcifying solution for 1–4 weeks depending on the level of calcification, dehydrated, and embedded in paraffin. Sections (4-μm thick) from paraffin-embedded specimens were stained automatically with HE and manually with MT stain. Full details of the methodology have been reported previously (23). Intramural calcification (**Figure 2A**) was approximated as a percentage of the total plaque area, while luminal calcification (**Figure 2B**) was quantified as a percentage of the luminal length of the calcification from the total luminal plaque length in the section.

Statistical Analysis

To determine the significance of the observed effects we formulated multivariable logistic regression models and tested a total of 12 different hypotheses. These models contained different combinations of main effects for gender, age, smoking, hypertension, diabetes, coronary artery disease, renal insufficiency, dyslipidemia, use of statin therapy, and use of warfarin. The response variables were measures of calcification: calcification of either the ICA or CCA in radiological analysis, and intramural and luminal CP calcification in *ex vivo* morphological analysis. Each hypothesis was tested on all these calcification types. The results are reported only for the model containing gender, age, smoking, and warfarin use because the other variables did not reach statistical significance in the tested models (except diabetes for luminal CP calcification, odds ratio [OR] 1.16, $P = 0.04$).

The analysis was complicated by the fact that all warfarin users had radiological calcification of the ICA. This phenomenon is known as "separation." For datasets that showed separation, the usual maximum likelihood-based estimation of logistic regression models does not allow customary estimation of odds ratios or confidence intervals. Therefore, we estimated the models using Firth's bias-reduced logistic regression (26). Firth's method results in narrower confidence intervals than the traditional logistic regression in a case of complete separation, but they might still be much wider than what one is used to encounter (27).

To determine the significance of the observed histological effects, a linear regression analysis was performed. Histological variables were measured on a percentage scale, which, however, could not be successfully transformed to resemble a normal distribution. Therefore, the significance was evaluated with a permutation test.

All analyses were performed in R 3.3.1 (28). Firth's method was used as implemented in the add-on package logistf (29). A $P < 0.05$ was considered statistically significant, and all reported

TABLE 2 | Results of the multivariable logistic regression model for radiological calcification (upper) and macroscopic calcification (lower).

	CCA				ICA†			
Independent variable	**OR**	**CI 2.5%**	**CI 97.5%**	***P***	**OR**	**CI 2.5%**	**CI 97.5%**	***P***
(Intercept)	0.0150	0.0014	0.1591	0.0000*	0.0366	0.0021	0.4795	0.0105*
Gender	0.8208	0.4950	1.3610	0.4440	1.3739	0.7147	2.7583	0.3467
Age	1.0360	1.0048	1.0680	0.0230*	1.0650	1.0289	1.1080	0.0002*
Ex-smoker	1.9372	1.0484	3.5797	0.0350*	2.2587	1.0168	5.0213	0.0455*
Current smoker	2.4842	1.2128	5.0887	0.0130*	1.5385	0.6888	3.4165	0.2905
Warfarin	2.6425	1.5088	4.6282	0.001*	18.2727	2.5307	2323.1240	0.0006*
	Intramural CP calcification				**Luminal CP calcification**			
Independent variable	**OR**	**CI 2.5%**	**CI 97.5%**	***P***	**OR**	**CI 2.5%**	**CI 97.5%**	***P***
(Intercept)	0.0284	0.0027	0.3022	0.0030*	0.1027	0.0159	0.6624	0.0170*
Gender	1.8804	1.0446	3.3851	0.035*	1.6705	1.1032	2.5296	0.0150*
Age	1.0596	1.0265	1.0936	0.0000*	1.0085	0.9843	1.0333	0.4930
Ex-smoker	1.8252	0.9459	3.5219	0.0730	1.3215	0.8002	2.1823	0.2760
Current smoker	1.2530	0.6287	2.4969	0.5220	1.5124	0.8543	2.6772	0.1560
Warfarin	1.8235	0.7838	4.2428	0.1630	1.6273	0.9704	2.7290	0.0650

All response variables were categorical: 0 = no calcification, 1 = calcification detected.

† Fitted using Firth's bias-reduced logistic regression to compensate for separation. Unusually wide confidence intervals stem from the complete separation present in the data.

OR, Odd's ratio; CI, confidence interval; CCA, common carotid artery; CP, carotid plaque; ICA, internal carotid artery.

**Indicates statistically significant ($p < 0.05$).*

confidence intervals (CIs) had a 95% coverage. Only complete cases, with no missing observations in the explanatory variables, were used for analyses.

RESULTS

Of the 500 study patients, 82 had received warfarin due to AF; the median duration of warfarin therapy was 1.6 years. Because the duration of warfarin therapy was not significantly associated with the degree of calcification, a dichotomous parameter describing warfarin therapy was used in the statistical analysis: 0 = the patient had never received warfarin therapy and 1 = the patient had received warfarin therapy for any period of time. Among all patients, 324 had a symptomatic CP, 102 had an asymptomatic CP, and in 74 cases it was uncertain whether the symptomatology was related to the CP. A small number of study patients did not undergo CEA, or their clinical data were missing, and accordingly, 479 patients (and CPs) were included in the multivariable analyses. For some patients, carotid artery MRA was performed instead of CTA; hence, 457 patients were included in the radiological data analyses and histological data were available for 477 CPs. The characteristics of the study patients are presented in **Table 1**.

Warfarin use was associated with increased vascular calcification, as observed in carotid artery CTAs (**Figure 3A**). Warfarin users had significantly more vascular calcification in their CCAs (OR 2.64, 95% CI 1.51–4.63, $P = 0.001$, **Figure 1B**) and markedly more in their ICAs (OR 18.27, 95% CI 2.53–2323, $P < 0.001$, **Figures 1A**, **3A**, **Table 2**). The CCA calcifications were generally small and non-stenosing, whereas those in the ICA were more prominent and associated with the stenosing CP. Coronary artery disease was observed more frequently in warfarin users (57 vs. 33%, $P = 0.025$) than non-users, but hypertension was less common (78 vs. 82%, $P = 0.035$, **Table 1**). Consistent with the expected high frequency of AF among warfarin users (82 vs. 5%, $P < 0.001$), the use of beta-blocking medication was also more common than in non-users (85 vs. 50%, $P < 0.001$). Warfarin users tended to have tighter carotid stenosis than non-users (degree of stenosis 69.4 vs. 63.7%), but this difference was not statistically significant. Given the nominal effects of warfarin in preventing thromboembolism, it was an expected finding that patients on warfarin had less symptomatic carotid stenosis than non-users (31/82 = 38 vs. 293/418 = 70%, $P < 0.001$). CP calcification, as observed in CTAs, was not associated with the symptom status of the plaque.

In multivariable analyses (**Table 2**), age was significantly associated with increased vascular calcification in CCAs (OR 1.04, 95% CI 1.01–1.07, $P = 0.023$, **Figure 3A**) and in ICAs (OR 1.07, 95% CI 1.03–1.11, $P < 0.001$, **Figure 3A**). Smoking had a similar effect: Vascular calcification was increased in CCAs among ex-smokers (OR 1.94, 95% CI 1.05–3.58, $P = 0.035$, **Figure 3A**) and current smokers (OR 2.48, 95% CI 1.21–5.09, $P = 0.013$, **Figure 3A**). However, the association between smoking and vascular calcification in ICAs was not uniform, as a significant association was seen among ex-smokers (OR 2.26, 95% CI 1.02–5.02, $P = 0.046$, **Figure 3A**) but not among current smokers. Other risk factors such as hypertension, diabetes, renal insufficiency, and dyslipidemia were not associated with vascular calcification in CCAs or ICAs, nor was statin use (**Table 1**). All variables that reached statistical significance were included in the multivariable statistical model.

Our core observation of increased CTA-detectable vascular calcification in warfarin users prompted closer macroscopic investigation of *ex vivo* CEA specimens, and examination

TABLE 3 | Results of the multivariable linear regression model for histological calcification.

	Intramural CP calcification				Luminal CP calcification			
Independent variable	**Effect**	**CI 2.5%**	**CI 97.5%**	***P***	**Effect**	**CI 2.5%**	**CI 97.5%**	***P***
(Intercept)	−10.5556	−27.9381	6.8269	0.9999	−3.6407	−17.4078	10.1264	0.9277
Gender	7.5644	3.5092	11.6197	0.0001*	0.5453	−2.6665	3.7571	0.3669
Age	0.2516	0.0230	0.4803	0.0156*	0.1310	−0.0500	0.3121	0.0694
Ex-smoker	5.8842	1.1381	10.6303	0.0083*	−0.4726	−4.2316	3.2863	0.6018
Current smoker	4.1863	−1.2210	9.5936	0.0692	0.0210	−4.2617	4.3036	0.4982
Warfarin	8.4588	3.3606	13.5570	0.0018*	1.6758	−2.3621	5.7136	0.2022

**Indicates statistically significant ($p < 0.05$).*

of whether differential morphological distributions of CP calcification could be found. Although intramural CP calcification was more often observed in warfarin users (**Figure 1C**) than non-users (93 vs. 81%, Fisher's exact test $P = 0.009$), this difference did not reach statistical significance in multivariable analyses (OR 1.82, 95% CI 0.78–4.24, $P = 0.163$, **Table 2**). Occasionally, distinct coral reef-like luminal calcifications were also observed in CPs (**Figure 1D**), as has been found in human aortas (25). In *ex vivo* analysis, the luminal calcifications protruded from the vessel wall like coral reefs and crumbled into small sand-like grains when cut by a scalpel, whereas the intramural CP calcifications resided within the vessel wall in a laminar fashion and were usually very solid and difficult to cut. Warfarin use tended to be associated with luminal CP calcification (43% calcification in warfarin-users vs. 32% in non-users, Fisher's exact test $P = 0.069$), and this tendency persisted in multivariable analysis (OR 1.63, 95% CI 0.97–2.73, $P = 0.065$; **Table 2**).

In multivariable analyses of macroscopic CP calcifications, female gender was associated with increased intramural calcification (OR 1.88, 95% CI 1.04–3.39, $P = 0.035$) as well as with luminal calcification (OR 1.67, 95% CI 1.10–2.53, $P = 0.015$; **Table 2**). Age increased intramural calcification (OR 1.06, 95% CI 1.03–1.09, $P < 0.001$) but not luminal calcification. Other risk factors including smoking, hypertension, renal insufficiency, dyslipidemia, and statin use were not statistically significantly associated with either intramural or luminal CP calcification.

In multivariable linear regression analysis of histological staining, the intramural calcified area of the carotid specimen was 8.5% larger in warfarin users compared with non-users; warfarin use was significantly related to intramural CP calcification (effect size 8.46, 95% CI 3.36–13.56, $P = 0.0018$, **Figures 2A**, **3B**, **Table 3**). In most CEA specimens, intramural calcification was observed within the atherosclerotic plaque, and only occasionally were minor calcifications observed in the medial layer backing the plaque. In addition, calcification was clearly deposited and mature in the atherosclerotic plaques of warfarin users. Females (7.6%, 95% CI 3.51–11.62, $P = 0.0001$) and ex-smokers (5.9%, 95% CI 1.14–10.63%, $P = 0.0083$) had more intramural CP calcifications, while older patients had less intramural CP calcifications (0.25%, 95% CI 0.02–0.48, $P = 0.0156$; **Figure 3B**). A correlation between warfarin use and luminal CP calcifications was not confirmed by histological analysis (**Table 3**). The lack of a correlation may reflect incomplete recovery of luminal calcifications, which easily detach during histological sample preparation.

DISCUSSION

This is the first report on increased carotid plaque calcification in patients on warfarin therapy. The association was strongest for radiologically determined calcification in the ICA (OR 18.27, 95% CI 2.53–2323, $P < 0.001$). The results confirm the previously observed association between calcification and warfarin use in other arterial beds in animal models (10, 11, 16), as well as in humans (12–19). In these human studies, such association was observed in coronary arteries (15, 16), peripheral arteries (medial pattern of calcification) (17), aorta (18), and aortic valve leaflets (19).

The pathology underlying atherosclerotic calcification is still unclear. Multiple sources of calcium have been proposed, including (a) apoptosis of smooth muscle cells (SMCs) or macrophages; (b) release of matrix vesicles, resembling bone formation; (c) diminished inhibition of calcification through deficiency of circulating mineralization inhibitors; and (d) bone generation resulting from perturbed differentiation of vascular SMCs or stem cells (3, 30–35). Furthermore, despite the long-term use of the vitamin K antagonist warfarin (since the 1950s), it took more than half a century to discover that this anticoagulant also affects the mineralization process of both bone and soft tissues (36). In fact, a preventive role for vitamin K in cardiovascular disease has been proposed based on its action as an activator of matrix Gla protein, a calcification inhibitor that is also expressed in vascular tissue (37). We realize that our methodology and findings do not permit elucidation of the mechanistic pathways leading to carotid artery calcification in our cohort. However, the present data revealed an ∼20-fold increase in the occurrence of calcification in association with warfarin therapy, which accords with the notion that extended suppression of vitamin K-dependent vascular matrix Gla protein plays an important role in the calcification of atherosclerotic plaques.

The prognostic implications of CP calcification relative to subsequent vascular events have been investigated in several studies and with variable results. Allison and co-workers evaluated computed tomography scans from 4,544 patients and

examined the presence of calcium in different arterial beds; the authors observed that, depending on the major artery involved, the calcification had differential prognostic effects. Thus, calcifications in the carotid arteries and in the thoracic aorta showed the most robust association with poor patient survival, the carotid calcification showing statistically significant hazard ratio (HR) values for premature all-cause death which ranged from 1.60 to 1.96 in multivariable models (38). In the Northern Manhattan study, CP calcification of 1,118 stroke-free subjects was assessed using high-resolution B-mode ultrasound. Patients with CP calcification had a significantly increased risk for combined vascular outcome (HR 2.5, 95% CI 1.0–5.8) compared to patients without plaques (39). Of note, Henein et al. found that long-term statin therapy accelerated coronary artery calcification; however, despite this increase in coronary calcification, the number of coronary events did not increase suggesting plaque repair and stabilization during statin treatment (40). In the present study, inclusion of statin use as a variable in the multivariable analysis did not affect the major observation, hence calcification in our study population was not explained by statin use.

In our cohort, the majority (83%) of calcifications represented the intramural type i.e., they were mainly located within the atherosclerotic plaques. Some calcifications showed the gross morphological features of coral-like calcification (luminal calcification), which tended to be overrepresented in warfarin users ($P = 0.065$). The clinical significance of calcification, i.e., its role in determining the vulnerability of an advanced atherosclerotic plaque, is still under investigation (4, 35, 41). Generally, calcium in atherosclerotic plaques has been linked with stability (42, 43), but evidence suggests that microcalcifications (typically 10 μm in diameter) derived from dying macrophages or SMCs in thin fibrous caps may trigger plaque rupture through locally increased stress, caused by the mismatch in material properties between the microcalcifications and the fibrous tissue present in plaques (41, 44–46). The different macroscopic and histological appearances of the calcification may represent different pathophysiological processes, in line with suggestions by other investigators (47), and may have different prognostic value. We realize that the results of each of the calcification grading method used in the present work yielded somewhat arbitrary results. However, all three different gradings complemented each other and provided as multifaceted picture of the phenotypes of the calcification process.

It could be argued that patients on warfarin had more advanced atherosclerotic disease in general and hence also more calcification in their carotid arteries, i.e., the association observed could be confounded by the indication. Indeed, there was a slight overrepresentation of coronary artery disease (**Table 1**) among warfarin users in this study. Importantly, our results are in line with previous findings by Peeters et al. who found that vascular (aortic) calcification was increased in AF patients who used a vitamin K antagonist (warfarin), and that such association was not present in AF patients taking one of the new direct oral anticoagulants that are non-vitamin K antagonists (18).

It has been acknowledged, however, that although atherosclerosis is a systemic disease, its burden is not similar across different vessel beds (38, 48). Moderate to strong correlations have been found between calcification in coronary arteries, aortic arch, and carotid arteries, implying that assessment of the amount of calcification in one arterial bed only gives a rough estimate of calcification in other atherosclerosis-susceptible arterial segments (49). Although all subjects in our study undergoing CEA had variable manifestations of long-standing general atherosclerotic disease and advanced stenosing carotid artery plaques, no significant difference in the degree of carotid stenosis was found between warfarin users and non-users. Since the degree of stenosis roughly reflects plaque size and therefore also disease stage, the above finding suggests that calcification reflected differences in the biochemical and pathophysiological processes in plaques derived from different patients rather than merely the stage of the disease.

The association between warfarin use and increased vascular calcification is a concern because of the wide use of warfarin, especially in patients with atherosclerotic cardiovascular disease, and the positive association between arterial calcification and vascular events and all-cause mortality (38). Our data do not establish whether calcification should be considered a marker of a vulnerable atherosclerotic plaque or rather a sign of plaque evolution toward "end-stage" stabilization and hence a better prognosis. We observed that although the CPs were more calcified in warfarin users than in non-users, in the user group there were fewer symptomatic plaques (38 vs. 70%, $P < 0.0001$). This finding may imply that arterial calcification signifies *in situ* plaque stabilization, at least in the carotid arterial segment studied here. However, during anticoagulation, the thromboembolic event originating from the plaque may have been prevented, which may have at least partially concealed the underlying atherosclerotic vasculopathic process and its prothrombotic and thromboembolic potential.

Finally, the clinical significance of our findings and the potential additional impact of accelerated calcification on the evolution of carotid disease remain to be determined. However, the results of this study reveal that warfarin use is associated with calcification of carotid atherosclerotic plaques present in the bifurcation area, i.e., in the predilection site of stroke-causing plaques. Further investigations may also address the evolution of carotid calcification in patients on anticoagulants lacking an effect on vitamin K.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by HUS eettinen toimikunta, PL 705, 00029 HUS

Biomedicum Helsinki 2 C 7.krs, Tukholmankatu 8 C, Helsinki. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KN: design, data analysis, drafted the manuscript for intellectual content, data acquisition, and interpretation of the data. SMK: design, data acquisition, analyzed the data (radiology), and manuscript revision. LM: design, data acquisition, histological analysis, and manuscript revision. JT: statistical analysis of the data. PI: design, data acquisition, interpreted the data, and manuscript revision. HH, JS, and PS: design, data acquisition, and manuscript revision. PV: responsible for the carotid endarterectomies and manuscript revision. SK: data acquisition (patient interviews, coordination). IP: design and conceptualized study on pharmacologic viewpoint and manuscript revision. HS and LV: design and conceptualized study on radiologic viewpoint and manuscript revision. MM: design, interpreted the data (histology), and manuscript revision. LS: design, interpreted the data, and manuscript revision. PK and PL: design and conceptualized study, interpreted the data, and manuscript revision. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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Subclinical Carotid Artery Atherosclerosis and Cognitive Function: A Mini-Review

Håkon Ihle-Hansen[1], Hege Ihle-Hansen[1,2], Else Charlotte Sandset[2] and Guri Hagberg[1,2]*

[1] Department of Medicine, Bærum Hospital- Vestre Viken Hospital Trust, Drammen, Norway, [2] Oslo Stroke Unit, Department of Neurology, Oslo University Hospital, Ullevål, Norway

Carotid artery atherosclerosis, the result of a multitude of vascular risk factors, is a promising marker for use in risk stratification. Recent evidence suggests that carotid artery atherosclerosis affects cognitive function and is an independent risk factor for the development of cognitive impairment. Both atherosclerosis and cognitive impairment develop over a prolonged period (years), and due to the aging population, markers to identify persons at risk are needed. Carotid artery atherosclerosis can easily be visualized using non-invasive ultrasound, potentially enabling early and intensified risk factor management to preserve cognitive function or delay further decline. However, the burden of atherosclerosis and temporal exposure required to pose a risk of cognitive impairment is unclear. This mini-review aims to explore the available evidence on the association between carotid atherosclerosis and cognition, and furthermore identify the remaining gaps in knowledge.

Keywords: IMT, cognitive function, dementia, plaque, carotid artery atherosclerosis

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Reviewed by:
Marina Sorrentino Hernandes, Emory University, United States
Theodoros Karapanayiotides, Aristotle University of Thessaloniki, Greece

****Correspondence:***
Håkon Ihle-Hansen
haaihl@vestreviken.no

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INTRODUCTION

The prevention of cognitive impairment is one of the most significant challenges of our time with up to 10 million new cases each year (1). The consequences of underlying vascular risk factors such as hypertension increase the risk of both atherosclerosis and cognitive impairment. Monitoring and treating vascular risk factors mid-life is a promising strategy to prevent dementia later in life (2). Furthermore, the burden of atherosclerosis correlates to the underlying burden of vascular risk factors (3) and can be viewed as a surrogate marker of total vascular risk.

Vascular risk factors including atherosclerosis seem to contribute not only to vascular cognitive impairment, but also in the pathophysiology of Alzheimers disease (4). It has been proposed that there may be a convergence of mechanisms in vascular and neurodegenerative processes that cause impairments of cognition. These mechanisms are not yet fully elucidated, but most likely mediated through small vessel disease, endothelial dysfunction, silent ischemia, and reduced cerebral blood flow, which precedes neurodegeneration and amyloid accumulation (5).

Atherosclerosis represents a systemic multifactorial and inflammatory disease affecting the vascular bed (6). It develops gradually over years, first as a thickening of the vessel wall's innermost layer - the intima (7), this can either abate or progress into an atherosclerotic plaque and a vascular stenosis (8). Several studies have shown an independent association between atherosclerosis and

increased risk of cognitive impairment (9, 10). Predilection sites for atherosclerosis are large and medium-sized arteries as well as areas where laminar blood flow is disturbed.

The carotid artery is ideally placed for ultrasound examination and assessment of atherosclerosis. Different types of angiography examinations are available but either demand more resources or are associated with radiation exposure, leaving ultrasound best suited for screening purposes. Atherosclerosis in the carotid arteries correlates with the presence of atherosclerosis in other vessels (11). Definitions of subclinical atherosclerotic disease in various studies include increased intima-media thickness (IMT), atherosclerotic plaques, and asymptomatic stenosis. Assessment of subclinical carotid artery atherosclerosis holds promise as a marker to identify persons at risk and those who may benefit from intensified risk factor management to prevent further progression of atherosclerosis and cognitive decline.

Symptomatic atherosclerosis in pre- and intra- cerebral vessels increases the risk of brain damage with an associated increased risk of cognitive impairment (12). However, the link between subclinical atherosclerosis (meaning nearly or completely asymptomatic) and cognitive function in stroke-free subjects is not as clear, the available evidence is mainly from large population-based cohort studies.

In this mini-review, focusing on subclinical atherosclerosis located in the carotid arteries, we aim to explore the currently available evidence on the association between carotid atherosclerosis and cognition. Furthermore, evaluate any potential progressive relationships, and identify the remaining gaps in knowledge.

SUBCLINICAL CAROTID ATHEROSCLEROSIS AND COGNITION

Several large population studies have assessed the association between atherosclerosis and cognitive function, 20,000 with cross sectional design and 50,000 with a longitudinal design with long term follow-up (up 20 years) between initial assessment of atherosclerosis and outcome, i.e., worsening in cognitive performance or dementia (13). The studies included in our mini-review are described in detail in **Table 1**.

Association between subclinical atherosclerosis and cognitive performance in subjects free of known cognitive impairment was explored in 8 studies with a cross sectional design (14–21). Seven cross-sectional studies have found an association between markers of atherosclerosis and cognitive function (14–16, 18–21).

Four studies found an association between greater IMT and reduced performance in some specific cognitive domains (14, 16, 18, 22). The majority of studies included subjects with more advanced atherosclerosis, i.e., plaque, plaque burden, and stenosis (14–16, 20, 21), supporting the notion of an inverse association between increasing atherosclerotic burden and cognitive function.

Nine studies including a total of 23,000 patients showed associations between higher IMT and deterioration of cognitive performance over time (9, 13, 23–30). On the other hand, the level of IMT was not associated with decreased cognitive performance in five studies including in total 27,000 patients (10, 31–34).

The location of the IMT measurement may be of importance. In the Framingham study, greater IMT in the internal carotid artery was associated with impaired cognitive function. However, no such association was found when assessing the common carotid intima-media thickness (ccIMT) and cognitive impairment (32).

Further, eight studies reported associations between carotid plaque/stenosis and decreasing cognitive performance and cognitive impairment in long-time follow-up (10, 13, 27, 30–33, 35), and four studies showed that plaque/stenosis was superior to IMT at predicting cognitive decline (10, 31–33).

DISCUSSION

There is a significant association between different subclinical atherosclerosis measures and cognition in large population studies, both in studies with cross-sectional design and in longitudinal studies showing progressive changes over time.

The current evidence suggests a stronger association between cognitive impairment and more pronounced subclinical atherosclerosis. In the Cardiovascular Health Study and the Framingham study, asymptomatic $\geq$50% carotid artery stenosis (conventionally defined as significant atherosclerosis) predicted poorer cognitive performance (10, 32). Both studies failed to find an association between ccIMT and cognition.

Some studies reported no association between continuous measures of IMT and cognitive function, while as a dichotomized variables were significant (35). While increased IMT may represent non-atherosclerotic age-associated changes in the vessel wall, vessel wall tension, or an adaptive response to changes in flow, it is believed that IMT in the upper reference range is less likely to reflect these non-atherosclerotic processes.

Whether the location of atherosclerosis is relevant is still unclear. In the Framingham study, they found that IMT in the internal carotid artery (ICA), in contrast to ccIMT, was more associated with cognitive impairment (32). Atherosclerosis develops earlier in vessel bifurcations and origins such as the carotid bulb and proximal ICA which could explain associations between IMT and cognitive impairment in ICA, but not common carotid artery. However, atherosclerosis (including increased IMT) in other locations than the carotid arteries have also been associated with reduced cognition, supporting the hypothesis that atherosclerosis is a systemic disease of the vascular bed (36).

The exact pathophysiological mechanisms of atherosclerosis-induced cognitive impairment have not yet been identified. Population-based studies do not have the ideal design to illicit an answer and mechanisms may include cerebral changes resulting from silent embolization, inflammation or hypoperfusion (2, 37, 38). Increased arterial stiffness leads to increased pulse-wave velocity,pulsatile pressure and flow in the small vessels (2, 39), and a potential failure in the blood-brain barrier. Since the pathological mechanisms remain unknown, the possibility of reverse causality or that atherosclerosis and cognitive impairment develop in parallel cannot with certainty

TABLE 1 | Excerpts from relevant populations-based studies.

Author, journal, year study	Population size and age	Measurements	Observation time	Outcome	Adjusted for
Gustavsson, Ann Neurol 2020, Malmö Diet and Cancer Study	N 6,103, mean age 57.5	Carotid plaques and IMT	20 years (1991/1994–2014)	*Carotid plaques*: Vascular Dementia HR 1.90 [95% CI 1.07–3.38]. *IMT*: Dementia HR 1.14 [95% CI 1.03–1.26]; Vascular Dementia HR 1.32 [95% CI 1.10–1.57]	Cardiovascular risk factors, education, ApoE, age, sex
Wendel, Stroke 2009, Baltimore Longitudinal Study of Aging	N 538, mean age 54.9	ccIMT	Up to11 years (mean 4 years)	*ccIMT* associated with decline in performance on multiple measures of verbal and nonverbal memory	Age, sex, race, cardiovascular risk factors
Van Oijen, Ann Neurol 2007, Rotterdam Study	N 6,647, mean age 72.4	ccIMT, carotid plaques	mean 9.0 years (1990/1993–1997/1999)	*ccIMT* in the fifth quintile compared with the first, and *Carotid plaques* in 5 or 6 locations compared with subjects without carotid plaques were predictor of dementia	Age and sex and cardiovascular factors
Knopman, Neurology 2001, Atherosclerosis Risk in Communities cohort (ARIC)	*N* 10,963, age range 47–70	ccIMT, divided into tertiles (mean of three sites bilaterally)	Mean 6 years	*ccIMT* were not associated with change in cognitive test scores	Cardiovascular risk factors, sex, race, education level, site, central nervous system medication and age
Wendell, Stroke 2012, Baltimore Longitudinal Study of Aging	N 364, age 60–95 (mean 73.6, median 73)	IMT and carotid plaque	Up to 14 years (mean 6.7, median 7,0)	*IMT:* >2.5-fold increased risk of dementia [HR 2.55 (95% CI 1.32–4.96)] among individuals in the upper quintile of IMT. *Plaque*: Approximately 2.0-fold increased risk of dementia [HR 1.98 (95% CI 1.06–3.70)] among individuals with bilateral plaque.	Cardiovascular risk factors, ApoE
Arntzen, 2012, Cerebrovasc Dis. Tromsø Study	N 4,371	ccIMT and plaque	7 years	*Plaques*: Presence of plaques was significantly associated with change in cognitive test scores. The number of plaques and the total plaque area were associated with lower scores on the verbal memory test. *ccIMT*: No significant association was seen between ccIMT and cognitive test scores.	Sex, age, education, depression and vascular risk factors
Moon, Stroke 2015, Korean Longitudinal Study on Health and Aging	N 348, mean age 71.7	ccIMT and plaque	5 years follow up (2005/2006–20210/2011)	*Plaque*: not associated with cognitive decline after multiple adjustments. *ccIMT*: independent risk factor for the future progression of cognitive dysfunction [HR 1.251 (95% CI 1.006–1.555)].	Hypertension, Cumulative Illness Rating Scale-Geriatric, depression, education and sex.
Johnston, Ann Intern Med 2004, Cardiovascular Health Study	N 4,006 right-handed 65 years of age or older	ccIMT and Left Internal carotid artery stenosis (> or =75% narrowing of diameter)	Up to 5 years	*Left internal carotid stenosis:* Average decrease of more than 1 point annually in Modified Mini-Mental State Examination, OR, 6.7 (95% CI 2.4–18.1) compared with no stenosis. *ccIMT* left side was not associated with cognitive decline after adjustment.	Right-sided stenosis
Romero, Stroke 2009, Framingham study	N1,971 mean age, 58 years	ccIMT and carotid stenosis	Average of 4 years	*Internal carotid stenosis >50%:* associated with poorer performance on executive function ($\beta = -0.42 \pm$ SE 0.18; $P = 0.02$) *ccIMT:* not associated with cognitive function	Age, sex, time to MRI/NP, diabetes, smoking, hypertension treatment, systolic blood pressure, and cardiovascular disease
Sander, Geriatric Psychiatry 2009, INVADE study	N 2,693, mean age 67.7	ccIMT	2 years	*ccIMT:* Significant higher C-IMT in those who developed cognitive decline compared to those who did not. (0.87 vs. 0.78 mm; $p < 0.0001$).	Age, gender, prevalent ischemic heart disease, peripheral artery disease, hypertension, blood glucose, carotid plaques, education level, physical activity and the Geriatric Depression Scale

(Continued)

TABLE 1 | Continued

Author, journal, year study	Population size and age	Measurements	Observation time	Outcome	Adjusted for
Newman, JAGS 2005, Cardiovascular Health Study Cohort	N 3,602, median age 74 (65–97)	ccIMT, iIMT and carotid stenosis	Mean 5,4 years	*ccIMT and iIMT:* highest quartile associated with increased risk of dementia [HR1,6 (95% CI 1.1–2.2) vs. 1,5 (95%CI 1.1–2.0) respectively]. *Carotid stenosis:* (regardless degree of stenosis) not associated with dementia	Age, race, education, income, ApoE, and Modified Mini-Mental State Examination score at the time of the brain magnetic resonance scan.
Zhong, Atherosclerosis 2012, Beaver Dam Offspring Study	N 1,651, mean age 66.8	IMT and plaque	Mean 9.2 years (range: 3–13 years)	*IMT:* associated with incidence of cognitive impairment [HR: 1.09, (95% CI: 1.01–1.18)] for each 0.1 mm increase in IMT. *Plaque:* not associated with incident cognitive impairment or cognitive test performance 10 years later.	Age, sex, and education, cardiovascular risk factors and SF-36 mental health
Carcaillon, Alzheimer's Dementia 2015, Three-City Study	N 6,025, aged 65–86 years	IMT and plaques	Mean 5.4	*Plaque*: Only plaque were independently related to Vascular or mixed dementia, HR 1.92 [95% CI 1.13–3.22]	Age, sex, ApoE, education, cardiovascular risk factors, personal history of coronary heart disease and stroke
Gardener, 2017, Stroke, Northern Manhattan Study	N 826, mean age 70 years	ccIMT and plaques	Mean 5 years	*ccIMT*: Those with greater ccIMT exhibited worse cognitive performance. *Carotid plaque* not significantly with cognition at baseline or over time.	Age, education, race and vascular risk factors
Komulainen, Neuroepidemiology 2007	*N* 91 women, age 60–70	IMT	12 years	*IMT*: Increased IMT at baseline was an independent predictor for poorer cognitive performance	Age, education, depression, cardiovascular risk factors, cardiovascular disease, hormone replacement therapy, alcohol consumption and physical activity
Hsiu-Fen, Atherosclerosis 2020, Kaohsiung Atherosclerosis Longitudinal Study (KALS)	N 528, mean age 53.9 years	ccIMT and plaques	10 years	ccIMT in the top quartile of and plaques were associated with low 10-year cognitive test scores	Age, sex, educational status, diabetes, hypertension, hypercholesterolemia, and smoking status
Mathiesen, Neurology 2004, Tromsø study	*N* 189 subjects with stenosis was compared to 201 control subjects mean age was 67.7 years	Carotid stenosis (≥35%)	Cross-sectional	*Carotid stenosis:* associated with poorer neuropsychological performance	Age, sex, years of education, MRI lesions, current smoking, and cholesterol-lowering and antihypertensive treatment
Zhong, Atherosclerosis 2011, Beaver Dam	N 2,794, mean age 49 years (21-84)	IMT and plaque	Cross sectional	*IMT* and presence of *plaque* were associated with cognitive performance	Adjusting for age, sex and education
Ihle-Hansen, Journal of Alzheimer's Disease 2019, Cardiac Examination 1950 Study	N 3,413, mean age 63.9 years (63–65)	Carotid plaques	Cross sectional	*Carotid plaque burden* was in contrast to diameter [B *–0.17 (95% –0.32 –0.01)]* or area [B *–0.02 (95% –0.03 –0.01)]* of the thickest plaque not associated with cognitive performance	Sex, education, history of stroke and cardiovascular risk factors
Auperin, Stroke 1996, EVA Study	N 1,389, mean age 65.0 (59–71)	ccIMT and plaques	Cross sectional	*Plaques*: Poor cognitive functioning was associated with plaques. *ccIMT*: there was only a weak association in the subgroup of men with plaques. No association was found in women.	Age, educational level, depressive symptomatology, systolic blood pressure, body mass index, and tobacco and alcohol consumption

(Continued)

TABLE 1 | Continued

Author, journal, year study	Population size and age	Measurements	Observation time	Outcome	Adjusted for
Suemoto, Aterosclerosis 2015, ELSA-Brasil	N 8,208, Mean age 49.6	ccIMT	Cross-sectional study	*ccIMT:* associated with worse performance on the delayed word recall (DWRT) [β = −0.433, (95%CI = −0.724; −0.142)].	Age, sex, race, marital status, income, education, cardiovascular risk factors, self-reported heart failure, alcohol use, thyroid function and depression
Zeki Al Hazzouri, Stroke 2015. Coronary Artery Risk Development in Young Adults study	N 2,618, mean age 45.3 years	IMT	Cross sectional. UL at baseline, cognitive test 5 years later	*IMT*: negatively associated with processing speed [−0.06; (95% CI −0.09 to −0.02)]	Age, sex, race, education, glomerular filtration rate and cardiovascular risk factors
Del Brutto, J Stroke Cerebrovasc Dis. 2020, The Atahualpa project	N 561	IMT	cross-sectional	No association	Age and education
Xiang, J Clin Neurosci, 2013	N 2,015	IMT, plaques and stenosis	Cross sectional	*IMT:* OR 1.96 [95% CI 1.23–3.16] and *hyperdense plaque* OR 4.72 [95% CI 2.56–11.2] were associated with poor cognitive performance. Patients with severe (≥70%) *carotid artery stenosis* had a lower Mini-Mental State Examination score compared with the mild to modest (40–70%) carotid artery stenosis group. Cognitive performance differed between patients with left and right carotid artery stenosis.	Age, sex, education, cardiovascular risk factors

IMT, intima-media thickness; ccIMT, common carotid IMT; iIMT, internal carotid IMT; HR, hazard ratio; CI, confidence interval; OR, odds ratio; VD, vascular dementia; ApoE, Apolipoprotein E.

be excluded. A major limitation of the available evidence is the absence of a universal understanding of how to define and assess subclinical atherosclerosis. Measurement of increased IMT, which is thought to represent the first structural change in the atherosclerotic process, is affected by the exact timing of measurement (varies throughout a cardiac cycle), the location of measurement, and the software algorithm used. Carotid plaques which are more strongly associated with traditional cardiovascular risk factors (3) and proven to be a better predictor of a future cardiovascular event, are highly age-dependent, with a lower prevalence in younger populations (3). Plaque detection rate is also affected by the resolution of the ultrasound devices. As most of the studies were conducted in the '90s with older ultrasound devices, an underestimation of plaque occurrence is likely. Furthermore, the definition of plaque is not consistent between the different studies.

As with the assessment of atherosclerosis, evaluation and definition of cognitive impairment lack standardization. The use of different cognitive test batteries, and the definition of cognitive impairment across studies makes it difficult to draw clear conclusions. There are conflicting findings regarding which cognitive domains that are most vulnerable to atherosclerotic carotid disease. In general, vascular cognitive impairment is typically characterized by reduced speed of information processing, complex attention, and frontal-executive functioning (40). However, it seems likely that vascular disease contributes to the cascade of neurodegeneration (2), also affecting other cognitive domains.

FUTURE PERSPECTIVES

Despite associations between atherosclerosis and cognitive function seen in many populations, the amount of atherosclerosis required to pose a risk of cognitive impairment is unclear and is likely both age and person dependent.

Ultrasound of the carotid arteries is a cheap and non-invasive and technique to quantify atherosclerotic burden. Future studies should use standardized imaging protocols, standard definitions of atherosclerosis, and predefined outcome measures. Whether subclinical atherosclerosis poses different risk at different ages and whether different locations, and or intensifying risk factor management can contribute to halting further cognitive impairment needs further exploration.

CONCLUSION

Subclinical carotid artery atherosclerosis provides additional information about vascular risk factors burden in realtion to cognitive performance. More research is needed to address whether the assessment of carotid artery atherosclerosis could be used to identify people at increased risk of cognitive impairment and justify intensified risk factor management.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Emerging Role of Carotid MRI for Personalized Ischemic Stroke Risk Prediction in Patients With Carotid Artery Stenosis

*Kelly P. H. Nies[1,2], Luc J. M. Smits[3], Mohamed Kassem[1,2], Paul J. Nederkoorn[4], Robert J. van Oostenbrugge[1,5] and M. Eline Kooi[1,2]**

[1] Department of Radiology, CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, Netherlands, [2] Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, Netherlands, [3] Department of Epidemiology, Maastricht University, Maastricht, Netherlands, [4] Department of Neurology, Amsterdam University Medical Center, Amsterdam, Netherlands, [5] Department of Neurology, Maastricht University Medical Center, Maastricht, Netherlands

Rupture of a vulnerable carotid plaque is an important cause of ischemic stroke. Prediction models can support medical decision-making by estimating individual probabilities of future events, while magnetic resonance imaging (MRI) can provide detailed information on plaque vulnerability. In this review, prediction models for medium to long-term (>90 days) prediction of recurrent ischemic stroke among patients on best medical treatment for carotid stenosis are evaluated, and the emerging role of MRI of the carotid plaque for personalized ischemic stroke prediction is discussed. A systematic search identified two models; the European Carotid Surgery Trial (ECST) medical model, and the Symptomatic Carotid Atheroma Inflammation Lumen stenosis (SCAIL) score. We critically appraised these models by means of criteria derived from the CHARMS (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modeling Studies) and PROBAST (Prediction model Risk Of Bias ASsessment Tool). We found both models to be at high risk of bias. The ECST model, the most widely used model, was derived from data of large but relatively old trials (1980s and 1990s), not reflecting lower risks of ischemic stroke resulting from improvements in drug treatment (e.g., statins and anti-platelet therapy). The SCAIL model, based on the degree of stenosis and positron emission tomography/computed tomography (PET/CT)-based plaque inflammation, was derived and externally validated in limited samples. Clinical implementation of the SCAIL model can be challenging due to high costs and low accessibility of PET/CT. MRI is a more readily available, lower-cost modality that has been extensively validated to visualize all the hallmarks of plaque vulnerability. The MRI methods to identify the different plaque features are described. Intraplaque hemorrhage (IPH), a lipid-rich necrotic core (LRNC), and a thin or ruptured fibrous cap (TRFC) on MRI have shown to strongly predict stroke in meta-analyses. To improve personalized risk prediction, carotid plaque features should be included in prediction models. Prediction of stroke in patients with carotid stenosis needs modernization, and carotid MRI has potential in providing strong predictors for that goal.

Keywords: ICA stenosis, ischemic stroke, TIA, prediction, vulnerable plaque, MRI

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***Correspondence:**
M. Eline Kooi
eline.kooi@mumc.nl

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INTRODUCTION

Stroke is the second leading cause of death and the second largest contributor to global disability-adjusted life years (DALYs) since 2015 (1). Around 15% of all acute ischemic strokes are associated with extracranial carotid stenosis due to atherosclerosis (2). While currently a trend of a decreasing incidence of ischemic stroke is seen as a result of improved management of cardiovascular disease, projections made for European countries show that within 30 years the total number of ischemic strokes will increase by around 13% due to demographic changes (3, 4). The management of individuals at risk of stroke will need to be further improved to reduce the disease burden.

Current guidelines for patients with carotid artery stenosis distinguish them into two categories: patients to be treated only by best medical therapy, and patients eligible for additional surgical intervention by Carotid Endarterectomy (CEA), alternatively, Carotid Arterial Stenting (CAS).

Medical decisions are to a large degree dependable upon the degree of stenosis as well as other important risk factors such as clinical symptoms, age, and sex (5). In general, the benefit of performing CEA is seen in the group of recently symptomatic patients with a degree of stenosis of 70–99% and is considered in symptomatic male patients with 50–69% carotid stenosis (6). However, for symptomatic patients with 50–69% stenosis, the number needed to treat (NNT) to prevent one recurrent ischemic stroke is relatively high (NNT:15) (5, 7).

For patients with an asymptomatic 50–99% carotid stenosis, the risk of an ipsilateral ischemic stroke could now, due to improvements in best medical therapy, be lower than 1% per annum (8). Reported procedural risks of ischemic stroke and death when performing CEA measured after 2005, are 2.68% (95% CI, 2.12–3.31) and 1.50% (95% CI, 1.01–2.07) in symptomatic and asymptomatic patients, respectively (9). This can imply that, in some patients, revascularization causes more harm than benefit (10). In particular, in the group of symptomatic patients with 50–69% stenosis or asymptomatic patients, physicians may want to take additional risk factors (apart from the degree of stenosis) into consideration when making treatment decisions.

Results from the European Carotid Surgery Trial (ECST) have shown that almost half of symptomatic patients had a degree of stenosis <30% (11). Other factors must therefore be considered to improve risk stratification. Ischemic stroke caused by carotid artery disease is typically the result of embolization after carotid plaque rupture (12). An inflammatory response is triggered by the accumulation of oxidized low-density lipoprotein (LDL) in the arterial intima potentially leading to foam cell formation (13). Apoptosis and necrosis of the foam cells leads to the build-up of a lipid-rich necrotic core (LRNC). Plaque neovessels support the entry of more monocytes into the plaque, however, these vessels are fragile, which could cause intraplaque hemorrhage (IPH) (14). Also fissures or disruption of the fibrous cap (FC) may contribute to the development of IPH (15). The FC is separating the lumen from the thrombogenic content of the plaque. Therefore a thin or ruptured fibrous cap (TRFC) contributes, together with IPH and a LRNC, to an increase in probability of plaque rupture (13). Plaque rupture releases the contents of the plaque which can lead to thrombus formation, embolization, downstream arterial occlusion, and subsequent stroke (16).

Non-invasive modalities to visualize the carotid plaque are ultrasonography, computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI) (17–20). Ultrasonography and CT are unable to reliably differentiate the LRNC from IPH. PET provides information on inflammation in the plaque, but not on plaque composition. MRI is able to distinguish clearly between different soft tissues and is the only modality that enables the assessment of the presence of IPH, one of the most important vulnerable plaque features (12). MRI can facilitate the measurement of all the hallmarks of plaque vulnerability by using multiple different high spatial resolution contrast weightings and it is extensively validated to identify plaque burden, IPH, ulcerations, LRNC, and TRFC (12, 21).

Risk prediction models can help clinicians in weighing risks and benefits of treatment decisions. A risk prediction model is a mathematical equation that uses patient risk factor information as an input to estimate the probability of the patient having the health outcome of interest, now or in the future. The most widely used model for calculating the risk of ischemic stroke in symptomatic patients with carotid stenosis is the ECST medical score, which includes, besides the severity of stenosis, several additional risk factors such as hypertension, diabetes, and ulceration of the plaque (22). Besides the ECST medical model, recently another ischemic stroke risk prediction model has been developed and validated in symptomatic patients with carotid stenosis, the SCAIL-score, that is based on degree of stenosis and plaque inflammation as quantified with ^{18}F-FDG PET-CT (23). However, other than ulceration and inflammation, features of plaque vulnerability have not been included in any prediction model for the risk of ischemic stroke in patients with carotid stenosis to date. Although some characteristics have in the meantime shown to be of high prognostic value for the occurrence of new or recurrent ischemic stroke with an even 10-fold increase in ischemic stroke in symptomatic patients with IPH on carotid MRI (24).

Since the development of the ECST medical score, novel MRI techniques to visualize the different components of the atherosclerotic carotid plaque have become available, and could improve prediction of individual ischemic stroke risk. In this review, we will systematically appraise the existing prognostic prediction models for the medium to long-term (≥90 days) risk of ischemic stroke in patients with carotid stenosis. In addition, we will discuss the potential additional predictive value of several MRI-based plaque features.

OVERVIEW OF PREDICTION MODELS

We performed a literature search in Pubmed to identify prediction models for medium to long-term (≥90 days) ischemic stroke risk in patients with medically managed carotid stenosis. The following search string was used in January 2021 to identify

publications of interest; [("Risk score*" or "Prediction model*" or "predictive model*" or "prognostic model*")] AND (Carotid) AND (Stroke* OR Transient Ischemic Attack* OR TIA*). In total 265 results were evaluated and exclusion was based on: (1) not developed and/or validated in patients with carotid stenosis, (2) non-ischemic stroke as outcome, and (3) short term risk prediction (<90 days). This resulted in 11 articles of interest and in total two different predictive models both for patients with symptomatic carotid stenosis, while no models for asymptomatic patients could be identified within our search criteria. Additional publications on these predictive models were tracked using the article's list of references and articles citing the publication of interest. The final selection of articles was critically appraised by means of a data extraction and methodological assessment form based on the CHARMS (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modeling Studies) and PROBAST (Prediction model Risk Of Bias ASsessment Tool) criteria (25, 26). The different models were assessed for their general features, development, validation, performance, and feasibility in clinical practice by two assessors (KN and LS). Conflicts were resolved through joint discussion.

Based on CHARMS and PROBAST criteria, the ECST medical model, and symptomatic carotid atheroma inflammation lumen stenosis (SCAIL)-score both presented a high risk of bias. The derivation of the ECST medical model was of good quality, however clinical data based on trials from the 80s and 90s were used that no longer represent current ischemic stroke risks on best medical treatment and overall performance statistics were lacking. The SCAIL model has a high risk of bias due to a.o. inadequate reporting of derivation methods and insufficient derivation and validation sample size, especially when correcting for a range of clinical parameters. The findings are summarized in **Table 1**, and more elaborately discussed below.

ECST Medical Model

The ECST medical model was first established in 1999 by Rothwell et al. on the basis of data of symptomatic patients with 0–69% carotid stenosis in the ECST (6). The degree of stenosis was determined with ECST criteria, and the following predictors were selected: cerebral vs. ocular events, plaque surface irregularity, any events within the past 2 months, and carotid stenosis (per 10% increase). During the development of the first version of the model, the study was split in two groups; one of patients with 0–69% carotid stenosis used for derivation, and one of patients with ≥70% stenosis used for external validation. In order to validate the study in a population from different hospitals, the data was later transformed to match the ECST to the NASCET method for determining the degree of stenosis (27). Where the ECST method uses the estimated position of the vessel wall at the site of the stenosis in the denominator, the NASCET method uses the distal normal lumen diameter, which results in different degrees of stenosis (28). With the newly determined degree of NASCET stenosis, the model was re-derived in patients with 50–99% NASCET stenosis. As a result other predictors were selected in this second version of the model [predictors: stenosis (per 10%), near occlusion, male sex, age (per 10 years), time since last event (per 7 days), presenting event (ocular, single TIA, multiple TIAs, minor ischemic stroke, major ischemic stroke), diabetes, previous myocardial infarction, peripheral vascular disease, treated hypertension, irregular/ulcerated plaque]. The resulting number of selected variables was much larger than in the 1999 version. Assuming that the same candidate predictors were used as in the original development in 1999, the model would have in total 17 candidate predictors and two additional degrees of freedom due to categorization. Considering there were 227 events in the dataset, the events per variable (EPV) was approximately 12, above the generally suggested minimum of 10 EPV (29).

The ECST data on which the model was based, were gathered during 1981–1991 with follow-up extending until 1998. Since then and more specifically from the early 2000s onwards, drug treatment has changed rigorously, with a >60% increase in statin use within a time period of 12 years and an increase in anti-platelet use (30). The use of statins causes a relative risk reduction of 21% for stroke, while anti-platelet is associated with a 12% risk reduction of serious vascular events (31). Because of this, the ECST model may over-estimate the risk of ischemic stroke. The authors also didn't report the full model, since the intercept was not given.

Internal validation was not performed or reported on. External validation was performed using data from the North American Symptomatic Carotid Endarterectomy Trail (NASCET). Calibration appeared good. A calibration plot showed agreement between predicted and observed medical risk. C-statistic, sensitivity, and specificity, were not reported. Derivation and external validation was reported in the same publication. As the authors note themselves, models often perform less effective in an independent sample when they are validated by researchers other than those who constructed the model (22).

The ECST-score has been simplified into color-coded risk tables to increase usability and counteract overfitting with the disadvantage that this results in a loss of accuracy to some extent, since hazard ratios (HRs) calculated at two decimal level are rounded to whole numbers. However, this way of presentation is understandable in the context of the facilities at hand at the time the model was developed. The prediction model is also available online (www.stroke.ox.ac.uk). Explanatory texts provided in a link on the webpage are not accessible to everyone visiting the site, which hinders careful consideration of the model for clinicians using this webpage. Overall, even with good derivation methods, the model has a high risk of bias according to PROBAST principles, mainly due to incomplete reporting and development in an outdated dataset, and not due to methods of development.

Symptomatic Carotid Atheroma Inflammation Lumen Stenosis

A recently published model for the estimation of the risk of recurrent ischemic stroke included 18F-flueorodeoxyglucose (18F-FDG) standardized uptake values

TABLE 1 | Overview and assessment of prediction models of recurrent acute ischemic stroke in patients with carotid stenosis.

	ECST medical model (6, 22)	**SCAIL (23)**
Model characteristics	• 11 predictors • Target group: patients with TIA/ischemic stroke and 50–99% stenosis • Prediction horizon: 5 years • Outcome: ipsilateral ischemic stroke • Method: Cox proportional hazards	• 2 predictors (or 9 predictors by correction for clinical parameters) • Target group: patients with TIA/ minor ischemic stroke and 50–99% stenosis • Prediction horizon: 90 days • Outcome: ipsilateral ischemic stroke • Method: Cox proportional hazards
Development	• Derivation population: symptomatic patients (ischemic stroke/TIA) with 50–99% stenosis + EPV ∼ 12 - Handling of missing values not reported - Derivation data no longer reflecting ischemic stroke risk with current best medical treatment ± Simplified risk scores	• Derivation population: symptomatic patients (minor ischemic stroke/TIA) with ≥50% stenosis - EPV < 2 (*n* of candidate predictors unclear) - No censoring of patients with CEA ± Simplified risk scores
Validation	• Validation population: Symptomatic patients (TIA or ischemic stroke) with 50–99% stenosis - No internal validation - Validation by same authors in same paper	• Validation population: Symptomatic patients (minor ischemic stroke/TIA) with ≥50% stenosis - Low number of events - 9-factor model was used - Validation by same authors in same paper
Performance	+ Good calibration - No C-statistic given - No sensitivity or specificity reported	+ High C-statistic - Unclear what the performance of the 2-predictor model is
Feasibility	+ Web-based calculator available - No disclaimer and no access to explanatory texts on website	+ Only 2 predictors (without correction for clinical parameters) - Low face validity - PET/CT is expensive and patients are exposed to ionizing radiation
Overall risk of bias	High risk of bias - Data collection prior to current best medical treatment - No clear performance indicators	High risk of bias - Very low EPV - Validation performed with low number of events - Long-term prognostic power for patients with carotid stenosis not yet clear

on positron emission tomography-computed tomography (PET-CT) as a parameter for plaque inflammation. This model, i.e., SCAIL categorizes 18F-FDG uptake into four different SUVmax ranges with increasing risk points. The basic version of this model included only two predictors; 18F-FDG uptake and the degree of NASCET stenosis categorized in the ranges <50, 50–69, and >70%. Inclusion criteria of the derivation cohort included a carotid stenosis of >50%, however some patients originally classified as moderate stenosis were re-measured and re-classified with a stenosis between 30 and 49% and remained included. In total 109 patients with previous non-severe ischemic stroke or TIA in the previous 30 days were used for derivation. While 37 recurrent ischemic strokes occurred in this dataset, only eight were after the PET-CT examination, therefore only these events should be included. Notably, after deriving an alternative model using only those eight events, the authors corrected for several clinical risk factors including; age, sex, hypertension, diabetes mellitus, smoking, antiplatelet, and statin treatment in the model, thereby considerably decreasing the study's already low number of EPV, and increasing the risk of overfitting. This effectively changed the two-predictor model to a nine-predictor model.

Validation was performed in a cohort from two centers with in total 87 patients with a previous TIA or minor ischemic strokes with a maximum time period between index event and inclusion of 14 days (no mean presented). However, carotid revascularization was performed in 44% and it is not clear if these patients were censored at the time of surgery. In the validation study it is also not specified if PET-CT imaging was performed before or after recurrent ischemic stroke. Based on the model that included only the eight events occurring after PET-CT imaging, model performance, as expressed by the C-statistic was 0.82 (95% CI, 0.66–0.97) in the derivation cohort.

External validation resulted in a performance of 0.77 (95% CI, 0.67–0.87) at 90 days. Pooling of the derivation and validation studies was used to determine the sensitivity and specificity of the model. The scores were categorized into low (0–1), medium (2–3), and high (4–5) risk of recurrent ischemic stroke. Only 9% of patients could be categorized as low risk, and those with medium risk still had 18% risk of recurrent ischemic stroke (time frame unreported). Dependent on the score threshold of >3 or >4, sensitivity was 81 and 38% and specificity was 54 and 90%, respectively (23). Overall, the model was appraised at high risk of bias, mainly due to low EPV and the small validation cohort.

Overall Considerations of Current Models

Both models were assessed at high risk of bias according to PROBAST guidelines, hindering justification of their use in medical practice. The ECST medical model appears to have good calibration in the population used for validation. Limitations are

that proof of sensitivity and specificity and overall predictive power in conventionally used C-statistics and the receiver operating characteristic (ROC) was not provided, therefore the discriminative ability is not clear. A strength of this study is a good EPV made possible by the large scale of the study. However, ischemic stroke risks have decreased significantly since data collection making the model outdated for use in current medical practice.

The SCAIL model demonstrates the potential of using plaque vulnerability features in a risk model. With only two predictors, its predictive capacity is remarkable. However, the model is prone to overfitting because of the low EPV. In addition, the model performance is only reported combined with a correction for a large range of clinical risk factors, which actually transforms the model into a multi-factor model.

If future larger validation studies provide proof of performance without adjustment by other clinical parameters, the model faces other issues in terms of clinical implementation, because of cost-effectiveness and availability of the imaging modality. PET-CT is costly with a factor two higher costs compared to MRI and there are less PET-CT scanners available compared to MRI (32). Besides this, there are insufficient events in the derivation dataset to correct for clinical risk factors, therefore the 2-predictor model should be used to minimize the effect of overfitting. Consequently, the model may lack validity since the clinicians could hesitate using a model with only two parameters while other parameters have been shown to be predictive of recurrent stroke as well. The model also categorizes the majority of patients in a median risk profile where considerable risk of recurrent ischemic stroke still occurs. Consequently, there is a low probability of the model being implemented in clinical practice.

MRI may provide a more accessible and cost-effective method to measure vulnerable plaque features for inclusion in risk stratification. There is a need for a modernized prediction model of current risk of ischemic stroke. MRI-measured vulnerable plaque features have shown value as independent predictors and their inclusion in prediction models could provide improved identification of individuals categorized at high risk of ischemic stroke.

CAROTID MR IMAGING

Several imaging biomarkers have been suggested to provide insight into plaque vulnerability (18, 33). A vulnerable plaque is defined as a plaque that is prone to rupture. It is characterized by the presence of a large LRNC that is separated from the lumen by a TRFC. Upon rupture the blood gets in contact with the thrombogenic plaque content, which can cause thrombosis, embolization, and consequently, ischemic stroke (34). MRI is established as the most suited imaging technique to evaluate plaque composition, with its superior ability to differentiate between soft tissues (**Figure 1**) (35). Expert recommendations on carotid vessel wall MRI protocols have been published (18). For high resolution MR imaging, dedicated carotid radiofrequency coils are required, although IPH can be detected using a standard multi-channel neurovascular coil (18, 36). First, MRI methods to identify the different plaque features will be described. Next, the predictive value of the different plaque features were gathered from two large meta-analyses and will be discussed below (**Figure 2**).

Degree of Stenosis

Generally, moderate stenosis is categorized as 50–69% stenosis, while the degree of stenosis is considered to be severe for 70% and above (38). The best non-invasive method for measuring the degrees of stenosis 70–90% is contrast-enhanced (CE)-MRA with a sensitivity and specificity of 0.94 (95% CI 0.88–0.97) and 0.93 (95% CI 0.89–0.96), respectively (**Figure 1**). Compared to the sensitivity and specificity of ultrasound and CTA, MRI performs significantly better in the different stenosis categories (38). For 50–69% of stenosis, MRI sensitivity is lower compared to higher degrees of stenosis, i.e., 0.77 (95% CI 0.59–0.89), while specificity remains very high (38). Time of flight (TOF)-MRA is not recommended because turbulent flow of recirculating blood can lead to underestimation of the degree of stenosis (39).

Plaque Volume

Plaque volume can be determined by drawing manual or (semi-)automated contours delineating the outer- and inner-vessel wall on T_1-weighted black-blood images. Pre-pulses are used to suppress the signal of blood to prevent plaque-mimicking artifacts (35). To account for changes in lumen size and wall thickness, the normalized wall index (NWI) is used as a reliable and reproducible method for calculating the percentage of wall area in total vessel area (40).

In response to an increase in atherosclerotic plaque volume, the artery may enlarge to allow enough luminal area for blood flow, which means that plaques could already be present without causing stenosis (41). An increase in plaque volume is also associated with a decrease of FC thickness and an increase of lipid proportion of the total plaque, further indicating its involvement in plaque vulnerability (41). Plaque progression is shown to be an independent predictor of recurrent ischemic stroke. Annual progression of carotid plaque volume in symptomatic patients (30–69% stenosis) was associated with an increased chance of recurrent ischemic stroke (HR: 1.19 per 10 mm^3; 95% CI 1.03–1.37) (42). However, since this was determined in a relatively small study (63 patients, nine ischemic strokes), the need for larger trials to further assess the predictive value of plaque progression is needed.

Intraplaque Hemorrhage

MRI is the only method that allows to accurately assess IPH presence in the carotid plaque. IPH can be recognized as a hyperintense signal in the bulk of a plaque in a hyper T1-weighted MR image, because of the methemoglobin shortening the T_1-relaxation time (43). Magnetization-prepared rapid acquisition gradient (MP-RAGE), also referred to as inversion recovery turbo field echo (IR-TFE), is the most common sequence to visualize IPH presence with a high specificity (97%) and sensitivity (80%) compared to histology (44). Magnetization-prepared rapid

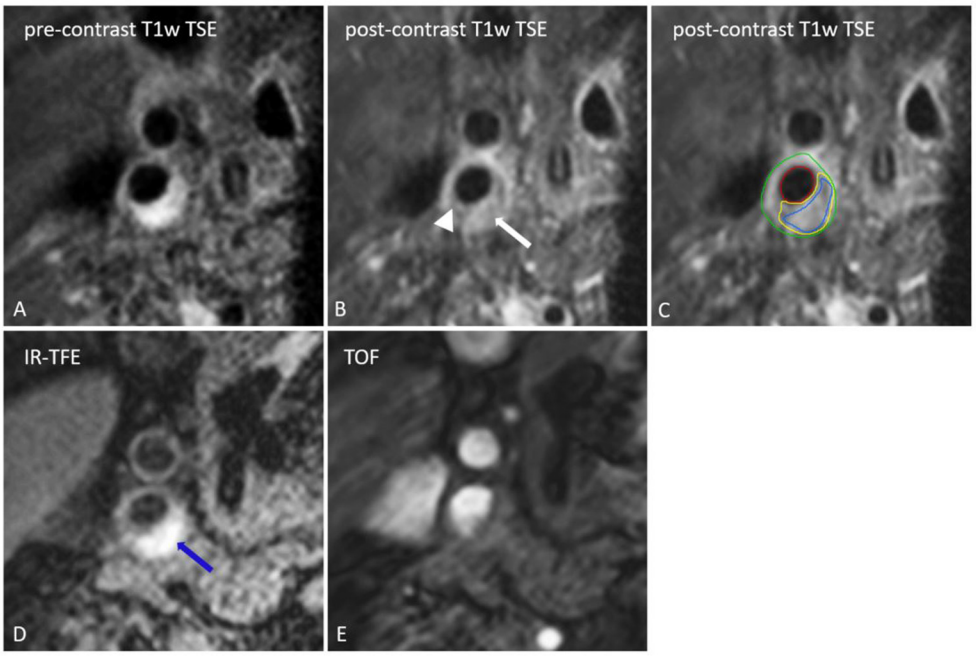

FIGURE 1 | Transversal MR images of the right internal carotid artery. The black blood pre-contrast image **(A)** is used to draw the contours of the lumen and outer vessel wall. The lipid-rich necrotic core shows no contrast-enhancement on the post-contrast black-blood T1w quadruple inversion recovery (QIR) turbo spin echo (TSE) image **(B)** and includes the entire area of hemorrhage (IPH) [IPH: blue, lipid-rich necrotic core: yellow, lumen: red, outer vessel wall: green on **(C)**]. IPH [blue arrow on **(D)**] appears as a bright signal on the inversion recovery turbo field echo images (IR-TFE; **D**). A thin or ruptured fibrous cap (TRFC) can be identified by the interruption of juxtaluminal signal enhancement on the post-contrast T1w image (arrow head). With a contra-indication for contrast injection the T2w image or time of flight (TOF) image **(E)** can be used for TRFC assessment.

acquisition gradient is able to suppress plaque components other than IPH with inversion-recovery preparation, allowing a clear differentiation between IPH, other plaque components and the lumen (45). Alternatively, 3D Simultaneous Non-contrast Angiography and IPH (3D-SNAP) has been developed to image stenosis and IPH using a single sequence (45). Other new developments include Multicontrast ATherosclerosis Characterization (MATCH), which simultaneously acquires hyper T1w, gray blood, and T2w images to visualize IPH, LRNC, and calcifications with a single 5 min sequence (46). Further clinical validation of these new sequences is needed.

IPH contributes to plaque vulnerability by causing an enlargement of the necrotic core size (47). IPH is out of the available plaque MRI predictors the most extensively validated and was shown to be a strong and independent predictor for ischemic stroke (24). Schindler et al. performed a meta-analysis with data pooled from seven cohort studies including 696 patients and reported an unadjusted ipsilateral ischemic stroke HR of 10.2 (95% confidence interval [CI]: 4.6–22.5) in symptomatic patients with vs. without IPH, and a HR of 7.9 (95% CI: 1.3–47.6) in asymptomatic patients. After adjusting for confounders, IPH remained significant and was identified as a strong independent ischemic stroke predictor (24). They also showed that the HR for severe degree of stenosis of 70–99% vs. <50% stenosis in symptomatic individuals was lower compared to IPH, i.e., 3.3 (95% CI: 1.4–7.8) (**Figure 2**).

At present, approximately 30% of ischemic stroke are categorized as cryptogenic because of a degree of stenosis <50%, however in some of these patients plaque rupture may also be the underlying cause of stroke, since Schindler et al. have demonstrated that in patients with <50% stenosis and IPH, ischemic stroke risk is increased from 0.7 to 9.0% with a mean follow-up of 18 months (24, 48, 49).

Lipid-Rich Necrotic Core and Thin or Ruptured Fibrous Cap

Both the LRNC and the overlying FC can be visualized by comparing pre- and post-contrast T_1 weighted black blood images, where the LRNC is the region within the bulk of the plaque that shows no or hardly no contrast enhancement, while a TRFC is identified as an interruption or absence of contrast enhancement in the juxtaluminal tissue overlying the LRNC (35). In case of a contraindication for contrast injection, a hypointensive signal on T_2 weighted images is indicative for a LRNC, but it is sub-optimal to detect the LRNC because of an approximately two-fold lower signal-to-noise ratio (18).

Advanced plaques are characterized by a large LRNC separated from the lumen by a FC (12). A TRFC and presence of a LRNC increase the risk of ischemic cerebrovascular events by almost 6- and 3-fold, respectively, as reported by Gupta et al. from a clustered group of symptomatic and asymptomatic

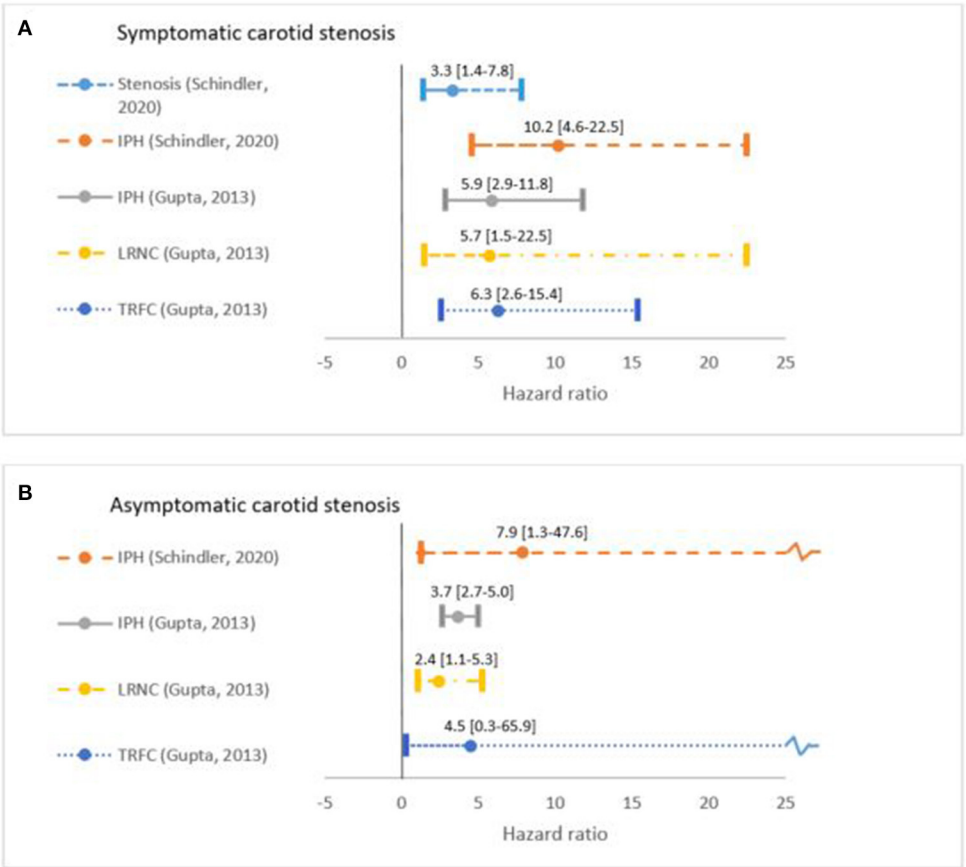

FIGURE 2 | Overview of predictive value in Hazard Ratio [95% confidence interval] of plaque vulnerable features as reported in two meta-analyses. Schindler et al. (24) included 560 symptomatic and 136 asymptomatic participants with 66 ipsilateral ischemic strokes gathered from seven studies. The meta-analysis by Gupta et al. (37) consists of in total 779 patients (ratio symptomatic and asymptomatic unclear) with at least 169 ipsilateral ischemic strokes and TIAs (exact number unclear). Plaque volume is not included in this overview due to the lack of reported predictive value in meta-analyses. Patients are grouped into **(A)** symptomatic and **(B)** asymptomatic when data was available and hazard ratios were reported for the degree of stenosis, intraplaque hemorrhage (IPH), thin or ruptured fibrous cap (TRFC), and lipid-rich necrotic core (LRNC). Hazard ratios reported in Gupta et al. (37) include both ischemic stroke and TIA, while Schindler provided ischemic stroke hazard ratios.

patients (**Figure 2**) (37, 50). A TRFC is also strongly associated with the presence of IPH (51).

DISCUSSION

A systematic search of prediction models for medium to long term risk of ischemic stroke resulted in the identification of two models for symptomatic carotid stenosis, and no models for asymptomatic carotid stenosis. Current prediction models, and in particular the ECST medical model, have provided clinicians with guidance in the selection of treatment based on the patients' risk of ischemic stroke. In clinical practice, its use accounts especially for borderline cases. We have appraised the prediction models according to CHARMS and PROBAST principles and were unable to find all crucial information on aspects of development, validation, and performance. While for both models claims are made of good performance after external validation, it should be noted that while the ECST medical model was validated in a good independent dataset and calibration appeared good, performance in terms of discrimination was not reported. SCAIL did report performance measurements, however the validation dataset was too small for accurate assessment. SCAIL has included more parameters than advised according to guidelines, resulting in increased chance of overfitting and potential loss of usability in different datasets other than the derivation data. Categorization of data and/or simplification of the model into risk scores was performed in both models to increase ease of use in clinical practice, however this decreases the accuracy of a model and when the model is presented in a web-based or an app-based approach simplification would not be needed. This was done for the ECST model with a web-based approach (www.stroke.ox.ac.uk) that has the potential for convenient implementation in clinical workflow.

The ECST-model provides good face validity and is therefore recommended in some national guidelines (52). However, this model is based on outdated patient data since treatment regime has changed dramatically in the last decades. The SCAIL model provides an interesting approach with only two parameters, when not correcting for other clinical risk factors, however

development was performed in a very small sample size and due to the requirement of an additional of PET-CT examination it may struggle in face validity and feasibility in clinical practice. This model does show the great potential for using carotid plaque imaging for risk stratification models.

The use of carotid imaging of the plaque vulnerability in prediction models has not been fully exploited. Magnetic resonance imaging is currently the most promising imaging modality which can visualize the hallmarks of plaque vulnerability. For both symptomatic and asymptomatic patients, vulnerable plaque features on MRI showed strong associations with an increased risk of ischemic stroke. With a 10-fold increase in risk of ischemic stroke when IPH was present, or a HR close to six for the TRFC, the inclusion of these factors in a newly derived prediction model is expected to present greater predictive power. For any new prediction model, it would be important to use recent patient data, preferably collected after 2010 since best medical treatment was then last subject to vigorous changes by increased statin and anti-platelet use.

Ultimately, cost-effectiveness will play an important role in the adoption of new models in clinical practice. Feasibility of inclusion of certain plaque features in clinical practice will need to be reviewed by consultation of experts, analysis of costs associated with extra measurements, and the impact on the burden of disease.

In conclusion, current ischemic stroke risk prediction models for patients with symptomatic carotid artery disease have a high risk of bias, whereas there are currently no models to estimate the risk of ischemic stroke in asymptomatic carotid stenosis. There is an urgent medical need for modernized predictive models based on data from recent trials with the inclusion of newly identified carotid vessel wall imaging-based predictive factors. Carotid MRI biomarkers of plaque vulnerability, especially IPH, are most promising for this purpose.

AUTHOR CONTRIBUTIONS

KN, LS, and MKo contributed to the design of the study. KN and LS performed the analysis. KN wrote the first draft of the manuscript. MKa wrote sections of the manuscript. PN and RO provided feedback on intellectual content. All authors contributed to manuscript revision, read, and approved the submitted version.

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Carotid Atheroinflammation Is Associated With Cerebral Small Vessel Disease Severity

Nicholas R. Evans[1,2], Jason M. Tarkin[3], Jessica Walsh[2], Mohammed M. Chowdhury[4], Andrew J. Patterson[5], Martin J. Graves[5], James H. F. Rudd[3] and Elizabeth A. Warburton[2]*

[1] Department of Medicine, University of Cambridge, Cambridge, United Kingdom, [2] Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom, [3] Division of Cardiovascular Medicine, University of Cambridge, Cambridge, United Kingdom, [4] Department of Surgery, University of Cambridge, Cambridge, United Kingdom, [5] Department of Radiology, University of Cambridge, Cambridge, United Kingdom

Background: Atherosclerosis is a systemic inflammatory disease, with common inflammatory processes implicated in both atheroma vulnerability and blood-brain barrier disruption. This prospective multimodal imaging study aimed to measure directly the association between systemic atheroma inflammation ("atheroinflammation") and downstream chronic cerebral small vessel disease severity.

Methods: Twenty-six individuals with ischemic stroke with ipsilateral carotid artery stenosis of ≥50% underwent ^{18}fluoride-fluorodeoxyglucose-positron emission tomography within 2 weeks of stroke. Small vessel disease severity and white matter hyperintensity volume were assessed using 3-tesla magnetic resonance imaging also within 2 weeks of stroke.

Results: Fluorodeoxyglucose uptake was independently associated with more severe small vessel disease (odds ratio 6.18, 95% confidence interval 2.1–18.2, $P < 0.01$ for the non-culprit carotid artery) and larger white matter hyperintensity volumes (coefficient = 14.33 mL, $P < 0.01$ for the non-culprit carotid artery).

Conclusion: These proof-of-concept results have important implications for our understanding of the neurovascular interface and potential therapeutic exploitation in the management of systemic atherosclerosis, particularly non-stenotic disease previously considered asymptomatic, in order to reduce the burden of chronic cerebrovascular disease.

Keywords: atherosclerosis, blood-brain barrier, carotid artery, cerebrovascular disease/stroke, leukoaraiosis, carotid-cerebrovascular interface

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****Correspondence:***
Nicholas R. Evans
ne214@cam.ac.uk

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INTRODUCTION

Atherosclerosis is a systemic inflammatory disease that may cause stroke through destabilization of atherosclerotic plaques and consequent thromboemboli (1). However, it is increasingly recognized that the effects of atherosclerosis extend beyond a single "vulnerable plaque," and instead involve the overall burden from the systemic nature of atherosclerosis on the individual "vulnerable patient" (2).

This is particularly true in the neurovascular setting, where the brain represents an end-organ highly sensitive to insult from the general metabolic environment. The presence of vascular risk factors may exacerbate inflammation within atheroma (atheroinflammation) (3–6), disrupt blood-brain barrier (BBB) integrity (7), and promote neuroinflammation in individuals without stroke, potentially priming the brain for injury (8). Furthermore, systemic inflammation itself may also promote an increase in BBB permeability (9). Consequently, chronic pro-inflammatory states, such as that seen in atherosclerosis, may have a role in compromising BBB integrity. Such BBB dysfunction is implicated in the development of chronic cerebral small vessel disease (SVD) (10); focal lacunar infarcts or subcortical diffuse white matter change (leukoaraiosis) characterized by neuronal loss, demyelination, and gliosis (10). SVD is a major risk factor for both stroke and dementia (11), and is independently associated with poorer recovery after stroke (12) and stroke recurrence (13).

The direct relationship between carotid atherosclerosis and SVD remains unclear. Although leukoaraiosis is positively associated with both carotid intima-media thickness (IMT) and presence of atheroma, negative associations have been reported with the degree of luminal stenosis (14). These inconsistent findings may be due to variability in the extent of inflammation within atheroma, which is independent of stenosis severity (15). Inflammation within atheroma can be measured *in vivo* by positron emission tomography (PET) using ^{18}fluoride-fluorodeoxyglucose (FDG), a radionuclide analog of glucose (16). FDG uptake is increased in symptomatic carotid atheroma (15), and correlates with histological macrophage density but not plaque size (17).

This study examines the direct association between carotid artery atheroinflammation, measured by FDG-PET/CT, and the severity of cerebral SVD. We hypothesized that increased carotid artery FDG uptake would be associated with more severe leukoaraiosis.

MATERIALS AND METHODS

Participants

The Imaging Carotid Atherosclerosis in the Recovery and Understanding of Stroke Severity (ICARUSS) Study prospectively recruited individuals presenting with an ischemic stroke within the previous seven days due to ipsilateral common or internal carotid artery stenosis of ≥50% measured on computed tomography angiography (CTA) [using the North American Symptomatic Carotid Endarterectomy Trial method (18)] at Addenbrooke's Hospital, Cambridge, United Kingdom. Cardiovascular risk factors and stroke severity were recorded at baseline. Only individuals with evidence of brain infarction on diffusion-weighted imaging (DWI) were enrolled. The minimum age for study eligibility was 40 years. Individuals with atrial fibrillation were excluded.

Anonymized imaging reads were performed for the full study cohort after study completion, with readers (NRE, JMT, JW, MMC) blinded to the clinical data. PET and MRI analyses were analyzed independently and matched with clinical information and each other only after analysis of the full cohort was complete.

All participants provided written informed consent in accordance with the Declaration of Helsinki. The study protocol was approved by a national research ethics committee (Nottingham One Research Ethics Committee, 14/EM/0128).

PET/CT Protocol

FDG-PET/CT (Discovery 690 GE Healthcare, Little Chalfont, UK) scans were performed with 64-slice computed tomography within 14 days of ischemic stroke. Participants fasted for 6 h prior to injection. Participants were injected intravenously with a target of 250 MBq of FDG (sourced from Erigal Ltd, Keele, UK), followed by a 90-min uptake time, as per previous work (19). A silence protocol (minimal vocalization, only small sips of water permitted) was adopted during this uptake period to reduce physiological tracer uptake in neighboring structures. In participants without diabetes, blood glucose concentrations were confirmed as ≥7.0 mmol/L prior to tracer injection. Participants with diabetes mellitus were instructed to take their usual oral antidiabetic medications as normal, but insulin was omitted within the 4 h prior to imaging.

PET imaging datasets were analyzed using OsiriX (version 5.7.1, OsiriX Imaging Software, Geneva, Switzerland). Co-registered PET and CT images were resampled to 3 mm slice thickness and regions of interest (ROIs) drawn manually on fused PET/CT images along the common carotid and internal carotid artery to encompass the region 0.9 cm proximal and 3 cm distal to the carotid bifurcation as per established methodology (15). ROIs were then transferred onto co-registered PET to produce standardized uptake values of the maximum uptake within the ROI (SUV_{max}). To compensate for blood pooling, the tissue SUV was adjusted for venous SUV – the average of mid-luminal ROIs in the jugular vein over five contiguous 3 mm slices without evidence of spill-over from neighboring structures – to give the maximum target-to-background ratio (TBR_{max}); a measure of radiotracer uptake validated for use in vascular PET imaging (17).

TBR_{max} for culprit and non-culprit carotid arteries were compared for the most diseased segment (MDS) and whole vessel (WV). The MDS considers the most diseased 9 mm of the artery (based on tracer uptake) and represents the mean of the TBR_{max} of the ROIs in three contiguous axial slices where the central ROI constitutes the point of highest tracer uptake in the artery as per previous methodology (15). The WV is the median of tracer uptake across all 14 axial slices of the artery. An experienced reader (MMC) performed reproducibility and quality assurance by repeating ROIs in 20% of the FDG-PET/CTs.

MRI Protocol

Participants had brain imaging performed within 2 weeks of stroke using a 3-tesla whole body magnetic resonance imaging (MRI) scanner (MR750, GE Healthcare, Waukesha, WI) with a 12-channel head, neck, and spine coil with a brachial plexus attachment. Sequences included T1, T2, DWI, fluid-attenuated inversion recovery (FLAIR), and gradient echo sequences.

Assessment of Cerebral Small Vessel Disease

The extent of WMH was measured both semi-quantitatively and quantitatively. Semi-quantitative measures were taken from the FLAIR sequence using the scoring system proposed by Fazekas et al. (20) and later modified by Pantoni et al. (21). The Fazekas score has been dichotomized previously (22), and in this study we dichotomized global (whole brain) periventricular and deep white matter hyperintensities according to no/mild or moderate/severe leukoaraiosis [using the visual scale described by Pantoni et al. (21)] given that the majority of our cohort showed some small vessel disease.

Quantitative measurement of WMHs was performed by measuring WMHs in the hemisphere contralateral to the acute stroke and multiplying by two. Measurement was conducted using semi-automatic ROI marking using Jim Imaging Software (version 7.0, Xinapse Systems Ltd., Essex, United Kingdom).

MRI interpretation was performed by two experienced readers for all scans (NRE and JW). Intra-class correlation coefficients for inter-rater reliability were calculated subsequently.

Inflammatory Biomarker

Venous blood was drawn at the time of FDG-PET/CT for high-sensitivity C-reactive protein (hsCRP) as a marker of inflammation.

Statistical Analysis

Continuous data was tested for normality using the Shapiro-Wilk method. Parametric data was reported as mean ± standard deviation (SD) and non-parametric data reported as median and inter-quartile range (IQR). Unpaired groups were compared using *t*-testing (parametric readings) or Wilcoxon rank sum testing (non-parametric readings). Comparison between culprit and contralateral non-culprit arteries in the same individual used equivalent paired testing. Associations were tested using two-tailed Spearman's rho correlation (non-parametric or ordinal data) or Pearson's correlation coefficient (parametric data).

Multivariable analysis (logistic regression and linear regression) initially included all variables considered in univariable analysis (age, sex, smoking status, diabetes mellitus, hypertension, pre-stroke statin, pre-stroke antiplatelet, cardiovascular history), with goodness of fit optimized subsequently with backwards elimination of variables to achieve the lowest Akaike information criteria.

Tracer uptake was compared across stenosis categories ("1–29%," "30–49," "50–69%," "70–89%," "90–99%") in both symptomatic and asymptomatic arteries using Kruskal-Wallis one-way ANOVA testing (for non-parametric data).

The cut-off for statistical significance was set at $P = 0.05$. Data was analyzed using R (version 3.6.1, 2019, R Foundation for Statistical Computing, Vienna, Austria).

Data Availability

The corresponding author had full access to all the data in the study and takes responsibility for its integrity and the data analysis. The full anonymized dataset is available upon reasonable request from the corresponding author.

TABLE 1 | Clinical characteristics of study cohort ($n = 26$).

Mean age (years)	74.8 (SD 9.7)
Men	18 (69.2%)
Median BMI	26 (IQR 3.9)
Smoking history (current or ex-smokers)	17 (65.4%)
Diabetes mellitus	4 (15.4%)
Hypertension	17 (65.4%)
Pre-stroke statin	9 (34.6%)
Pre-stroke antiplatelet	8 (30.8%)
Cardiovascular history (previous ischemic heart disease/ myocardial infarction)	8 (30.8%)
Median National Institutes of Health Stroke Scale (NIHSS)	4.5 (IQR 10.75)
Thrombolysed	6 (23.1%)
Modal degree of symptomatic stenosis	70–89%

RESULTS

Study Population

Of the 31 participants recruited to the ICARUSS study, 28 underwent FDG-PET/CT (of the three recruited who did not undergo scanning: two deteriorated clinically, becoming too unwell to continue in the study, and one was unable to complete imaging due to claustrophobia).

Of this 28, 26 had imaging suitable for analysis (one participant had an uninterpretable PET scan and one subject declined MRI). All participants had bilateral carotid atherosclerosis. Eight (30.8%) participants had co-existent coronary artery disease, and four (15.4%) had a clinical diagnosis of peripheral arterial disease. Clinical characteristics are shown in **Table 1**.

All acute infarcts were cortical in their distribution, consistent with probable artery-to-artery embolization. Reflecting this, in all cases the carotid pathology was felt by the clinical team to be the causative etiology for the acute infarct. The median DWI lesion volume was 3.36 ml (IQR 14.4 ml).

PET Tracer Uptake in Culprit and Non-culprit Atherosclerotic Plaque

FDG uptake was significantly higher in the culprit artery than in the contralateral non-culprit carotid artery for both the MDS [median TBR_{max} (IQR) 2.08 (0.52) vs. 1.89 (0.40), respectively, $P < 0.001$] and WV measures of uptake [median TBR_{max} (IQR) 1.92 (0.41) vs. 1.71 (0.31), respectively, $P < 0.001$]. No relationship was observed between FDG MDS TBR_{max} and the degree of luminal stenosis ($P = 0.91$). There was a moderate association between hsCRP and non-culprit WV TBR_{max} ($r_s = 0.50$, $P = 0.02$). Inter-rater reliability of FDG reads was 0.93.

Chronic Small Vessel Disease

Of the 26 participants, 15 (57.7%) had no/mild leukoaraiosis, 11 (42.3%) had moderate/severe leukoaraiosis. The pattern of disease was predominantly peri-ventricular. The median WMH volume was 3.11 ml (IQR 7.43 ml). The group with moderate/severe leukoaraiosis were older than those with no/mild leukoaraiosis (mean age 79.4 ± 9.7 vs. 71.5 ± 8.5 years,

TABLE 2 | Comparison of dichotomized groups of small vessel disease severity.

	No/Mild leukoaraiosis ($n = 15$)	Moderate/Severe leukoaraiosis ($n = 11$)	Significance
Mean age (SD) (years)	71.5 (± 8.5)	79.4 (± 9.7)	$P = 0.04$
Number of males (%)	11 (73.3%)	7 (63.3%)	$P = 0.60$
Mean BMI (SD)	26.0 (± 4.2)	28.3 (± 5.3)	$P = 0.26$
Current/former smoker (%)	10 (66.7%)	7 (63.3%)	$P = 0.87$
Diabetes mellitus (%)	1 (6.7%)	3 (27.3%)	$P = 0.15$
Hypertension (%)	11 (73.3%)	6 (54.5%)	$P = 0.32$
Pre-stroke statin (%)	7 (46.7%)	2 (18.2%)	$P = 0.13$
Pre-stroke antiplatelet (%)	5 (33.3%)	3 (27.3%)	$P = 0.74$
History of cardiovascular disease (%)	5 (33.3%)	3 (27.3%)	$P = 0.74$
Total cholesterol	4.55 (± 1.3)	4.5 (± 0.88)	$P = 0.91$
Median NIHSS (IQR)	5 (12)	4 (8)	$P = 0.70$
Thrombolysed	2 (13.3%)	4 (36.4%)	$P = 0.17$
Modal degree of symptomatic artery stenosis	70–89%	70–89%	
Maximum stenosis in symptomatic artery			
CCA	1 (6.7%)	1 (9.1%)	
ICA	14 (93.3%)	10 (90.9%)	$P = 0.82$
Modal degree of asymptomatic artery stenosis	30–49%	30–49%	
Maximum stenosis in asymptomatic artery:			
CCA	3 (20%)	2 (18.2%)	
ICA	12 (80%)	9 (81.8%)	$P = 0.90$
Mean onset-to-FDG-PET/CT (SD) (days)	9.2 (± 4.8)	8.9 (± 4.7)	$P = 0.88$

$P = 0.04$), otherwise there were no other significant differences in clinical characteristics between the cohorts (**Table 2**).

Multiple logistic regression showed FDG uptake to be independently associated with severity of leukoaraiosis, for both plaque and average whole vessel and in both culprit and contralateral non-culprit arteries (**Table 3**; **Figure 1**). The strongest associations were for the non-culprit artery, in particular the WV uptake [adjusted OR 6.18 (95% confidence interval 2.1–18.2), $P < 0.01$]. This model also suggests a lower odds of moderate/severe leukoaraiosis in individuals taking statins and increased odds of more severe small vessel disease with increasing age. The effects of diabetes and smoking were inconsistent (**Table 3**).

Quantitative measures of WMH produced a similar pattern. On univariable analysis, there was no relationship between culprit carotid MDS or WV TBR_{max} ($r_s = 0.30$, $P = 0.14$ and $r_s = 0.20$, $P = 0.34$, respectively). In contrast, there was a trend of increasing strength of association between WMH volume with median non-culprit MDS TBR_{max} ($r_s = 0.39$, $P = 0.05$), and the WV TBR_{max} of the non-culprit carotid ($r_s = 0.50$, $P = 0.01$).

Linear regression of WMH volume, adjusting for cardiovascular risk factors, broadly supported the findings in the semi-quantitative analysis. Again, FDG TBR_{max} was independently associated with increased WMH volumes for diffuse measures of atheroma inflammation (non-culprit artery readings and the median whole vessel uptake in the culprit carotid), but not when considering the focal uptake in the culprit plaque (**Table 4**). Furthermore, this analysis also indicated a consistent independent positive association between age and WMH volume, and a negative association between statin use and WMH volume, in-keeping with the results observed in the semi-quantitative analysis. There were no significant interactions between these variables.

Inter-rater reproducibility of Fazekas scoring had an ICC of 0.91 across all scans. Inter-rater reproducibility of WMH volumes had an ICC of 0.99.

DISCUSSION

Our study is novel in relating the presence of leukoaraiosis to the physiological activity within systemic atherosclerosis measured using PET, rather than simply the degree of anatomical luminal stenosis. We demonstrate an independent association between atheroinflammation within carotid atherosclerosis and the severity of small vessel disease.

This relationship, and the strength of the regression models themselves, was stronger when considering the contralateral non-culprit artery rather than the culprit artery. The non-culprit artery is likely more representative of the overall burden of systemic atheroinflammation, in effect acting as a disease "barometer," as suggested by the correlation between neighboring arterial regions demonstrated by Rudd et al. (23). In contrast, the most diseased segment of the culprit symptomatic artery represents a region with potentially disproportionate uptake – a peak focus of inflammation possibly accentuated by the rupture itself – that may not be reflective of the global burden of atheroinflammation throughout the body. Supporting this, our results indicate more diffuse measures of FDG uptake in the culprit artery (i.e., the WV) are similar to those from the non-culprit artery. Given that WMHs represent chronic disease developing over a longer time course than acute stroke, it is therefore likely that the non-culprit artery gives a better representation of the long-term pathophysiology to which the brain has been exposed.

A possible mechanism linking atheroinflammation and SVD is the action of matrix metalloproteinases (MMPs), which may act locally and systemically. A single vulnerable plaque may rupture through MMP-mediated disruption of the fibrous cap (1, 24), but the elevated plasma concentrations (particularly of MMP-9) seen in atherosclerosis may also have important systemic effects (25, 26). MMP-9 is implicated in blood-brain barrier dysfunction (27–29), where increased permeability may promote the development of leukoaraiosis (30, 31). Previous studies have demonstrated an association between FDG uptake

TABLE 3 | Multiple logistic regression for moderate/severe leukoaraiosis severity for focal (MDS) and whole vessel (WV) FDG uptake in culprit and non-culprit carotid arteries.

Culprit artery			Non-culprit artery		
MDS TBR_{max}		**Adjusted R^2 = 0.48 ($P < 0.01$)**	**MDS TBR_{max}**		**Adjusted R^2 = 0.62 ($P < 0.001$)**
	OR (95% CI)	**Significance**		**OR (95% CI)**	**Significance**
FDG uptake	2.14 (1.07–4.28)	$P = 0.04$	FDG uptake	3.98 (1.84–8.59)	$P < 0.01$
Age	1.03 (1.01–1.05)	$P < 0.01$	Smoking	5.55 (1.23–25.0)	$P = 0.04$
Pre-stroke statin	0.64 (0.46–0.89)	$P = 0.02$	Age	1.03 (1.02–1.05)	$P < 0.001$
Smoking	2.96 (0.66–13.32)	$P = 0.17$	Pre-stroke statin	0.71 (0.54–0.93)	$P = 0.02$
WV TBR_{max}		**Adjusted R^2 = 0.49 ($P < 0.001$)**	**WV TBR_{max}**		**Adjusted R^2 = 0.57 ($P < 0.001$)**
	OR (95% CI)	**Significance**		**OR (95% CI)**	**Significance**
FDG uptake	1.52 (1.06–2.17)	$P = 0.03$	FDG uptake	6.18 (2.10–18.2)	$P < 0.01$
Age	1.03 (1.01–1.05)	$P < 0.01$	Age	1.03 (1.01–1.05)	$P < 0.01$
Pre-stroke statin	0.63 (0.46–0.86)	$P < 0.01$	Pre-stroke statin	0.72 (0.53–0.97)	$P = 0.04$
	Diabetes	2.15 (1.41–3.28)	$P < 0.01$		
	Smoking	8.34 (1.14–61.0)	$P = 0.05$		

FDG uptake refers to per unit increase in the stipulated TBR_{max}.

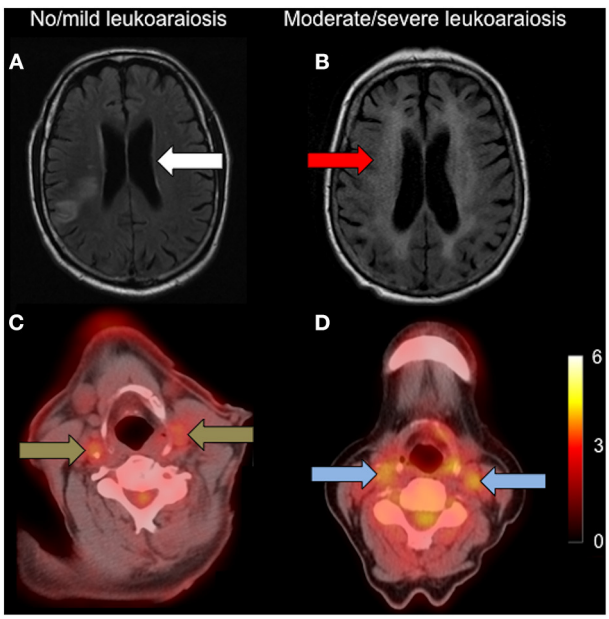

FIGURE 1 | Carotid FDG uptake according to leukoaraiosis severity. Left: **(A)**: axial FLAIR showing no/mild leukoaraiosis (white arrow) with **(C)**: associated low carotid FDG uptake (brown arrows); Right: **(B)**: axial FLAIR showing moderate/severe leukoaraiosis (red arrow) with **(D)**: higher associated carotid FDG uptake (blue arrows). Both FDG-PET/CT images are set to the same scale, with the scale bar showing FDG SUV.

and serum MMP-9 concentrations (23, 32). A 12-week course of atorvastatin 40 mg/day resulted in significant reductions in both atheroma TBR and MMP-9, with a moderate correlation between the reduction in plaque TBR and reduction in MMP-9 concentration (33). These relationships, and those between MMP-9 levels and blood-brain barrier dysfunction (27–29), and between blood-brain barrier permeability and the development of leukoaraiosis (30, 31, 34), indicate an association between the chronic atheroinflammation within carotid plaques and the development of leukoaraiosis.

Our finding that FDG uptake did not relate to the degree of luminal stenosis may explain the previously-reported inconsistent findings in the association between leukoaraiosis and the degree of stenosis (14), where plaques with similar degrees of stenosis may have different levels of atheroinflammation. The positive associations between SVD and increased IMT or presence of plaque are in-keeping with this hypothesis, as they may represent an earlier stage of atherogenesis (and one more associated with inflammation) than the degree of stenosis, where there may be more variability in plaque activity from highly inflamed early atheroma to older quiescent plaques.

Previous work has reported inconsistent associations between leukoaraiosis and a range of vascular risk factors (35). A notable exception is age, which most studies have found to be independently associated with the development of WMHs (13, 36). Our findings support this. Furthermore, the independent association of statin therapy with reduced SVD is potentially consistent with the pleiotropic effects of statins and hence relevant to the inflammatory hypothesis. The role of statins in WMH progression remains a subject of debate: in the PROSPER study there was no effect on WMH progression with pravastatin, though this cohort had low rates of atherosclerosis (37). In contrast, progression of confluent WMHs was found to be reduced by the use of pre-stroke statin therapy (38).

TABLE 4 | Linear regression for white matter hyperintensity volume (mL) for focal (MDS) and whole vessel (WV) FDG uptake in culprit and non-culprit carotid arteries.

Culprit artery			Non-culprit artery		
MDS TBR_{max}		**Adjusted $R^2 = 0.49$ ($P < 0.01$)**	**MDS TBR_{max}**		**Adjusted $R^2 = 0.59$ ($P < 0.001$)**
	Beta coefficient	**Adjusted significance**		**Beta coefficient**	**Adjusted significance**
TBR_{max}	3.53	$P = 0.08$	TBR_{max}	9.38	$P < 0.01$
Age	0.50	$P < 0.01$	Age	0.50	$P < 0.001$
Pre-stroke statin	−12.6	$P < 0.01$	Pre-stroke statin	−9.03	$P = 0.02$
Pre-stroke antiplatelet	6.05	$P = 0.15$	Pre-stroke antiplatelet	5.69	$P = 0.12$
WV TBR_{max}		**Adjusted $R^2 = 0.$ ($P < 0.001$)**	**WV TBR_{max}**		**Adjusted $R^2 = 0.62$ ($P < 0.001$)**
	Beta coefficient	**Adjusted significance**		**Beta coefficient**	**Adjusted significance**
TBR_{max}	8.91	$P < 0.01$	TBR_{max}	14.33	$P < 0.01$
Age	0.52	$P < 0.001$	Age	0.48	$P < 0.001$
Pre-stroke statin	−11.54	$P < 0.01$	Pre-stroke statin	−8.86	$P = 0.01$
Pre-stroke antiplatelet	6.69	$P = 0.07$	Pre-stroke antiplatelet	6.33	$P = 0.08$

Limitations and Future Work

Although the high sensitivity of PET enables detection of subtle physiological changes, allowing statistically significant differences to be detected despite small sample sizes, the limited size of our study means that further validation through replication in a larger cohort or meta-analysis would be advantageous.

Related to this, some caution must be exercised when interpreting the regression analyses given the relatively small sample size. The use of the Akaike information criteria in backwards elimination to optimize best-fit ensures that the selected models explain the greatest amount of variation using the fewest number of independent variables, hence reducing the risk of overadjustment bias. In our linear and logistic models, the consistent inclusion of age and pre-stroke statin in such optimized models is biologically plausible and supported by the existing literature as discussed above. Their presence is likely to be on the causal pathway, thereby reducing overadjustment bias further. Although the final models typically include three to four covariables for the study size of 26 participants, and hence not meet the "rule of ten" for the ratio of outcomes to variables, such a rule of thumb has been argued to be either too conservative or potentially of limited evidence basis (39, 40). However, further replication and validation in larger studies to accommodate more variables will be advantageous to reduce further the risk of overadjustment bias.

We did not measure MMPs in this study, though the association between FDG uptake and MMP-9 has been reported previously (23). Future studies measuring MMPs and other inflammatory biomarkers may further elucidate the mechanistic link underlying associations observed here.

In this study, we considered only carotid atherosclerosis. The overall burden of systemic atheroinflammation will reflect the totality of disease in other arterial territories (including coronary arteries, aorta, and peripheral arterial disease). However, previous work has demonstrated that atheroinflammation is strongly associated across neighboring arterial territories, and consequently the carotids (particularly the diffuse measure of uptake in the non-culprit artery, WV TBR_{max}) may serve as good surrogates of systemic atheroinflammation (23). Furthermore, we found a moderate association between the non-culprit WV TBR_{max} and serum hsCRP, suggesting that the carotid uptake is a reasonable reflection of systemic inflammation. Future work considering the global burden of atheroinflammation for the individual, incorporating atheroinflammation across coronary, aortic, and peripheral arterial disease, as well as comparison against healthy controls would help elucidate this relationship further.

Although highly sensitive, FDG uptake is non-specific. Although the measures taken here improve its specificity for inflammation, replication using newer radiotracers with higher specificity for inflammatory cells, such as ^{68}Ga-DOTATATE (19), would help characterize this relationship.

To elucidate the mechanisms underlying the associations observed in this study, future work should consider a range of biomarkers of systemic inflammation, and imaging of BBB integrity alongside carotid and brain imaging.

CONCLUSION

The observed association between carotid atheroinflammation and the presence of more severe small vessel disease has implications for our understanding of the neurovascular interface and may have future influence on how we manage "asymptomatic" atherosclerosis, with atheroinflammation treated more aggressively with anti-inflammatory agents. Canakinumab (a monoclonal antibody targeting interleukin-1β) has shown promise for reducing cardiovascular outcomes after

myocardial infarction (41), whilst colchicine has also been found to reduce cardiovascular outcomes in those with coronary artery disease (42, 43). Evidence for the benefit of such agents related specifically to carotid atherosclerosis is currently lacking (44), though the Colchicine for Prevention of Vascular Inflammation in Non-cardio Embolic Stroke (CONVINCE) study will consider the use of colchicine in a stroke setting. Such therapeutic approaches targeting systemic atheroinflammation may have an important role for reducing the burden of chronic small vessel disease and its clinical sequelae.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Nottingham One Research Ethics Committee, 14/EM/0128. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NE, AP, MG, JR, and EW participated in study design. NE, JT, JW, MC, and AP participated in data acquisition and analysis. NE performed the statistical analysis and drafted the manuscript. All authors participated in interpretation of the data and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT
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Hyoid Elongation May Be a Rare Cause of Recurrent Ischemic Stroke in Youth-A Case Report and Literature Review

Gang Liu[1†], Yuan Wang[1†], Changbiao Chu[1], Yi Ren[1], Yang Hua[2], Xunming Ji[3] and Haiqing Song[1]*

[1] Department of Neurology, Xuanwu Hospital, Capital Medicine University, Beijing, China, [2] Department of Vascular Ultrasound, Xuanwu Hospital, Capital Medical University, Beijing, China, [3] Department of Neurosurgery, Xuanwu Hospital, Capital Medicine University, Beijing, China

The investigation for etiology of ischemic stroke in young adults remains a diagnostic challenge. Hyoid bone–related carotid injury is a rare and under-recognized cause of ischemic stroke, without established guidelines. We describe a case of recurrent ischemic stroke in a young patient presumably attributed to an impingement of the carotid artery by an elongated hyoid bone, and present other cases reported in the literature. Based on the imaging study as well as the lack of other findings, we attributed recurrent neurovascular events to the repetitive mechanical stimulation by the elongated hyoid bone that caused a vessel wall injury with subsequent thrombus and embolus. Given repeated recurrence under antiplatelet treatment, anticoagulation was added. The following 2-year follow-up showed no new neurologic events or any other complaints. Among the young, a broad spectrum of possibilities should be considered and we call attention to this infrequent etiology of ischemic stroke.

Keywords: recurrent stroke, young adults, hyoid bone, carotid artery diseases, imaging diagnosis

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***Correspondence:**
Haiqing Song
songhq@xwhosp.org

†These authors have contributed equally to this work and share first authorship

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BACKGROUND

Every year, more than two million young adults experience an ischemic stroke worldwide. Stroke at young ages has been considered as an enormous socio-economic problem due to high health-care costs and loss of productivity (1). By contrast to stroke in the elders, stroke in young adults is more heterogeneous because of a wide spectrum of possible underlying risk factors and often rare etiologies (2). Meanwhile, investigations into the cause of ischemic stroke at a young age is often challenging.

As an uncommon etiology of stroke, hyoid bone elongation causes compression or localized trauma to the carotid artery. We describe a young patient with recurrent strokes resulting from mechanical interference of an elongated hyoid bone to the carotid artery. Previous reported cases from 1999 to present are also summarized (**Supplementary Table 1**).

CASE PRESENTATION

A 39-year-old male patient was admitted to the Neurology Department with the complaint of dysphasia with a sudden onset 2 years ago and sudden right limb weakness for 4 months, who had the habit of playing badminton and golf.

Two years ago, the patient experienced intermittent episodes of difficulty in speaking and language comprehension with resolution after about 2 h. Head magnetic resonance imaging (MRI) showed abnormal signal intensity in the left temporal lobe, indicating acute infarction, while head magnetic resonance angiography (MRA) was normal. The transesophageal echocardiogram (TEE) combined with color transcranial doppler (TCD) indicated paradoxical embolism from a patent foramen ovalis (PFO). He was diagnosed as cerebral infarction (left temporal lobe) with high possibility of cardiac embolism and PFO. Then, he underwent transcatheter PFO closure successfully. After that, he adhered to aspirin (100 mg once per day) and atorvastatin (10 mg once per day) therapy.

Four months before admission, the patient experienced weakness of right limbs and inability to speak with a sudden onset, and recovered within seconds spontaneously. The next day, he was noted by his colleagues due to difficulty speaking accompanied by low spirits, and was sent to the local hospital, where he was diagnosed as acute cerebral infarction. At that time, his head MRI revealed acute infarction on diffusion-weighted imaging (DWI) sequences in the left anterior cerebral artery (ACA) and middle cerebral artery (MCA) territory. The digital subtraction angiography (DSA) revealed M1 segment occlusion of the left MCA. He underwent endovascular therapy (thrombectomy) of the left proximal MCA, and recovered with sequelae of mild dysarthria and poor short-term memory. He was then discharged with a prescribed regimen of aspirin (100 mg once per day) and atorvastatin (10 mg once per day).

Approximately 2 months before his first visit to our department, although there were no new symptoms, a repeat head MRI showed hyperintensity on DWI and T2-weighted images, and hypointensity on T1-weighted images in the left frontal, temporal and parietal lobes with a normal MRA. A repeat MRI at our institution showed multiple lesions in the left MCA territory, indicating a convalescent ischemic stroke (**Figure 1**). A carotid ultrasound in neutral head position showed increased intima-media thickness (IMT) with single plaque formation in bilateral carotid arteries, whereas in the rotated neck position revealed a heterogeneous echo outside the left carotid bifurcation. When the patient was in the right lateral decubitus position with neck rotating to the left, the carotid duplex scan demonstrated a compressed and narrow lumen at the distal end of the left common carotid artery (CCA), which was related to the hyoid bone, and the transcranial color-coded Doppler (TCCD) showed a significantly decreased flow velocity of the left MCA (**Figure 2**). This phenomenon was not found in the rotation to right. And the compression of hyoid bone to carotid arteries in the right side was not recognized. He subsequently underwent a computed tomography angiography (CTA) of the neck and head, which revealed an enlarged left hyoid bone on close contact with carotid bifurcation, without evidence of artery stenosis (**Figure 3**). Time of flight-magnetic resonance angiograph (TOF-MRA) showed abnormal signal in the left-internal carotid artery (ICA) lumen, which was more be likely caused by artifact, because the signals of right CCA and bilateral vertebral artery (VA) were also decreased at the same level, as well as the flow on the left ICA on carotid ultrasound on neutral head position was normal. High-resolution magnetic resonance imaging (HR-MRI) displayed no abnormality in the arterial wall. Subsequent DSA revealed no dissection, stenosis or pseudoaneurysm of the internal and external cranial arteries, and no arterial repair or reconstruction was necessary. Extensive workup for multiple causes of stroke in young adults was unrevealing, including complete blood count, erythrocyte sedimentation rate, liver and renal function tests, lipid profile, electrolytes, hemoglobin A1c and C-reactive protein. Thyroid function analysis, tumor markers test, antithrombin III activity, protein C and protein S levels, homocysteine and D-Dimer levels were within the normal limits. Serologic tests of human immunodeficiency virus, hepatitis B and C viruses, syphilis, anti-cardiolipin antibodies, beta-2-glycoprotein antibody, antinuclear antibody and rheumatoid factor were negative. A transthoracic echocardiogram did not demonstrate thrombus, right-to-left shunting post PFO closure or valvular disease, and 24-h Holter monitoring demonstrated episodic bradycardia without atrial fibrillation.

Based on the imaging study as well as the lack of other findings, the working diagnosis was considered as the external compression of the left carotid artery by the hyoid bone, resulting in recurrent ischemic strokes. Given repeated recurrence under antiplatelet treatment, anticoagulation was added. The following 2-year follow-up showed no new neurologic events or any other complaints.

DISCUSSION

Carotid artery compression by anomalous cervical structures is rare and the mechanical impingement of the carotid vessels related to the bone structures, which eventually results in neurovascular events is even more uncommon. The stylohyoid complex, comprising the styloid process, the stylohyoid ligament and hyoid bone, is in proximity to the ICA (3). In 1937, Eagle first described a phenomenon called "Eagle syndrome" or "stylocarotid artery syndrome," representing neurologic symptoms caused by compression or irritation of the extracranial carotid artery due to an elongation of the styloid process more than 30 mm and possible ossification of stylohyoid ligament (4). However, rare studies of hyoid bone-related carotid artery disease have been reported.

The hyoid bone, an attachment locus for neck, tongue and throat muscles, is a midline structure in front of cervical spine, below the mandible, above the thyroid cartilage and at the level of the third cervical vertebra. Hyoid bone, consisting of the greater and lesser horns and the body, is horseshoe shaped, which ends anteriorly and superiorly to the carotid artery bifurcation. Fakhry et al. (5) analyzed 180 intact hyoid bones, found that characteristics of the hyoid bone were highly heterogeneous, which were closely associated with the sex, height, and weight of the individuals. In this study, the width of the hyoid bone, meaning the distance between the distal parts of the greater horns of the hyoid bone, was 40.78 ± 7.09 mm. The length of the hyoid bone, presenting the distance from the middle of the anterior part of the body to a hypothetical line connecting the distal parts of the

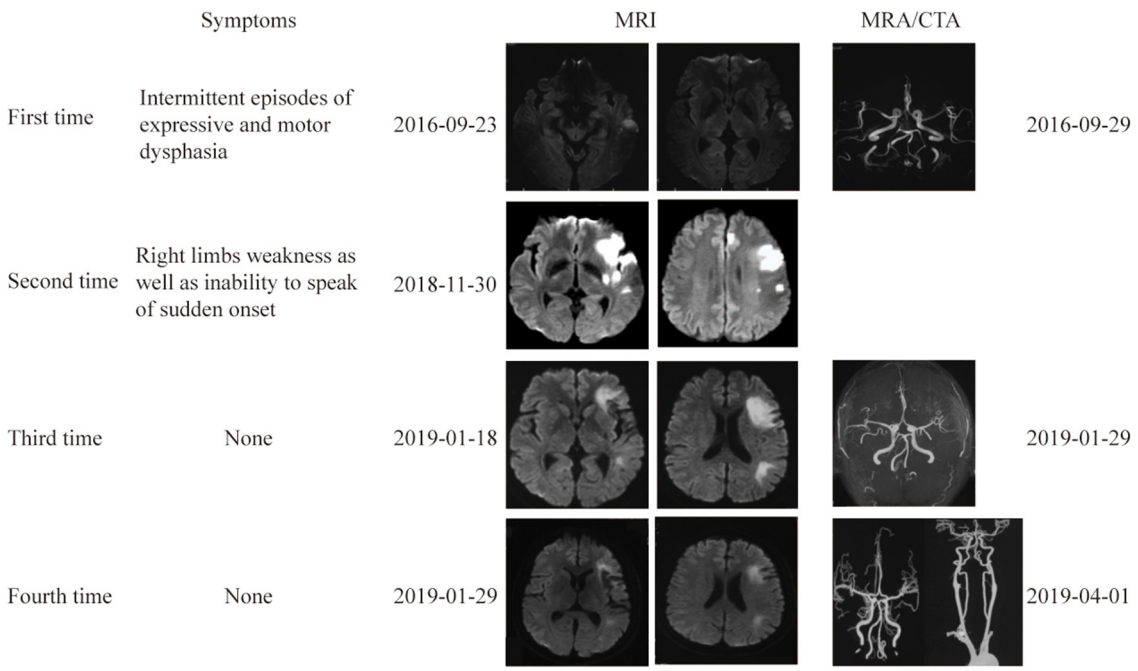

FIGURE 1 | Brain and vascular imaging at 4 different times. Brain MRI at 4 times showed multiple lesions in the left ICA territory. Vascular imaging showed no evidence of vascular stenosis or occlusion.

greater horns, was 36.38 ± 4.88 mm. And the width of the body was 20.91 ± 3.04 mm. Duan et al. (6) analyzed 74 intact hyoid bones and found that the length of the right greater horn was 31.4 ± 2.6 mm, of the left was 31.0 ± 2.5 mm.

The anatomy of the hyoid bone is variable and its position changes with swallowing, talking, and neck rotation (7, 8). Commonly, the carotid bifurcations are at the level of C3/4, and the ICA walks posterolaterally to the external carotid artery (ECA). The ICA lesions can be provoked by the movement and impingement of the greater horn of the hyoid bone.

Possible pathological presentations of hyoid bone-related carotid injury include dissection, pseudoaneurysm, stenosis or occlusion due to direct compression, and pressure-induced plaque formation and/or rupture. A possible explanation for carotid vasculopathy is the direct compression of the hyoid bone, leading to constructional changes in the carotid wall and/or an indirect effect via changes in blood flow and shear force. Each of these causes may potentially lead to stenosis, occlusion, or artery-to-artery embolism.

Pearlman et al. (9) reported an 83-year-old man with a suspected stenosis of the left ICA with hemodynamical deficiency. The left carotid endarterectomy revealed a paucity of plaque and obstructive lesion, but a long extension of the hyoid bone impinging on the artery was found, which created significant pressure over the ICA, resulting in a narrow lumen or occlusion of the artery in some certain positions. Previous studies (8–12) described several cases presented as embolic strokes due to chronic trauma to the ICA caused by an elongated hyoid bone, which accelerated plaque accumulation and increased the risk of artery-to-artery embolism. Another case report of a young male patient without any vascular risk factors or relevant family history demonstrated that ICA dissection was related to direct mechanical interference of the ICA by the hyoid bone when rotating or stretching neck (13). In a retrospective multicenter case-control study of carotid artery dissection patients, Renard et al. (14) found that shorter distances between the stylohyoid complex and ICA predispose to the occurrence of carotid artery dissection through mechanical injury. In another case, the patient's transient ischemic symptoms were contributed to the intermittent impingement on the ICA by the elongated hyoid wing, in the absence of atherosclerosis (15). Schneider et al. (16) reviewed three cases of pseudoaneurysm of the carotid artery caused by the mechanical injury of the hyoid bone. The phenomenon of hyoid mechanical trauma to the ICA leading to thrombus formation, embolization and recurrent TIAs, was termed as carotid artery entrapment by the hyoid.

In our case, the width and length of the hyoid bone was 65 mm and 32 mm respectively, the width of the body was 24 mm, and the length of the greater horn was 37.9 mm. We speculate that repetitive mechanical interference to the wall of the carotid artery caused a vessel wall injury with subsequent intimal thrombus formation and cerebral embolization that triggered recurrent neurovascular events. Additionally, luminal obstruction of the carotid artery might disturb the cerebrovascular flow by provoking movements. The hyoid bone movement induced by the extreme and routine neck rotation or stretching may be responsible for the vessel injury. The case reported here calls attention to the initial presentation as TIA followed by a stroke.

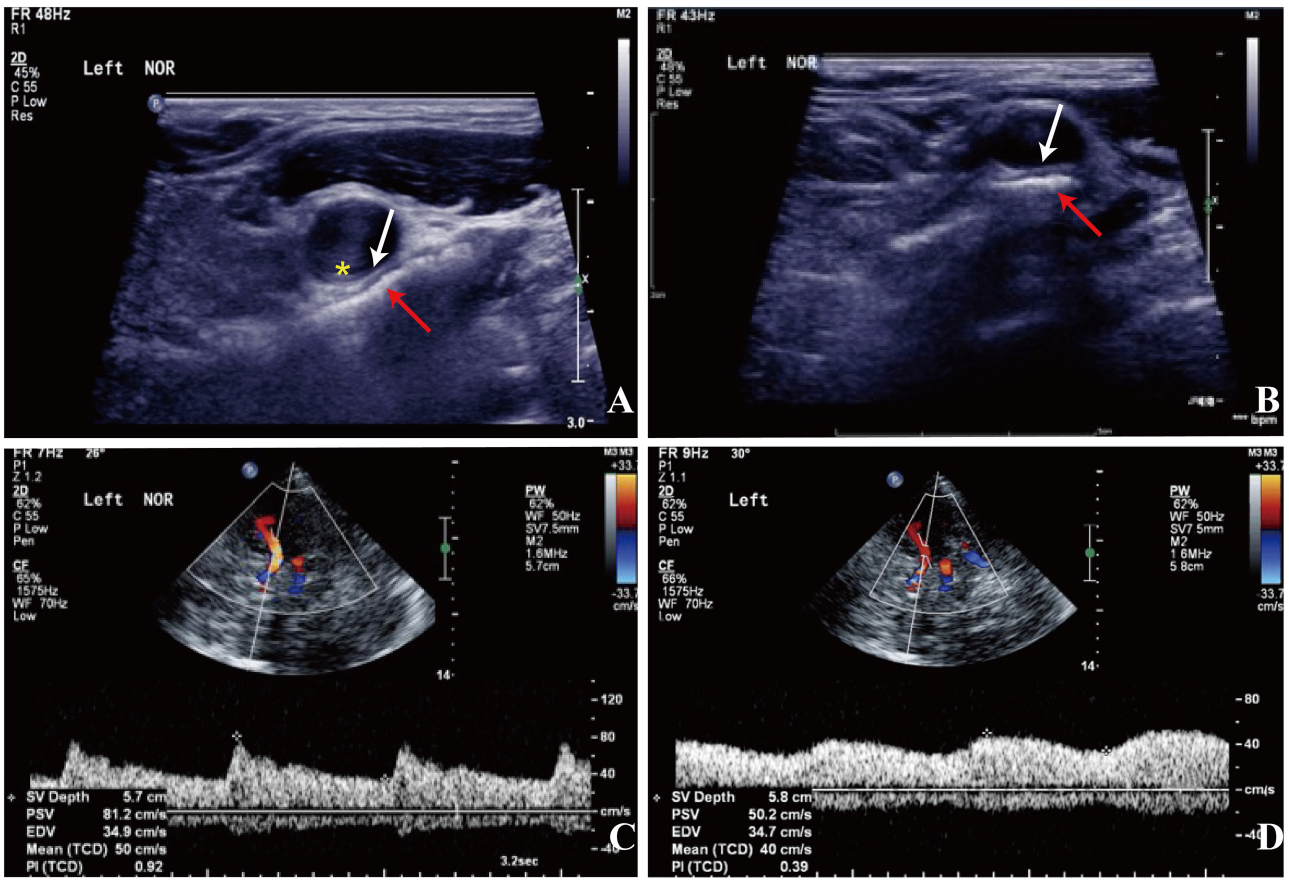

FIGURE 2 | Carotid doppler ultrasound spectrum (DUS) **(A,B)** and TCCD **(C,D)**. **(A,B)** There was a heterogeneous echo outside the left carotid bifurcation, and the lumen at the distal end of the left CCA was compressed by the hyoid bone in the rotated neck position (red arrow: the hyoid bone; white arrow: compressed arterial lumen; yellow asterisk: increased IMT). **(C)** The flow velocity of the left MCA was normal in the neutral position. **(D)** The flow velocity of the left MCA decreased significantly with neck rotation.

Despite transcatheter PFO closure and antiplatelet treatment, the patients suffered recurrent cerebrovascular events in the same artery territory. In the third episode, ultrasonography demonstrated variations in blood flow along with the alterations in hyoid positioning in relation to the carotid vessels, and the CTA identified a close contact between the left greater horn of the hyoid bone and the carotid artery.

Due to the heterogeneity of the symptomatology of the Eagle clinical picture and rare anomalies of hyoid bone, it's hard to make the diagnosis. Imaging studies are needed to determine whether compression of the carotid artery by the hyoid bone can occur. Ultrasonography allows to visualize compression of the carotid artery by the hyoid bone on head rotation and swallowing, though requiring considerable experience of the examiner. CTA is considered as an excellent option of diagnosis not only for estimating the length and thickness of the hyoid bone but also for determining its anatomical relationship with blood vessels and muscles, which was less operator dependent. Because CTA is static and lacks dynamic information, dynamic 3D-CTA may be useful for understanding the dynamic anatomical relationship of the carotid arteries with surrounding structures during head rotation and swallowing, which may be used to provide dynamic modalities in future assessment. HR-MRI, as an advanced MRI modality, can render arterial wall and characterize vessel wall pathology. Classic angiography with intra-arterial application of contrast agent and application of functional tests may provide evidence indicating underlying pathophysiology of hyoid bone-related carotid injury such as dissection, pseudoaneurysm, stenosis or occlusion.

In terms of treatment, there are no established treatment guidelines due to the scarcity of reported cases. Treatment varies depending on the pathology (17). Anticoagulation and/or antiplatelet treatment is usually initiated (8). When an artery-to-artery embolism is suspected or in cases of ICA dissection, anticoagulation therapy in the early phase can be considered in the absence of contraindications. Surgical partial bone resection, proved to be safe and effective (10), remains a viable option especially in cases of repeated recurrence under medication treatment, which restores the patient with physical and psychological freedom of neck movement. For our patient, there was no evidence of focal carotid stenosis, leading to a speculation of artery-to-artery embolism which was attributed

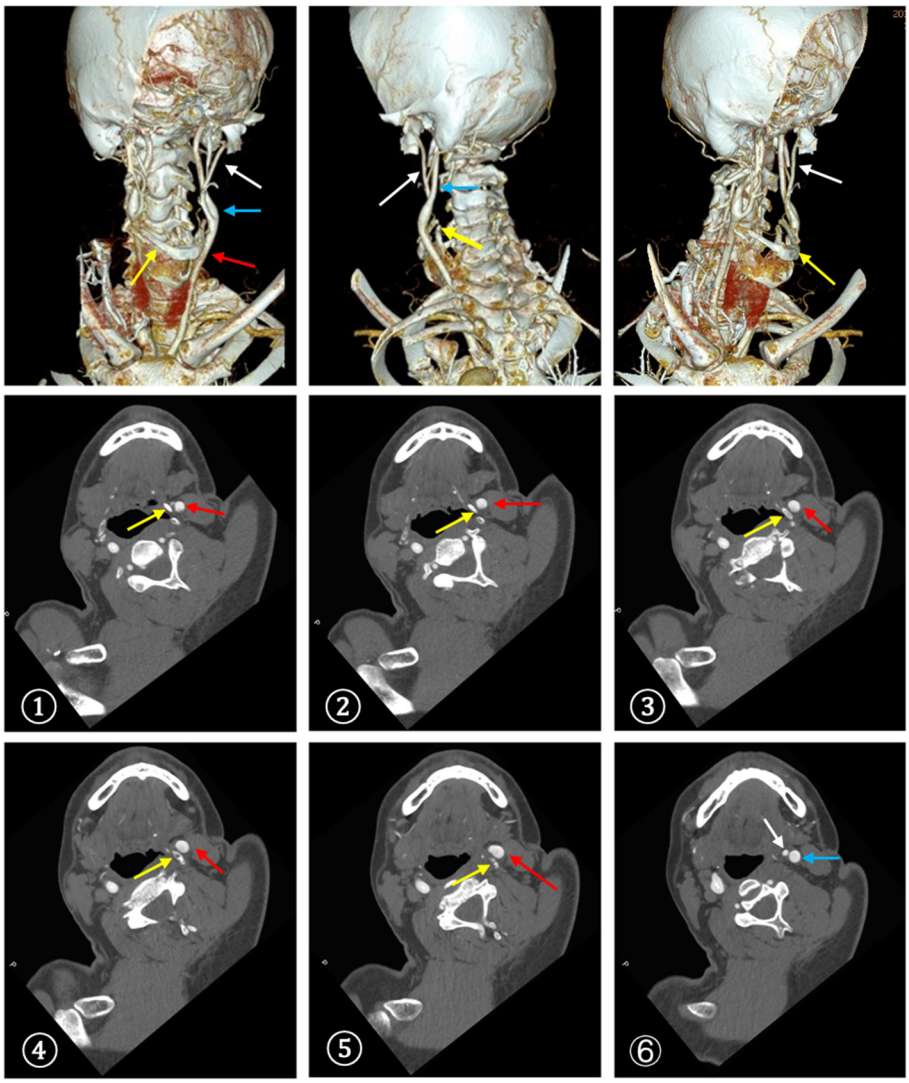

FIGURE 3 | CTA demonstrated a close contact between the enlarged left greater horn of the hyoid bone and the carotid bifurcation. ①-⑥, The serial CT slices from distal CCA to proximal ICA. (red arrow: CCA, blue arrow: ICA, white arrow: ECA, yellow arrow: hyoid bone).

to continued clot formation caused by localized trauma. We initiated anticoagulation therapy, and the patient remained free of ischemic event in the following 24 months.

Our study has several limitations. First, we didn't check whether the hyoid bone compress the carotid artery during swallowing or neck flection and lacks dynamic information. Second, due to the limited cases, there has been no established strategy in cases of hyoid bone compression-related embolic stroke. Although the patient remained free from ischemic events following 2 years, surgical resection should be recommended in this case. And long-term follow-up should be conducted.

CONCLUSIONS

Hyoid bone-related carotid artery injury is a rare etiology of stroke, which is unknown to many doctors, thus itis not considered in the differential diagnosis of the cause of a stroke. For patients with recurrent strokes or TIAs, especially in young patients, consideration of mechanical compression and trauma of the vessels should be entertained, if work-up for common etiologies reveals no clear cause. Carotid artery impingement with compression by the hyoid bone seems to be extremely uncommon and a diagnosis of exclusion. Imaging studies with provocative maneuvers are helpful to make the diagnosis. In addition, the optimal treatment remains unclear. The cases presented here (6, 7, 9, 11–13, 15–27) contribute to further delimitation of the clinical and radiological diagnostic criteria, exploratory findings, and management of hyoid impingement.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Xuanwu hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

GL and YW: drafting of the manuscript. GL, YW, and HS: concept and design. YW: acquisition, interpretation of data and obtained funding. HS and XJ: critical revision of the manuscript for important intellectual content. CC, YR, and YH: administrative, technical or material support. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.653471/full#supplementary-material

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Vascular Diameters as Predictive Factors of Recanalization Surgery Outcomes in Internal Carotid Artery Occlusion

Chengrui Yan[1†], *Jiaru Wang*[2†], *Ruohan Guo*[3†], *Weitao Jin*[1], *Yang Zhao*[1] *and Rong Wang*[4,1*]

[1] Department of Neurosurgery, Peking University International Hospital, Beijing, China, [2] Department of Radiology, Peking Union Medical College, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China, [3] Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China, [4] Department of Neurosurgery, Beijing Tiantan Hospital Capital Medical University, Beijing, China

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Edited by:
Peter Kelly,
University College Dublin, Ireland

Reviewed by:
George Magoufis,
Metropolitan Hospital, Greece
Ning Ma,
Capital Medical University, China

***Correspondence:**
Rong Wang
ronger090614@ccmu.edu.cn

[†] These authors have contributed equally to this work

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Background: Revascularization surgery sometimes can achieve recanalization in patients with internal carotid artery occlusion (ICAO). High-resolution vessel wall magnetic resonance imaging (HRVWI) is a feasible technique to give detailed characteristics of the vessel wall, which may help to identify patients that carry higher success rates and more suitable for revascularization surgery.

Objective: To examine the association between HRVWI characteristics of ICAO and the success rate of revascularization surgery in ICAO patients.

Methods: We conducted a retrospective analysis of 31 ICAO recanalization patients enrolled from October 2017 to May 2019. The clinical data of patients and lesions were collected and analyzed.

Results: A total of 31 ICAO patients were enrolled in this study. No significant differences were found between recanalization success and recanalization failure groups with regard to occlusion length, distal end of the occluded segment, and the treatment applied. The ipsilateral-to-contralateral diameter ratios (I/C ratios) of C1 or C2 and the diameter of C7 were positively related to recanalization success. A two-factor predictive model was constructed, and the I/C ratio of C2 < 0.86 and the diameter of C7 < 1.75 mm were separately assigned 1 point. The ICAO patients who scored 0, 1, or 2 points had a risk of 5.6% (1/18), 55.6% (5/9), or 100% (4/4) to fail in the recanalization.

Conclusions: The I/C ratios of C1 or C2 and the diameter of C7 are predictive factors of a revascularization surgery success in ICAO patients. A risk stratification model involving C2 and C7 was constructed for future clinical applications.

Keywords: outcome research, recanalization, internal carotid artery occlusion, high-resolution vessel wall magnetic resonance imaging, endovascular intervention, carotid endarterectomy

INTRODUCTION

Chronic internal carotid artery occlusion (ICAO) was usually formed based on progressive atherosclerosis at the bifurcation of the carotid artery (1). Progressive stenosis of internal carotid artery (ICA) could reduce the blood flow in the ICA perfusion area, potentially leading to stroke. However, extracranial-intracranial or intracranial collateral circulation established during the progression could compensate the compromised perfusion, which accounts for the fact that some patients are asymptomatic despite severe ICA stenosis or ICAO. Both symptomatic and asymptomatic ICAO patients are at high risk for stroke. Faught et al. (2) reported that the 4-year cumulative stroke rate of asymptomatic ICAO patients or patients with transient ischemic attack was 8–11%, while in patients with apoplectic carotid artery occlusion, the risk was a higher 33%, which was still as high as 12.5% even after tPA therapy (3).

Carotid endarterectomy (CEA) could directly revascularize the narrow or occluded ICA and improve intracranial blood flow. It applies to the cases with a short occlusive length in the extracranial part of ICA, with a recanalization rate of 40.7–87.5% (4). Meanwhile, endovascular treatment could be used to recanalize long occlusive lesions with a success rate of 61.6–88% (5, 6). For ICAO patients with distal occlusion, such as the clinoid segment and above, Liu et al. reported that the recanalization rate of hybrid treatment was 71.4% (7). Therefore, the combination of CEA and endovascular treatment, or hybrid treatment, is a feasible therapy. However, endovascular recanalization of ICAO is still technically challenging due to long occlusion length and wide individual variation of the occluded vessel course. Potential complications after wiring injury, including hemorrhage, pseudoaneurysm, and carotid-cavernous fistula, might be catastrophic. Therefore, a systematic pre-procedural evaluation is important to identify patients that carry a higher recanalization success rate. According to previous studies, length of occlusion, occlusion duration, plaque location, and distal ICA reconstitution at a higher segment might affect the success rates (3). However, these are all qualitative indicators, and quantitative indicators to predict the success rate are yet to be found.

Recently, high-resolution vessel wall magnetic resonance imaging (HRVWI) emerged as a practicable technique to visualize luminal thrombi and vessel wall in occluded ICA (8). We found that the diameters of the occluded vessel could predict the successful rate of recanalization. This study sought to examine the predictive value of the diameter of each segment of occluded ICA in terms of achieving carotid revascularization.

METHODS

Patients

We conducted a retrospective analysis of 31 ICAO recanalization patients who were treated at Peking University International Hospital, Beijing, China, from October 2017 to May 2019. Inclusion criteria were as follows: (1) patients should be over 18 years old; (2) diagnosed as symptomatic total occlusion or near-occlusion of the carotid artery by digital subtraction angiography (DSA); (3) the latest stroke occurred more than 8 weeks previously, and patients with more than two ipsilateral cerebral ischemia were given optimal medical treatment; (4) patients should have accepted a high-resolution vessel wall magnetic resonance imaging (HRVWI) examination with contrast before the procedure. All subjects were fully informed and gave written consent before they were enrolled in the study. This study was approved by the institutional review board of Peking University International Hospital.

The HRVWI was done using a double inversion recovery technique and 3D motion sensitized driven equilibrium rapid gradient echo (3D-MERGE) technique with contrast. The lesion locations were recorded according to the ICA classification proposed by Bouthillier et al. (9), in which the ICA is divided into seven segments, i.e., C1, cervical; C2, petrous; C3, lacerum; C4, cavernous; C5, clinoidal; C6, ophthalmic; and C7, communicating. The axial images would be reviewed, and independent neurosurgeons and radiologists would measure the diameter of the occluded ICA from C1 to C7 (**Figure 1**).

Treatment

All the patients would be given regular medical treatment including management of risk factors (elevated systolic BP, elevated low-density lipoprotein cholesterol level, diabetes mellitus, smoking, etc.). Aspirin (100 mg per day) and clopidogrel (75 mg per day) would be prescribed to the patient for more than 7 days. Patients were treated by either carotid endarterectomy (CEA) or hybrid surgery (**Supplementary Table 1**). The procedure was performed by experienced doctors in the operating room equipped with an angiographic fluoroscopy system (FD20 system, Philips, Germany). Patients treated by CEA would have a plaque resection and arterial catheter embolectomy with a Forgaty catheter under the microscope first. Cerebral angiography would be done after that. While for patients treated by hybrid surgery, endovascular recanalization would be further performed. The target common carotid artery was engaged with 8-F MPA guiding catheter. Guidewires and microcatheters were used to explore the distal true lumen of occluded ICA and try to re-enter it. After the microwire entered the distal true lumen, the microcatheter would be exchanged to a properly sized balloon. Pre-dilation with a balloon catheter would be performed for distal to proximal. Cerebral angiography would be done to confirm the recanalization. If severe residual stenosis or dissection was found, properly sized balloon-mounted stents for distal segment lesion and carotid artery self-expanding stents for proximal segment lesion would be done at that time if necessary. The sequential endovascular treatment was abandoned after 30 min of futile effort, or when the wire tip is confirmed to be extravascular.

Statistical Analysis

Statistical analysis is performed with SPSS 22.0 software. Categorical variables are described in numbers and percentages. Continuous variables are expressed as mean ± standard deviation (SD). The chi-square test or Fisher's exact test is used to compare groups of categorical data. The relationships

Abbreviations: CEA, carotid endarterectomy; HRVWI, high-resolution vessel wall magnetic resonance imaging; ICA, internal carotid artery; ICAO, internal carotid artery occlusion; I/C ratios, ipsilateral-to-contralateral diameter ratios.

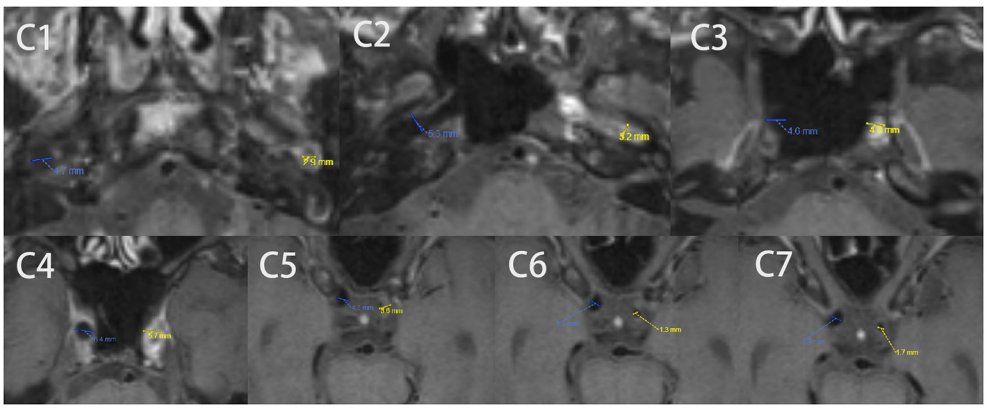

FIGURE 1 | A typical example of C1-C7 diameter measurements in the axial image by HRVWI of ICAO patients. High-resolution vessel wall magnetic resonance imaging (HRVWI) examination with contrast before the procedure. C0, common carotid artery; C1, cervical; C2, petrous; C3, lacerum; C4, cavernous; C5, clinoidal; C6, ophthalmic; and C7, communicating segment of internal carotid artery.

TABLE 1 | Clinical characteristics of patients.

	Success cases (*N* = 21)	Failure cases (*N* = 10)	Total (*N* = 31)	*p*-value
Male, %	20 (95.2)	6 (60.0)	26 (83.9)	0.027*
Age, years	61.57 ± 8.95	63.80 ± 10.56	62.81 ± 9.69	0.545
Hypertension, %	14 (63.6)	5 (50.0)	19 (61.3)	0.447
Diabetes, %	6 (27.3)	5 (50.0)	11 (35.4)	0.423
CAD, %	2 (9.1)	4 (40.0)	6 (19.4)	0.067
Hyperlipidemia, %	11 (50.0)	5 (50.0)	16 (51.6)	1.000
TC, mmol/L	3.11 ± 0.74	3.42 ± 0.79	3.21 ± 0.74	0.314
LDL, mmol/L	1.73 ± 0.56	1.84 ± 0.52	1.77 ± 0.53	0.613
HDL, mmol/L	0.91 ± 0.21	0.96 ± 0.25	0.93 ± 0.22	0.599
VLDL, mmol/L	0.50 ± 0.16	0.72 ± 0.32	0.56 ± 0.24	0.072
Triglyceride, mmol/L	1.20 ± 0.44	1.64 ± 1.00	1.34 ± 0.67	0.100
Homocysteine, μmol/L	12.58 ± 3.50	11.81 ± 2.06	12.52 ± 3.21	0.545
CRP, mg/L	3.90 ± 6.37	4.78 ± 6.13	4.04 ± 6.14	0.731
Smoking, %	8 (36.4)	2 (20.0)	10 (32.3)	0.677
Drinking, %	5 (27.3)	1 (10.0)	7 (22.6)	0.634
History of ICA stenting				0.106
Ipsilateral, %	0	1 (10.0)	1 (3.2)	
Contralateral, %	0	1 (10.0)	1 (3.2)	

*Values are mean ± SD or N (%). *p < 0.05; CAD, coronary artery disease; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very low density lipoprotein; CRP, C reactive protein.*

between HRVWI appearance and recanalization were assessed using Logistic regression. ROC curve was used to compare the predictive value HRVWI in recanalization surgery. The score-based prediction model was generated from the logistic regression equations by using a regression coefficient-based scoring method (10). A two-sided *p*-value of 0.05 was considered statistically significant.

RESULTS

A total of 31 patients were enrolled in the present study. The clinical characteristics of patients are summarized in **Table 1**. The male-to-female ratio is 5.2:1 (26 males: 5 females). The overall success rate of recanalization is 67.7% (21/31). Among the 31 patients, many cases had chronic comorbidities such as hypertension (59.3%), diabetes (34.4%), coronary artery disease (18.8%), and hyperlipidemia (50.0%). Meanwhile, 10 (31.3%) had a history of smoking and 7 (21.9%) have a history of drinking. Two of the 31 cases had a history of ICA stenting, one in the ipsilateral side and one in the contralateral side, and both of them failed in recanalization. No significant differences are found between the success and failure cases with regard to the comorbidities, history of smoking or drinking, and most of the biochemical indexes.

TABLE 2 | Clinical characteristics of lesions.

	Success cases (*N* = 21)	Failure cases (*N* = 10)	Total (*N* = 31)	*p*-value
Right side, %	12 (57.1)	8 (80.0)	20 (64.5)	0.214
Occlusion length				0.363
≥50 mm, %	16 (76.2)	9 (90.0)	25 (80.6)	
<50 mm, %	5 (23.8)	1 (10.0)	6 (19.4)	
Distal end of occluded segment				0.145
Proximal to C5, %	16 (76.2)	5 (50.0)	21 (67.7)	
Distal to or at C5, %	5 (23.8)	5 (50.0)	10 (32.3)	
Type of occlusion				0.704
Total occlusion, %	19 (90.5)	10 (100.0)	29 (93.5)	
Near-occlusion, %	2 (9.5)	0	2 (6.5)	
Treatment				0.067
Hybrid, %	12 (57.1)	9 (90.0)	21 (65.6)	
CEA, %	9 (42.9)	1 (10.0)	10 (31.3)	

Values are N (%). C3, lacerum segment; C4, cavernous segment; C5, clinoidal segment; CEA, carotid endarterectomy; ICA, internal carotid artery.

TABLE 3 | The I/C ratio and diameter of the occluded internal carotid artery.

	(Mean) I/C ratio			Diameter		
	Success (*N* = 22)	Failure (*N* = 10)	*p*-value	Success (*N* = 22)	Failure (*N* = 10)	*p*-value
Occlusive part	0.89 ± 0.06	0.77 ± 0.07	<0.001‡	/	/	/
Non-occlusive part	0.89 ± 0.08	0.72 ± 0.28	0.095	/	/	/
C1	0.93 ± 0.12	0.79 ± 0.15	0.009†	0.44 ± 0.10	0.43 ± 0.09	0.646
C2	0.93 ± 0.13	0.70 ± 0.16	<0.001‡	0.42 ± 0.09	0.36 ± 0.10	0.090
C3	0.88 ± 0.09	0.83 ± 0.10	0.177	0.39 ± 0.12	0.42 ± 0.09	0.516
C4	0.89 ± 0.10	0.82 ± 0.22	0.190	0.35 ± 0.10	0.36 ± 0.09	0.864
C5	0.87 ± 0.08	0.75 ± 0.28	0.236	0.28 ± 0.08	0.25 ± 0.07	0.303
C6	0.85 ± 0.12	0.68 ± 0.29	0.098	0.24 ± 0.06	0.20 ± 0.06	0.053
C7	0.93 ± 0.11	0.78 ± 0.34	0.188	0.23 ± 0.07	0.18 ± 0.05	0.032*
ACA	1.00 ± 0.63	1.02 ± 0.76	0.917	0.16 ± 0.05	0.17 ± 0.07	0.746
MCA	0.87 ± 0.34	0.82 ± 0.28	0.748	0.22 ± 0.04	0.21 ± 0.06	0.477

*Values are mean ± SD. *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$; I/C ratio, ipsilateral-to-contralateral diameter ratio; C1, cervical segment; C2, petrous segment; C3, lacerum segment; C4, cavernous segment; C5, clinoidal segment; C6, ophthalmic segment; C7, communicating segment; ACA, anterior cerebral artery; MCA, middle cerebral artery.*

The clinical characteristics of the lesions are summarized in **Table 2**. No significant differences are found between the success and failure cases in terms of occlusion length, the distal end of the occluded segment, and the treatment applied.

In all of the 31 cases, the lesions began at C1. Therefore, the occluded ICA could be separated into two parts, including the proximal occlusive part beginning at C1, and the distal non-occlusive part ending at C7. The mean ipsilateral-to-contralateral diameter ratios (I/C ratios) of each part is calculated as the geometric mean of the I/C ratio of each segment it contains. As **Table 3** showed, significant differences between groups are found in the I/C ratio of the occlusive part ($p < 0.001$), but not in that of the non-occlusive part distal to the lesion.

We also compared the diameter and the I/C ratio of each segment of ICA between cases that succeeded or failed in recanalization (**Table 3**). In C1 and C2 of the occluded ICA, significant differences are found in the I/C ratio ($p = 0.009$, $p < 0.001$). Meanwhile, a smaller diameter of C7 of the occluded ICA is significantly related to the failure of recanalization ($p = 0.032$).

ROC curves were plotted to evaluate the predictive value of the I/C ratios of C1 or C2, the diameter of C7, and certain combinations of the factors mentioned above (**Figure 2**). The results showed that the most efficient factor is the I/C ratio of C2 (AUC = 0.876, optimal cut-off = 0.86), while the I/C ratio of C1 and the diameter of C7 also bear moderately good efficiency (AUC = 0.779, optimal cut-off = 0.82; AUC = 0.729, optimal cut-off = 0.175). Among various combinations, the combination of data of C1, C2, and C7 show the highest efficiency (AUC = 0.971), closely followed by the combination of C2 and C7 (AUC = 0.952).

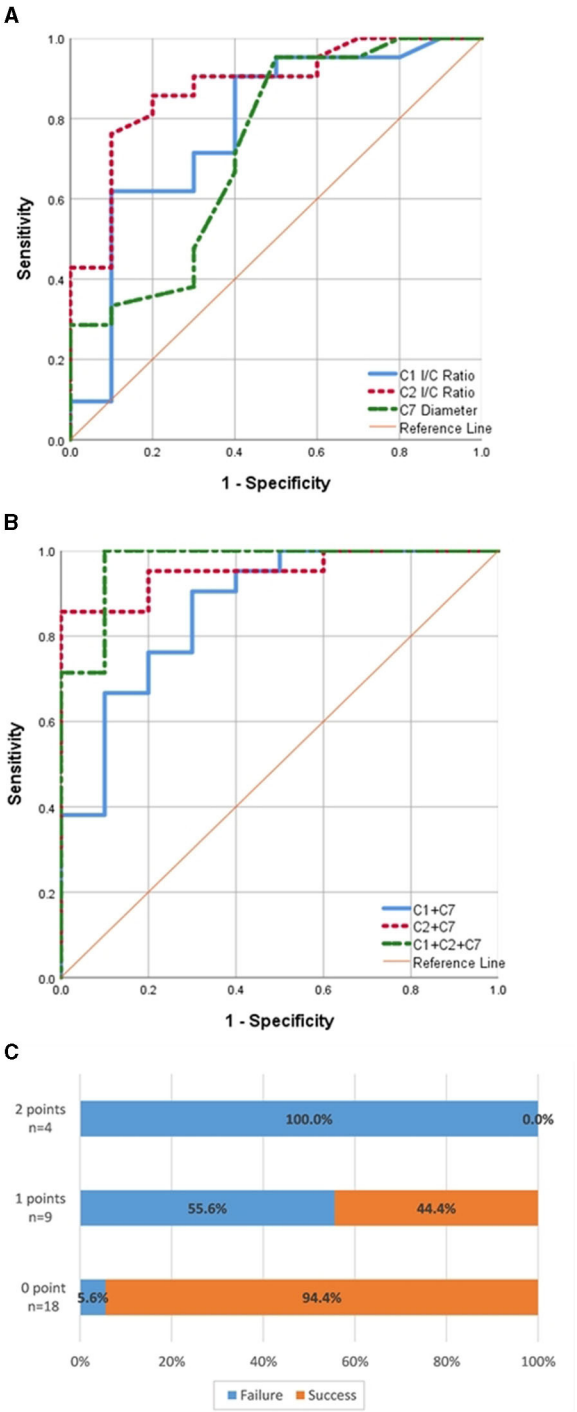

FIGURE 2 | (A) Receiver operating characteristic (ROC) curves to describe the performance of the I/C ratio of C1 or C2, the diameter of C7 in predicting the success of recanalization surgery. **(B)** ROC curves to describe the performance of the combination of the I/C ratio of C1 and the diameter of C7 (C1 + C7), the I/C ratio of C2 and the diameter of C7 (C2 + C7), the I/C ratio of C1 and C2 and the diameter of C7 (C1 + C2 + C7) in predicting the success of recanalization surgery. **(C)** Effects of the presence of 0–2 predictive factors associated with the failure or success of recanalization. y-Axis shows each group of patients scoring 0, 1, or 2 points and the actual number of patients is marked. x-Axis shows percentage of patients who failed or succeeded in recanalization in each group.

Considering strong collinearity between the data of C1 and C2 and the limited sample capacity, we omitted C1 and chose the data of C2 and C7 to construct a two-factor risk stratification model. In the multivariate analysis, the I/C ratio of C2 < 0.86 (OR = 19.814; 95% CI: 1.657–236.887) and diameter of C7 < 1.75 mm (OR = 42.720; 95% CI: 2.276–801.860) are both independently associated with recanalization failure. We assigned each variable 1 point as a risk score according to their β coefficient in logistic regression analysis (**Table 4**). The patients scored as 0, 1, or 2 points separately bear a failure risk of 5.6% (1/18), 55.6% (5/9), or 100% (4/4) (**Figure 2C**).

Within 2 weeks postoperatively, three male patients experienced TIA, among whom two succeeded in recanalization while one failed. No patients experienced death, stroke, hemorrhagic transformation, hyperperfusion syndrome, or other severe complications.

DISCUSSION

Optimal managements for internal carotid artery occlusion continue to be debated. Recent clinical trials showed that endovascular treatment could make a noticeable difference in the natural outcomes of patients with ICAO (11), including carotid endarterectomy (CEA) and carotid artery stenting (12–15). However, endovascular recanalization of ICAO is technically challenging. The visual clues for wiring across the occlusion, such as bridging collateral or distal artery reconstitution, are often lacking, and the potential complications after failing to wire through the right course, including hemorrhage, pseudoaneurysm, and carotid-cavernous fistula, could lead to severe consequences. Therefore, a predictive model is important to identify patients that carry higher success rates and are more suitable for the surgery.

In the present study, we found that the mean ipsilateral-to-contralateral diameter ratio (I/C ratio) of the proximal occlusive part of ICA, which might reflect its degree of atrophy, is significantly associated to the result of recanalization surgery. However, this is not the case when it comes to the mean I/C ratio of the distal non-occlusive part of ICA. The probable reason is that the perfusion from collateral circulation, which typically involves Willis circle or ophthalmic artery, etc. (16), protects the distal ICA segments against further atrophy.

We further analyzed the data of each single segment and found that the I/C ratios of C1 and C2 are positively related to recanalization procedure. According to previous studies, longer occlusion duration has a negative impact on the success rate of recanalization (5, 17). However, since clinical symptoms might not appear synchronically with the onset of ICAO, and there is hardly any image of ICAO obtained as evidence before clinical diagnosis, it is very difficult to determine the exact occlusion duration. The majority of ICAO cases are caused by atherosclerosis, especially in old patients (17, 18). As the occlusion duration gets longer, the thrombus gradually becomes fibrotic or calcified, and the occluded segments of ICA undergoes atrophy. In this case, the difficulty of wiring through the lesion will increase, so will the risk for development of

TABLE 4 | ICAO score and success rate of recanalization surgery.

	OR	95% CI	β coefficient	Point assigned	p-value
C2 I/C ratio < 0.86	19.8	1.7–236.9	2.986	1	0.018*
C7 diameter < 0.175	42.7	2.3–801.9	3.755	1	0.012*

**p < 0.05; OR, odds ratio; CI, confidential interval; C2, petrous segment; C7, communicating segment; I/C Ratio, ipsilateral-to-contralateral diameter ratio; ICAO, internal carotid artery occlusion.*

potential complications, e.g., arterial dissection (19, 20). The atherosclerotic lesion typically develops from C1 (5), which marks the bifurcation of the common carotid artery. The plaque forms under low shear stress and slow blood flow here, then gradually extends toward the distal of ICA (21, 22). Given the facts above, we assumed that C1 and C2 segments are usually affected in the early stage of ICAO and the ipsilateral-to-contralateral diameter ratios of C1 and C2 reflect the atrophy degree of the affected segments and, therefore, indirectly indicate the occlusion duration of ICA and influence the success rate of recanalization.

However, the difference could not be detected between success and failure cases in the case of diameters of C1 and C2 ($p = 0.687$; $p = 0.098$). Liu et al. (23) also reported that the proximal occlusion diameter did not show any impact on the success rate of recanalization by CEA. The probable reason for it might be that the individual differences in vascular diameters masked the degree of atrophy.

On the other hand, our study demonstrated that the diameter of C7 is also positively related to the success rate of recanalization surgery. Similar results are reported by Liu et al. (23), that no success of recanalization by CEA was achieved in ICAO cases with a distal occlusion diameter of ICA < 3 mm. We assumed that the diameter of the distal end of ICA might reflect perfusion pressure and the quality of collateral circulation. In most chronic ICAO patients, cerebral vascular collateral circulation can be established due to chronic hypoperfusion caused by arterial flow restrictions (16). With contrast injection from collateral pathways, a better vision of the distal ICA could be obtained, which provides clues of "road-map" in guidewire directing.

Based on the data we obtained, we constructed a two-factor model to predict the success of recanalization surgery, involving the I/C ratio of C2 and the diameter of C7, which separately reflect ICAO features in different aspects discussed above. In the 31 cases we have studied, the present model achieved a great efficiency in risk stratifying. Patients who got 2 points in this scoring system achieved no success in recanalization surgery (0/4), while most of the patients who got 0 point achieved successful recanalization (17/18).

Limitations of our research are evident. First, our sample capacity was relatively small, which merely reached the least requirement for logistic regression analysis. The formula we deduced to predict the success rate of recanalization should be further validated or revised in the future study of a larger group of ICAO cases. Second, this is a retrospective study and we only collected the data of the ICAO patients with available HRVMI results, which might cause selection bias.

In conclusion, to the best of our knowledge, this was the first study to clarify the association between the success rate of recanalization surgery and the vascular diameter data of ICA in ICAO patients. The predictive model we constructed can provide useful information in discriminating the population suitable for recanalization surgery.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Peking University International Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CY: original idea and data collection. RG and JW: data analysis and article writing. WJ and YZ: data collection. RW: article revision. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.632063/full#supplementary-material

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MINI REVIEW
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Non-stenotic Carotid Plaques in Embolic Stroke of Unknown Source

Joseph Kamtchum-Tatuene[1], Ali Z. Nomani[2], Sarina Falcione[2], Danielle Munsterman[2], Gina Sykes[2], Twinkle Joy[2], Elena Spronk[2], Maria Isabel Vargas[3] and Glen C. Jickling[2]*

[1] Faculty of Medicine and Dentistry, Neuroscience and Mental Health Institute, University of Alberta, Edmonton, AB, Canada, [2] Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada, [3] Division of Neuroradiology, Department of Radiology and Medical Imaging, Geneva University Hospital, Geneva, Switzerland

Embolic stroke of unknown source (ESUS) represents one in five ischemic strokes. Ipsilateral non-stenotic carotid plaques are identified in 40% of all ESUS. In this narrative review, we summarize the evidence supporting the potential causal relationship between ESUS and non-stenotic carotid plaques; discuss the remaining challenges in establishing the causal link between non-stenotic plaques and ESUS and describe biomarkers of potential interest for future research. In support of the causal relationship between ESUS and non-stenotic carotid plaques, studies have shown that plaques with high-risk features are five times more prevalent in the ipsilateral vs. the contralateral carotid and there is a lower incidence of atrial fibrillation during follow-up in patients with ipsilateral non-stenotic carotid plaques. However, non-stenotic carotid plaques with or without high-risk features often coexist with other potential etiologies of stroke, notably atrial fibrillation (8.5%), intracranial atherosclerosis (8.4%), patent foramen ovale (5–9%), and atrial cardiopathy (2.4%). Such puzzling clinical associations make it challenging to confirm the causal link between non-stenotic plaques and ESUS. There are several ongoing studies exploring whether select protein and RNA biomarkers of plaque progression or vulnerability could facilitate the reclassification of some ESUS as large vessel strokes or help to optimize secondary prevention strategies.

Keywords: stroke, carotid stenosis, carotid plaque, biomarkers, atherosclerosis

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****Correspondence:***
Joseph Kamtchum-Tatuene
kamtchum@ualberta.ca

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INTRODUCTION

Ischemic stroke is considered cryptogenic when no definite cause is identified during the baseline etiological workup (1). According to the Cryptogenic Stroke/Embolic Stroke of Undetermined Source International Working Group, the baseline etiological workup should include brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI), assessment of the heart rhythm with 12-lead ECG and continuous cardiac monitoring for at least 24 h with automated rhythm detection, transthoracic cardiac ultrasound, and imaging of cervical and intracranial vessels supplying the infarcted brain region (using CT, MRI, conventional angiography, or ultrasonography) (2).

Cryptogenic strokes represent ∼30% of all ischemic strokes. They could be further classified into three subgroups: stroke with no cause despite complete baseline workup, stroke with multiple possible underlying causes, and stroke with incomplete baseline workup (3). In the subgroup of cryptogenic strokes with complete workup, embolic stroke of unknown source (ESUS) is a clinical construct referring to non-lacunar ischemic strokes (size >1.5 cm on CT or >2.0 cm on diffusion MRI) of presumable embolic origin (superficial/cortical brain lesion) despite the absence of any obvious sources of cardiac or arterial embolism (e.g., atrial fibrillation, carotid, or intracranial stenosis > 50%) (**Figure 1**) (2). ESUS represent ∼17% of all ischemic strokes with a recurrent stroke rate of 4.5% per year despite antithrombotic therapy (4–6).

The definition of ESUS was based on the assumptions that cryptogenic strokes may be related to covert atrial fibrillation and that a relationship between non-stenotic atherosclerotic plaques (causing <50% stenosis) and stroke was unlikely. However, there is now evidence to suggest that ESUS represents a heterogeneous group including patients with various other potential causes of stroke besides atrial fibrillation (7–9). Such causes include atrial cardiopathy (10), patent foramen ovale (PFO) (11), cancer (12), and non-stenotic plaques affecting the aortic arch or carotid, vertebral, or intracranial arteries (7, 13, 14). Atrial cardiopathy is a concept referring to a dysfunction of the left atrium that is thought to favor and precede the onset of atrial fibrillation and its eventual detection by electrocardiographic devices. The diagnosis is based on the identification of imaging markers (e.g., left atrial enlargement, spontaneous echocontrast in the left atrium or the left atrial appendage, atrial fibrosis with delayed gadolinium enhancement on MRI), electrocardiographic markers (e.g., paroxysmal supraventricular tachycardia, increased P-wave terminal force in V1, interatrial block, prolonged PR), and blood biomarkers (e.g., N-terminal pro-brain natriuretic peptide, highly sensitive cardiac troponin T) (10).

Non-stenotic carotid plaques are found in 40% of patients with ESUS and 10–15% of patients with ESUS have mild stenosis (20–49%) (2, 15–17). Here we review the evidence supporting the relationship between non-stenotic carotid plaques with high-risk features and stroke in patients with ESUS. We present the remaining challenges in the process of formally establishing the causal link between non-stenotic plaques and ESUS, notably those related to the identification of blood biomarkers of vulnerable plaque. Finally, we discuss the management of non-stenotic carotid plaques in patients with ESUS and highlight areas for future research.

NON-STENOTIC CAROTID PLAQUES AS A POTENTIAL CAUSE OF ESUS

The relationship between non-stenotic carotid plaques and ESUS is supported by a set of three clinical observations.

First, in patients with ESUS, carotid plaques are more prevalent on the side of the stroke than on the contralateral side. In a cross-sectional study of 85 patients with ESUS, non-stenotic carotid plaques thicker than 3 mm were present in 35% of ipsilateral carotid arteries vs. 15% of the contralateral carotid arteries (18). A similar finding was observed in a review of 138 ESUS cases from the prospective multicenter INTERRSeCT study (The Predicting Early Recanalization and Reperfusion With IV Alteplase and Other Treatments Using Serial CT Angiography). The investigators found a non-stenotic carotid plaque ipsilateral to the stroke in 29.2% of patients and contralateral to the stroke in 18.7% (17).

Second, in patients with ESUS, there is a lower incidence of atrial fibrillation detected during follow-up in patients with ipsilateral non-stenotic carotid plaques than in those without, thus suggesting that non-stenotic carotid plaques may be related to the stroke. In 777 participants of the New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial vs. ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE-ESUS) trial who were followed up for a median of 2 years, the incidence of atrial fibrillation was 2.9 per 100 person-years in patients with ipsilateral non-stenotic carotid plaques vs. 5.0 per 100 person-years in those without (overall rate: 8.5 vs. 19.0%; adjusted hazard ratio: 0.57, 95% CI 0.37–0.84) (15).

Third, plaques with high-risk features are more prevalent on the side of the stroke in patients with ESUS. In a meta-analysis of 8 studies enrolling 323 patients with ESUS, plaques with high-risk features were present in 32.5% of the ipsilateral carotid arteries vs. 4.6% of the contralateral carotid arteries. More specifically, the odds of finding a non-stenotic carotid plaque with a ruptured fibrous cap in the ipsilateral vs. the contralateral carotid artery was 17.5, reinforcing the idea that non-stenotic carotid plaques should not be considered as benign coincidental findings in patients with ESUS (13).

High-risk plaques have features on brain or vascular imaging that are associated with a higher risk of stroke in patients with either symptomatic or asymptomatic carotid atherosclerosis, independent of the grade of stenosis (19–24). The most common high-risk plaque features are echolucency, impaired cerebrovascular reserve, intraplaque hemorrhage (**Figure 1**), silent brain infarcts, lipid-rich necrotic core, large juxtaluminal black hypoechoic area, large plaque volume, plaque thickness, microembolic signals, mural thrombus, neovascularization, plaque irregularity, plaque inflammation or hypermetabolism, thin or ruptured fibrous cap, and ulceration (19, 21, 25–31). The American Heart Association combines some of these features to derive a classification of atherosclerotic plaques into 6 types reflecting increasing instability and risk of cardiovascular events (**Table 1**) (32–37). On average, high-risk plaque features are three times more prevalent in patients with symptomatic vs. asymptomatic carotid stenosis (OR = 3.4, 95% CI: 2.5–4.6) (19). They are detected using various vascular imaging modalities (**Table 2**). To date, there are no data on the risk of recurrent stroke associated with each of the high-risk features in patients with ESUS. Analysis of secondary outcome data from the Carotid Plaque Imaging in Acute Stroke study (CAPIAS; NCT01284933) might help to address this knowledge gap (35, 39).

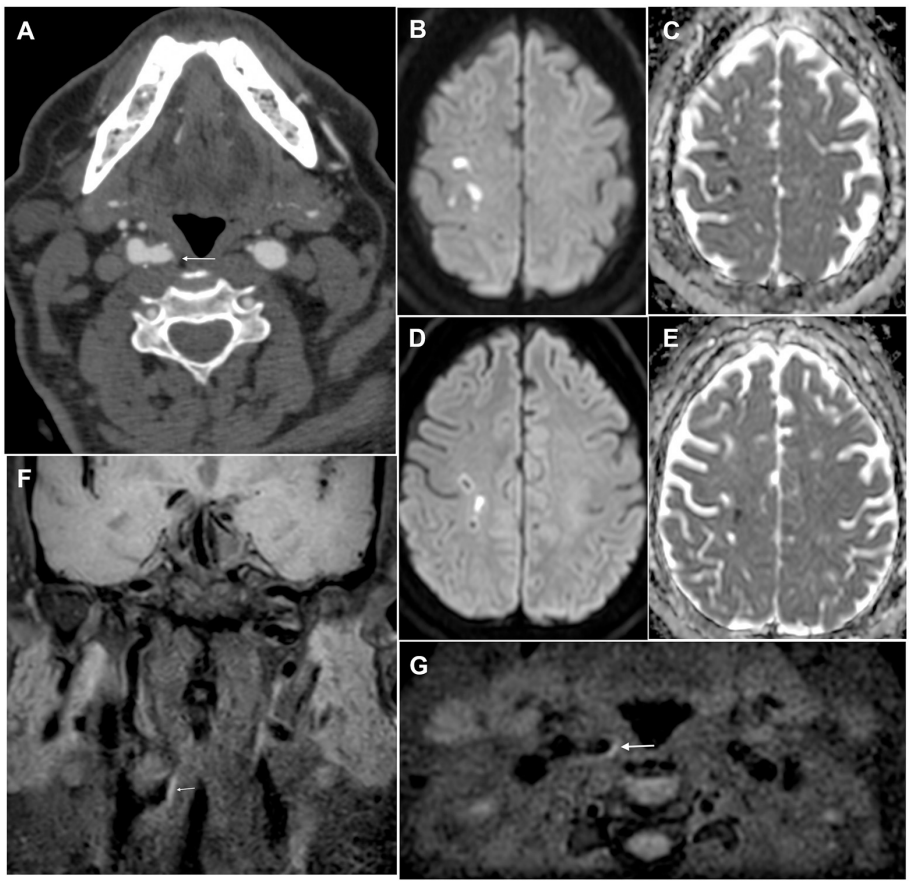

FIGURE 1 | Brain and plaque imaging findings in a 64-year-old man with ESUS. **(A)** Axial angio-CT scan slice showing a hypodense non-stenotic carotid plaque in the right internal carotid artery (white arrow). **(B–E)** Axial diffusion-weighted imaging slices (with corresponding ADC maps) showing multiple embolic strokes in the right pre-and post-central area. **(F,G)** Coronal and axial T1-weighted black blood sequence showing hyperintensity of the non-stenotic plaque in the right internal carotid artery (white arrow), thus confirming the presence of intraplaque hemorrhage.

CHALLENGES OF ESTABLISHING CAUSAL LINK WITH STROKE

Puzzling Clinical Associations

Although studies of high-risk features have provided evidence of an association between non-stenotic carotid plaques and brain infarction in patients with ESUS, establishing causality remains challenging in most cases. The dilemma rests on four clinical observations. First, high-risk features are often found in plaques in the absence of related clinical symptoms (19, 40). In a meta-analysis of eight studies enrolling 323 patients with ESUS, a non-stenotic carotid plaque with high-risk features was identified in the contralateral carotid artery in 4.6% of cases (95% CI: 0.1–13.1) (13). Likewise, in a meta-analysis of 64 studies enrolling 20,571 patients with asymptomatic carotid stenosis of various grades, 26.5% of patients were found to have at least one high-risk plaque feature (95% CI: 22.9–30.3). The highest prevalence was observed for neovascularization (43.4%, 95% CI: 31.4–55.8) and the lowest for mural thrombus (7.3%, 95% CI: 2.5–19.4). On average, intraplaque hemorrhage was found in 1 out of 5 patients (19). Second, high-risk plaque features are not specific for symptomatic carotid plaques. In a meta-analysis of data from 20 prospective studies enrolling 1,652 patients with symptomatic carotid stenosis, high-risk plaque features were identified in <1 in 2 patients (43.3%, 95% CI: 33.6–53.2) (19). Third, in patients with stroke, there is an association between the presence of high-risk plaque features and atrial fibrillation. In a study of 68 patients with embolic stroke, including 45 ESUS, the presence of high-risk plaque features on carotid ultrasound (ulceration, thickness $\geq$ 3 mm, and echolucency) was independently associated with detection of atrial fibrillation on admission or during follow-up (OR = 4.5, 95% CI: 1.0–19.6) (41). Fourth, in some patients with ESUS diagnosed using the current clinical definition, non-stenotic carotid plaques often coexist with other potential causes of stroke, including atrial fibrillation (8.5%) (15), intracranial atherosclerosis (8.4%) (42), PFO (5–9%) (43, 44), and atrial cardiopathy (2.4%) (45).

Lack of Reliable Biomarkers

The identification of an ipsilateral non-stenotic carotid plaque with or without high-risk features is not sufficient to reclassify ESUS as stroke due to large vessel disease. Further research is,

TABLE 1 | American Heart Association comprehensive morphological classification scheme for atherosclerotic lesions (32–34).

Plaque type	Description							
		Lipid rich necrotic core	**Fibrous cap**	**Calcification**	**Erosion/rupture**	**Intraplaque hemorrhage**	**Thrombus**	**Regression to normal**
Type I (Initial lesion)	Initial lesion, accumulation of smooth muscle cells and isolated foam cells, absence of a necrotic core.	Absent	Absent	Absent	Absent	Absent	Absent	Possible
Type II (Intimal xanthoma)	Multiple layers of foam cells, previously referred to as "fatty streak"	Absent	Absent	Absent	Absent	Absent	Absent	Possible
Type III (pre-atheroma)	Smooth muscle cells in a proteoglycan-rich extracellular matrix, multiple layers of foam cells, non-confluent extracellular lipid pools	Absent	Present (ill-defined)	Absent	Absent	Absent	Absent	Possible
Type IV (atheroma)	Confluent extracellular lipids	Present (well-formed)	Present (well-defined)	Absent	Absent	Absent	Absent	Not possible
Type Va (Fibroatheroma)	Confluent extracellular lipids with prominent proliferative fibromuscular layer	Present (well-formed)	Present (thick)	Possible[a]	Absent	Absent	Absent	Not possible
Type VI (Complicated atheroma)[b]	Inflammatory lesion with at least one high-risk feature	Present (large)	Present (thin or eroded)	Possible (partial calcification)	Possible (VIa if present alone)	Possible (VIb if present alone)	Possible (VIc if present alone)	Not possible

[a] *The plaque is assigned category Vb if predominantly calcified (fibro-calcific) or category Vc if predominantly fibrous (collagen-rich atheroma with smaller lipid core).*

[b] *The plaque is assigned category VIabc if erosion/ulceration, intraplaque hemorrhage and luminal thrombus are present concurrently.*

TABLE 2 | High-risk plaque features commonly used in clinical practice (13, 21, 25–31).

High-risk plaque features[a]	Imaging modality of choice	Description[b]	Alternative imaging modalities	Prevalence (%)in patients with ESUS
AHA type IV, V, VI (35–37)	MRI	Plaque with large lipid-rich necrotic core (>40% of the vessel circumference), ruptured fibrous cap, mural thrombus, or intraplaque hemorrhage (see below).	CT, US	In three studies including 82 patients with ESUS, an AHA plaque type IV-VI was found in the ipsilateral carotid in 38% of cases on average (35–37).
Echolucency	US	Hypoechoic area within the plaque on B-mode (reference = sternocleidomastoid muscle)	Not applicable	In a study of 44 patients with ESUS, an ipsilateral echolucent non-stenotic carotid plaque was found in 50.0% (38)
Impaired cerebrovascular reserve	TCD	<10% increase of blood flow in the ipsilateral MCA while breathing 5% CO_2 for 2 min.	BOLD-MRI	Not applicable for non-stenotic plaques
Intraplaque hemorrhage	MRI	Intraplaque hyperintensity on T1W FAT SAT (black blood) and 3D-TOF	MRI	In five studies including 162 patients, intraplaque hemorrhage was found in the ipsilateral carotid in 24.4% of cases (13).
Ipsilateral silent brain infarcts	MRI	Non-lacunar hyperintensity of the brain parenchyma, in the territory of the internal carotid artery, visible on T2W and FLAIR, or DWI (if acute)	CT (would appear as a hypodensity)	No data available for patients with ESUS
Lipid-rich necrotic core	MRI	Collection of foam cells, cholesterol crystals and apoptotic cells that appears iso/hyper-intense on T1W and iso/hypo-intense on T2W.	CT, US (although it is difficult to make the difference with intraplaque hemorrhage on these modalities)	No data available for patients with ESUS
Microembolic signals	TCD	Random audible transient increase (variable threshold) of the Doppler signal within the monitored arterial blood flow, generating a high-intensity signal on the doppler imaging (PWV and M-Mode), visible and moving in the direction of the flow. Duration of recording ≥1 h.[c]	Not applicable	No data available for patients with ESUS
Mural thrombus	MRI	Filling defect on contrast MRI, hyperintense signal adjacent to the lumen on T1W	CT, US	In three studies enrolling 94 patients with ESUS, plaque thrombus was identified in the ipsilateral carotid in 6.9% of cases (13).
Neovascularization	CEUS	Enhancement of the plaque on pulse inversion harmonic imaging (microbubbles carried into the plaque by the blood entering the neovessels)	DCE-MRI	No data available for patients with ESUS
Plaque irregularity	MRI	0.3–0.9 mm fluctuations of the surface of the plaque	CT, CEUS	No data available for patients with ESUS
Thin/ruptured fibrous cap	MRI	Disrupted or invisible dark band adjacent to the lumen on 3D-TOF	CEUS	In two studies enrolling 50 patients with ESUS, a thin or ruptured fibrous cap was found in the ipsilateral carotid in 23.6% of cases (13).
Ulceration	MRI	Depression > 1 mm on the surface of the plaque	CTA, CEUS (the threshold is 2 mm in ultrasound studies)	No data available for patients with ESUS

[a] *The following high-risk features are used less often: juxta-luminal black hypoechoic area and plaque volume assessed by ultrasound, plaque inflammation measured by standardized (18) F-FDG uptake on positron emission tomography-computed tomography, carotid temperature assessed by microwave radiometry.*

[b] *For simplicity, the description of each high-risk feature is based on its appearance on the imaging modality of choice.*

[c] *The sound threshold and the number of MES for a positive examination is variable across studies.*

AHA, American Heart Association; BOLD, blood oxygen level-dependent; CEUS, contrast-enhanced ultrasound; CI, confidence interval; CT, computed tomography; DCE, dynamic contrast-enhanced; ESUS, embolic stroke of undetermined source; FLAIR, fluid-attenuated inversion recovery; MCA, middle cerebral artery; MRI, Magnetic Resonance Imaging; T1W, T1-weighted imaging; T2W, T2-weighted imaging; TCD, transcranial Doppler ultrasound; and 3D-TOF, 3-dimensional time of flight.

therefore, needed to determine whether combination of vascular imaging findings, clinical data, and candidate biomarkers of plaque progression/instability or atheroembolism (46–82) into multiparameter scores could improve the ability to (1) establish a causal link between ESUS and a non-stenotic carotid plaque, (2) predict plaque progression or stroke recurrence, and (3) select

patients who might benefit from adjuvant anti-inflammatory and lipid-lowering therapies as briefly discussed in the next section. Some biomarkers of plaque progression and instability that warrant further investigation specifically in patients with ESUS are presented in **Table 3**. There are several ongoing projects exploring biomarkers in patients with ESUS or cryptogenic stroke, notably the Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome study (SECRETO, NCT01934725) (95), the Carotid Plaque Imaging in Acute Stroke study (CAPIAS, NCT01284933) (35), and the Biomarkers of Acute Stroke Etiology study (BASE, NCT02014896) (96). Efforts to establish a causal relationship between non-stenotic carotid stenosis and ESUS using biomarkers and multimodal vascular imaging in well-phenotyped prospective cohorts will also benefit from research aiming to identify alternative causes of stroke in patients with ESUS (14, 68, 97–104).

CHALLENGES OF SECONDARY STROKE PREVENTION

As a result of the challenges to determine the root cause of an ESUS, the optimal treatment strategy for patients with ESUS remains unclear, and a tailored approach would likely be the most appropriate (9). In this section, we briefly describe the strategies that have been explored so far and discuss possible future directions.

Dual Antiplatelet Therapy and Antiplatelet Switch

Following the results of the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) (105) and the Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) (106) trials, patients with ESUS are treated with Aspirin-based dual antiplatelet therapy for 21 days provided that their baseline NIHSS is low. After 3 weeks, patients ideally return to single antiplatelet therapy and switching from Aspirin to Clopidogrel is considered in patients who had an ESUS while on Aspirin (107). A meta-analysis of data from CHANCE and POINT showed that extending the treatment beyond 3 weeks might increase the bleeding risk without additional benefit for secondary stroke prevention (108). Whether the presence of ipsilateral non-stenotic carotid plaque with or without high-risk features would modify the magnitude (absolute risk reduction) and duration (beyond 21 days) of the benefits derived from dual antiplatelet therapy in patients with ESUS remains unknown. In patients allergic to Clopidogrel and in carriers of a CYP2C19 loss of function allele, Ticagrelor might be an alternative according to findings of the Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA [acetylsalicylic acid] for Prevention of Stroke and Death (THALES) trial (109–112). The ongoing Clopidogrel with Aspirin in High-risk patients with Acute Non-disabling Cerebrovascular Events II (CHANCE-2, NCT04078737) trial is evaluating the superiority of the Ticagrelor-Aspirin combination over Clopidogrel-Aspirin therapy in CYP2C19 loss of function carriers with minor stroke or transient ischemic attack (TIA) (113). There is currently no evidence supporting the use of dual antiplatelet therapies not containing Aspirin or triple antiplatelet therapies (with or without Aspirin) for secondary stroke prevention in patients with acute stroke or TIA (114).

Anticoagulation

The New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial vs. ASA [Acetylsalicylic Acid] to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE-ESUS) and the Randomized Double-Blind Evaluation in Secondary Stroke Prevention Comparing The Efficacy Of Oral Thrombin Inhibitor Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source (RE-SPECT-ESUS) trials have shown that universal full-dose oral anticoagulation is not an effective strategy to reduce the risk of stroke recurrence in patients with ESUS (5, 6). These results are likely explained by the heterogeneity of stroke mechanisms in patients with ESUS as discussed earlier, with atrial fibrillation being diagnosed in only 24.8% of cases at 24 months using insertable cardiac monitors (115). Moreover, there is no evidence that patients with ESUS and ipsilateral non-stenotic carotid plaques should be treated differently than those without plaques. In a subgroup analysis of data from 2,905 patients with non-stenotic carotid plaques enrolled in the NAVIGATE-ESUS trial, there was no difference between Rivaroxaban and Aspirin with respect to the prevention of ipsilateral ischemic stroke [Hazard ratio [HR] = 0.6, 95% CI: 0.2–1.9]. Major bleeding complications were significantly more frequent in patients taking anticoagulation (HR = 3.7, 95% CI: 1.6–8.7) (16).

In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, the combination Rivaroxaban-Aspirin (2.5 mg twice daily plus Aspirin 100 mg once per day) was superior to Aspirin alone (100 mg once daily) for the prevention of cardioembolic strokes (HR = 0.4, 95% CI: 0.2–0.8) and ESUS (HR = 0.3, 95% CI: 0.1–0.7) but there was no effect on the incidence of stroke due to moderate-to-severe carotid stenosis (HR = 0.9, 95% CI: 0.5–1.6) (116). Although these results suggest that the combination of Aspirin and low-dose Rivaroxaban could be an effective secondary stroke prevention strategy, they are not directly applicable to patients with ESUS since all patients with acute stroke (<1 month) were excluded from the trial due to the perceived higher risk of major intracranial bleeding (117). Furthermore, the baseline proportion of patients with non-stenotic carotid plaque, with or without high-risk features, was not reported. The prevalence of ipsilateral non-stenotic carotid plaque in participants diagnosed with ESUS during follow-up was also not reported.

According to currently available data, patients with ESUS and features of atrial cardiopathy, notably atrial enlargement, constitute the only subgroup that may benefit from anticoagulation (118). However, since these results are derived from a *post-hoc* analysis of the NAVIGATE-ESUS trial, they might not be used to justify universal prescription of anticoagulation until confirmation is obtained in dedicated trials. The ongoing Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke (ARCADIA,

TABLE 3 | Biomarkers of potential interest for the study of non-stenotic carotid plaques in ESUS.

Biomarker	Type	Main source	Key evidence	Specific target of a drug previously tested in human trials	References
Lectin-like oxidized LDL receptor 1 (LOX-1)	Protein	Endothelial cells, smooth muscle cells, fibroblasts	In 4,703 participants from the Malmo Diet and Cancer Cohort, higher plasma levels of soluble LOX-1 were associated with higher risk of stroke during a mean follow-up of 16.5 years (HR = 1.5, 95% CI: 1.3–2.4). In 202 patients undergoing carotid endarterectomy, plasma levels of soluble LOX-1 were correlated with the plaque content of oxidized LDL, proinflammatory cytokines, and matrix metalloproteinases.	No	(46–49, 59, 75)
Omentin-1	Protein	Visceral adipose tissue, stromal vascular cells, lung, heart, placenta, ovaries	In 173 patients with acute ischemic stroke, serum levels of omentin-1 were lower in subjects with unstable plaque (n= 38, echolucent, thin fibrous cap, ulcerated) than in those with stable plaques (median of 53 vs. 62 ng/mL).	No	(69)
Lipoprotein-associated phospholipase A2 (Lp-PLA2)	Protein	Monocytes, macrophages, T lymphocytes, and mast cells	In 1,946 participants of the Northern Manhattan study, there was a dose-response relationship between Lp-PLA2 mass and the risk of first-ever stroke due to large vessel atherosclerosis (HR = 1.4, 4.5, and 5.1 for quartiles 2, 3, and 4 compared with quartile 1 in multivariable survival analysis).	Yes (Darapladib)	(52, 53, 83)
Chitinase-3-like-1 (YKL-40)	Protein	Inflammatory cells	In 1,132 patients with carotid atherosclerotic plaques of various grades, higher levels of YKL-40 were associated with plaque instability (n = 855, echolucency) after adjusting for various demographic and cardiovascular risk factors (OR = 2.1 and 1.7 for quartiles 3 and 4, respectively).	No	(56, 59)
Granzyme B	Protein	T lymphocytes	In 67 patients with severe carotid stenosis undergoing revascularization, higher plasma levels of granzyme B were found in patients with unstable plaques (n = 16, echolucent) than in those with stable plaques (median of 492.0 vs. 143.8 pg/mL)	No	(57)
Vimentin	Protein	Endothelial cells, macrophages, and astrocytes	In 4,514 patients with carotid plaques in the Malmo Diet and Cancer Cohort, higher plasma levels of vimentin at baseline were associated with the incidence of ischemic stroke after a mean follow-up of 22 years (HR = 1.66, 95% CI: 1.23–2.25).	Yes (Withaferin-A)	(65, 84)
Macrophage chemoattractant protein (MCP-1/CCL2)	Protein	Monocytes	In the Athero-EXPRESS biobank, higher plaque levels of MCP-1 levels were found in symptomatic (vs. asymptomatic) plaques and in vulnerable (vs. stable) plaques.	No	(61)
Matrix metalloproteinase 9 (MMP9)	Protein	Macrophages, foam cells	Serum levels of MMP9 were higher in large artery atherosclerosis strokes (n = 26, 1,137 ng/mL) vs. cardioembolic strokes (n = 86, 517 ng/mL). MMP9 >1,110 ng/mL had 85% sensitivity and 52% specificity for differentiating large vessel from cardioembolic strokes.	No	(59, 66)
Complement 5b-9	Protein	Liver	In 70 patients with acute ischemic stroke, serum C5b-9 levels were higher in patients with unstable plaques (n = 37) than in those with stable plaques (median of 875 vs. 786 ng/mL). There was also a positive correlation with plaque burden and grade of stenosis.	Yes (Eculizumab)	(76, 85)
Interleukin 1β (IL-1β)	Protein	Monocytes, macrophages	A higher expression of IL-1β and other components of the NLRP3 inflammasome was observed in 30 plaques when compared with 10 healthy mesenteric arteries, both at the protein and the mRNA level.	Yes (Anakinra, Rilonacept, Canakinumab)	(77, 86–88)
Interleukin 6 (IL-6)	Protein	Monocytes, macrophages	In a sub-analysis of data from 703 participants of the population-based Tromsø study, higher plasma levels of IL-6 were independently associated with plaque progression after a 6-year follow-up (OR 1.4, 95% CI 1.1–1.8 per 1 SD increase in IL-6 level).	Yes (Ziltivekimab, Tocilizumab)	(71–74)

(Continued)

TABLE 3 | Continued

Biomarker	Type	Main source	Key evidence	Specific target of a drug previously tested in human trials	References
C-Reactive Protein (CRP)	Protein	Hepatocytes, white blood cells, adipocytes, smooth muscle cells	In a prospective observational study enrolling 271 participants, higher levels of CRP (quartile 4 vs. 1) were associated with plaque progression after a follow-up of 37 months (OR = 1.8, 95% CI: 1.03–2.99).	No	(78, 89)
CD36	Protein	Various cells including monocytes, endothelial cells, adipocytes, platelets.	In 62 patients with severe carotid stenosis undergoing revascularization, plasma levels of soluble CD36 were higher in those with symptomatic ($n = 31$) and unstable (echolucent, $n = 20$) plaques.	No	(60)
Lipoprotein (a)	Lipoprotein	Food/Liver	In 876 consecutive patients with carotid atherosclerosis (2.5% occlusions), plasma lipoprotein (a) was an independent predictor of carotid occlusion (OR=1.7, 95% CI: 1.2–2.3 per 1 SD increase), suggesting that it plays a role in plaque destabilization/rupture, thrombosis, and impaired fibrinolysis. In 225 patients with coronary artery disease who underwent intra-coronary optical coherence tomography imaging of culprit plaque, the prevalence of thin fibrous cap atheroma was significantly higher in the group with higher serum lipoprotein (a) levels (>25 mg/dL, n=87): 23 vs. 11%.	Yes (AKCEA-Apo(a)-LRx)	(79–81, 90, 91)
Non-HDL cholesterol	Lipoproteins	Food/Liver	In 2,888 patients with carotid plaque, including 1,505 with vulnerable plaques (echolucent, irregular, or ulcerated), higher serum levels of non-HDL cholesterol were independently associated with plaque vulnerability (OR = 1.5 for tertile 3 vs. 1, 95% CI: 1.2–1.8).	Yes (various class of lipid lowering drugs)	(51, 92, 93)
Uric acid	Xanthine (purine derivatives)	Various cells	In a study including 88 patients with carotid plaques (44 symptomatic), serum uric acid levels were significantly higher in patients with symptomatic plaques (7.4 vs. 5.4 mg/dL) who also had higher plaque expression of xanthine oxidase as assessed by immunohistochemistry.	Yes (allopurinol)	(82)
Neutrophil count	Cells	NA	In 60 patients with recently symptomatic carotid artery disease, higher neutrophil count (>5,900/μL) was associated with detection of microembolic signals on transcranial Doppler monitoring.	No	(58)
miR-199b-3p, miR-27b-3p, miR-130a-3p, miR- 221-3p, and miR-24-3p	RNA	Various cells	In 60 patients with moderate or severe asymptomatic carotid stenosis, higher plasma levels of the micro-RNAs were associated with plaque progression ($n = 19$) after 2 years of follow-up.	No	(62)
miR-200c	RNA	Various cells	In 22 patients undergoing carotid endarterectomy, higher levels of miR-200c were found in patients with unstable plaques (echolucent symptomatic) and were positively correlated with biomarkers of plaque instability (matrix metalloproteinase—MMP1, MMP9; interleukin 6, macrophage chemoattractant protein 1—MCP-1)	No	(59, 94)
Resistin and chimerin mRNA	RNA	Various cells	In an analysis of 165 carotid plaque (67% unstable based on histological criteria), Resistin and chemerin mRNA expression was 80 and 32% lower, respectively, in unstable vs. stable plaques.	No	(70)

NCT03192215) (101), Apixaban for Treatment of Embolic Stroke of Undetermined Source (ATTICUS, NCT02427126), and A Study on BMS-986177 (oral factor XIa inhibitor) for the Prevention of a Stroke in Patients Receiving Aspirin and Clopidogrel (AXIOMATIC-SSP, NCT03766581) trials will, hopefully, provide conclusive results to guide patient care. Likewise, in the Oxford Vascular Study, a large patent foramen ovale is present in 36% of patients with a cryptogenic stroke aged >60 years (119) and associated with a 2.5 times higher risk of recurrent ischemic stroke (120), thus suggesting it might be worth trialing PFO closure or anticoagulation in elderly patients with a large PFO. However, the causal relationship between the PFO and the recurrent stroke was not formally established and the prevalence of ipsilateral non-stenotic carotid plaque not reported. Because PFO closure or anticoagulation are not expected to prevent strokes due to large vessel atherosclerosis, trials of PFO closure or anticoagulation in elderly patients with a large PFO should carefully plan subgroup analyses according to the presence of alternative candidate causes of the recurrent stroke, notably an atrial cardiopathy or an ipsilateral non-stenotic carotid plaque that may coexist with PFO (43, 44, 121).

Other Therapies and Interventions

Currently, patients with ESUS receive intensive lipid-lowering therapy (e.g., statins, ezetimibe) to achieve a level of LDL cholesterol <70 mg/dL (1.8 mmol/L) as early as possible after stroke (122–124). The treatment is maintained long-term if well-tolerated, even in older adults (125–128). Specific targets of LDL cholesterol have not been assessed in patients with ESUS and it is unknown if the presence of an ipsilateral non-stenotic carotid plaque would modify the effect of lipid-lowering drugs as suggested by findings of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) (129). Furthermore, the potential role of newer classes of lipid-lowering drugs for plaque stabilization and secondary stroke prevention is yet to be defined. Such drugs include proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (small interfering RNA—inclisiran or monoclonal antibodies—evolocumab or alirocumab) and Apo(a) antisense oligonucleotides that reduce plasma levels of both LDL cholesterol and lipoprotein(a) [Lp(a)]; as well as anti- angiopoietin-like 3 monoclonal antibodies that do not affect Lp(a) levels and bempedoic acid (92, 130–135). Like ezetimibe (93, 136), the new lipid-lowering drugs may be useful as add-on or statin-sparing agents in cases of allergy or intolerance to statins, familial hypercholesterolemia, refractory hypercholesterolemia, or in patients with high Lp(a) levels at the time of stroke since statins increase plasma levels of Lp(a) (90, 137). There are reports of an association between high Lp(a) levels and cryptogenic stroke (138, 139) suggesting that Lp(a) could represent a biomarker to guide optimization of lipid-lowering therapy in patients with ESUS as is the case in other cardiovascular diseases.

Systemic inflammation, a hallmark of atherosclerosis, modulates the risk of stroke and the effect of lipid-lowering agents (140–142). This explains the benefit of various anti-inflammatory drugs (e.g., canakinumab, colchicine) for the prevention of atherosclerotic cardiovascular diseases (86, 87, 143). In patients with ESUS and ipsilateral non-stenotic carotid plaque, the effect of anti-inflammatory agents is worth exploring, especially in those with high-risk plaque features since they would not be offered revascularization procedures as first-line treatment according to current guidelines (144–146). Data from the ongoing Colchicine for Prevention of Vascular Inflammation in Non-Cardioembolic Stroke (CONVINCE, NCT02898610) might answer the question of whether patients with ESUS with or without ipsilateral non-stenotic carotid plaques would benefit from the addition of low-dose colchicine to best medical therapy for secondary stroke prevention (147). The relevance of serial vascular imaging to monitor carotid plaque progression and stability is another aspect of the management that remains unexplored.

Besides pharmacological treatments, there is a variety of lifestyle interventions that are beneficial for cardiovascular risk reduction and are recommended by the American Heart Association for secondary stroke prevention no matter the suspected underlying etiology. Such interventions include smoking cessation, regular physical activity, weight loss, improved sleep hygiene, avoidance of noise and air pollution, reduction of salt and sugar intake, higher consumption of fish, fruits, and vegetables (148–155).

CONCLUSION

ESUS is a common subtype of stroke that is frequently associated with an ipsilateral non-stenotic carotid plaque. Evidence suggests that advanced multimodal vascular imaging and biomarkers might help reclassify some ESUS as large vessel strokes. However, the precise algorithm for this reclassification remains to be designed. Despite significant research efforts since the term ESUS was coined in 2014, the optimal management strategy for patients with ESUS remains unclear. There are several ongoing trials investigating various interventions. While waiting for more evidence to support the design of tailored therapeutic guidelines for the various well-phenotyped subgroups of patients with ESUS, clinicians should continue to fully implement all previously validated stroke prevention strategies, whether an ipsilateral non-stenotic carotid plaque is present or not. Such strategies include short-term dual antiplatelet therapy if appropriate, long-term intensive lipid lowering therapy, control of modifiable cardiovascular risk factors (e.g., hypertension, diabetes, smoking, obesity), and lifestyle changes.

AUTHOR CONTRIBUTIONS

JK-T did the literature search and wrote the manuscript. MV and JK-T prepared the figure. AN, SF, DM, GS, TJ, ES, MV, and GJ critically revised the manuscript. All authors approved the final version.

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REVIEW
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Asymptomatic Carotid Disease and Cognitive Impairment: What Is the Evidence?

Hediyeh Baradaran[1]*, *Amir Hossein Sarrami*[1] and *Ajay Gupta*[2,3]

[1] Department of Radiology and Imaging Sciences, University of Utah, Salt Lake City, UT, United States, [2] Department of Radiology, Weill Cornell Medicine, New York, NY, United States, [3] Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY, United States

The development of cognitive dysfunction and dementia is a complex, multifactorial process. One of the contributors to various types of cognitive dysfunction is carotid atherosclerosis which can frequently be seen in asymptomatic individuals. There are a number of different manifestations of asymptomatic carotid atherosclerosis including arterial stiffness, carotid intima-media thickening, flow-limiting stenosis, and complex, atherosclerotic plaque. Each of these forms of atherosclerosis may contribute to cerebral parenchymal damage, contributing to cognitive dysfunction. In this review article, we will discuss each of these forms of carotid atherosclerosis, present the potential mechanistic underpinnings behind an association, and then review the scientific evidence supporting potential associations to cognitive dysfunction and dementia.

Keywords: carotid atherosclerosis, cognitive impairment (CI), dementia, carotid stenosis, carotid plaque (CP)

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***Correspondence:**
Hediyeh Baradaran
hediyeh.baradaran@hsc.utah.edu

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INTRODUCTION

With an ever-increasing aging world population, there is increasing demand for identifying effective preventative and treatment strategies for the development of dementia and cognitive dysfunction (1). Early identification and effective treatment of dementia and cognitive dysfunction has been an ongoing challenge due to the multifactorial nature of disease development. One of the factors that appears to be contributing to the development of cognitive dysfunction and dementia is carotid atherosclerotic disease, including carotid stiffness, increased carotid intima media thickness, flow-limiting carotid stenosis, and high-risk carotid plaque features (2, 3). While traditionally thought to primarily contribute to ischemic stroke, there is increasing evidence of the contribution of carotid atherosclerotic disease to the development of cognitive impairment and dementia. Though the exact mechanisms by which each of these manifestations of carotid atherosclerosis contribute to the development of dementia is still under investigation, they each appear to contribute in unique but perhaps overlapping ways. In this article, we will review the scientific evidence supporting the links between each of these disease processes and the development of cognitive dysfunction.

Though there are many contributing factors in the development of dementia, in this review, we will focus on the role of asymptomatic carotid artery atherosclerosis in contributing to cognitive dysfunction and dementia (**Figure 1**). Asymptomatic carotid artery disease, which is more commonly seen in male patients, is frequently associated with vascular risk factors such has hyperlipidemia, diabetes, smoking, and hypertension. Manifestations vary, often starting as minimal wall thickening and then ultimately leading to flow-limiting stenosis and/or vulnerable plaque components which may rupture leading to cerebral

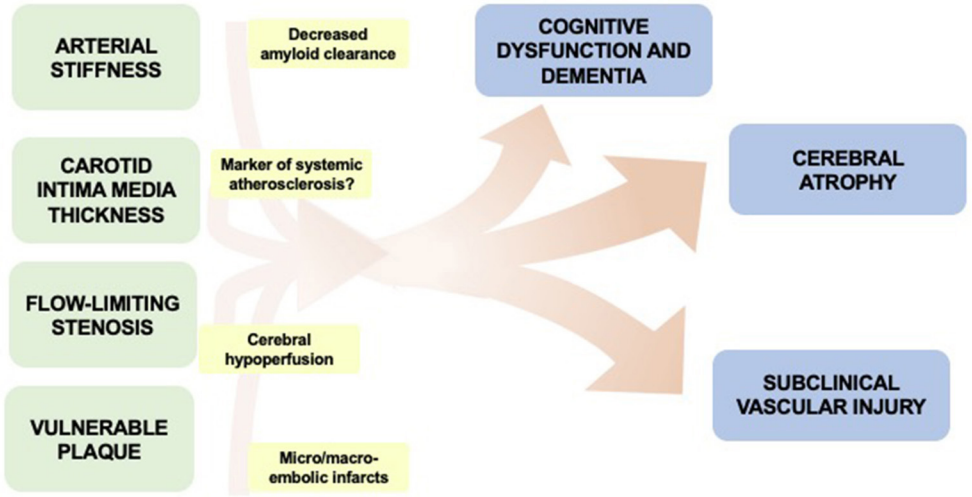

FIGURE 1 | Overview of potential associations between manifestations of asymptomatic carotid disease and cognitive impairment.

ischemia. Currently, there is clinical equipoise with regard to optimal treatment for asymptomatic carotid atherosclerotic disease due to difficulties in balancing the risk and benefit calculations with treatment. Though the primary concern with carotid atherosclerosis is ischemic stroke, we will review some of the associations of asymptomatic carotid atherosclerosis to cognitive dysfunction and dementia.

First, we will discuss the often clinically silent presence of carotid stiffness and its association with cognitive impairment. We will then review a common finding indicative of subclinical atherosclerosis—carotid intima-media thickening. Then we will discuss the evidence supporting an association between flow-limiting extracranial carotid stenosis and cognitive impairment. Finally, we will review the relevant evidence behind specific carotid plaque features in the development of mild cognitive impairment and dementia.

SEARCH METHODS FOR REVIEW

We performed a robust search of the available medical literature searching for manuscripts with key terms related to carotid atherosclerosis, carotid stenosis, arterial stiffness, and carotid plaque along with any terms related to cognitive impairment, dysfunction, or dementia. The primary search was performed using PubMed and included the use of MeSH terms. In addition, we evaluated cited references in each of the manuscripts we evaluated.

CAROTID STIFFNESS AND COGNITIVE IMPAIRMENT

Definition and Measurement

Stiffening of the carotid artery or other elastic arteries is the gradual loss of elastin fibers and accumulation of stiffer collagen fibers in the media over time (4, 5). This process, which can occur independent of the development of atherosclerosis, leads to loss of the ability of vasculature to appropriately accommodate to changes in blood pressure variation (6). This loss of responsive distensibility leads to higher pulsatile pressures and eventually increased flow load experienced by cerebral microvasculature and ultimately the brain parenchyma (4).

Arterial stiffness is not routinely measured in clinical practice but has been well-studied in several epidemiologic cohort studies. It is most commonly measured via indirect methods by measurement of pulse wave velocity (PWV) (7). Pulse wave velocity is an estimation of central arterial stiffness via measurement of pressure waves in two different vascular beds, commonly the carotid and femoral arterial beds (8). This indirect measure is a surrogate for aortic stiffness and has been widely used in multiple cohort studies. In addition to these indirect measures of central arterial stiffness, there are additional methods to directly measure vascular stiffness, specifically in the carotid artery (7, 9). These are most commonly performed via ultrasound measurement techniques.

Potential Mechanisms

Since there are many shared risk factors for the development of arterial stiffness and other common cardiovascular diseases, it can be difficult to determine the specific effects of arterial stiffness on the downstream cerebral parenchyma. One of the major vascular risk factors contributing to increased arterial stiffness is increasing age. In addition to age, hypertension, diabetes, and smoking are additional factors that seem to accelerate the development of arterial stiffness (10). A major proposed mechanism by which arterial stiffness contributes to cognitive dysfunction is through the increased flow load experienced by the cerebral parenchyma leading to end-organ damage (11, 12). The resultant damage may manifest as cerebral small vessel disease evident on brain imaging, including white matter hyperintensities, covert brain infarctions,

or cerebral microbleeds. These findings of cerebral small vessel disease are also independently associated with cognitive impairment and dementia, in addition to stroke and overall mortality (13–16).

Stiffness and Imaging Markers Associated With Cognitive Impairment

Arterial stiffness has been associated with several imaging findings which are in turn also associated with cognitive dysfunction and dementia (**Table 1**). Specifically, there have been several studies showing that decreased carotid compliance (or increased carotid stiffness), is associated with decreased total brain and cortical gray matter volumes and also decreased volume in the hippocampal and parahippocampal regions (11, 17, 18). In the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study in 422 participants free from cerebrovascular disease and dementia, the authors found that carotid stiffness was associated with lower whole brain (-0.127 ± 0.037 SD/SD, $p < 0.001$), gray matter (−0.079 ± 0.038 SD/SD, $p = 0.038$), and white matter volumes (−0.128 ± 0.039 SD/SD, $p = 0.028$) along with lower memory scores (11). In the SMART-MR study of 526 participants, the authors found a cross-sectional association with increased carotid stiffness and lower total brain and cortical gray matter volume ($B = -0.24\%$, 95% confidence interval [CI] −0.44 to −0.04%, and B = −0.47%, 95% CI −0.75 to −0.19%) but this association was no longer significant when evaluated prospectively after a mean of 4 years (17). When evaluating 614 participants in the Atherosclerosis Risk in the Community Study (ARIC), authors found a significant association between decreased carotid stiffness and lower parahippocampal and hippocampal volumes 20 years later [$R = 0.218$(0.144–0.291), $p < 0.001$ and $R = 0.181$ (0.105–0.255), $P < 0.001$], even after adjusting for confounders. Decreased total brain volumes and decreased volumes in the parahippocampal and hippocampal regions are independently associated with cognitive dysfunction and dementia (19).

In addition to decreased cerebral parenchymal volumes, there is evidence of the association between carotid stiffness to imaging findings of cerebral small vessel disease, including white matter hyperintensities, covert brain infarctions, and cerebral microbleeds, including in the AGES-Reykjavik, SMART-MR, and ARIC epidemiologic cohort studies (20–22). In the SMART-MR study, there was a significant association between carotid stiffness and larger volume of white matter hyperintensities ($B =$ 0.09%, 95% CI −0.01 to 0.19%) as well as cortical and subcortical brain infarcts (RR = 1.44, 95% CI 1.14–1.81). In the ARIC study, this association was found to be significant 20 years after the carotid stiffness measures (20). These imaging markers are also independently associated with mortality, stroke, cognitive dysfunction, and dementia (14, 16, 23).

Stiffness and Cognitive Impairment

Though there is fairly robust evidence of an association between carotid stiffness to brain imaging markers that are associated with dementia, the association of stiffness to cognitive impairment and dementia are more clinically relevant. There are several strong studies demonstrating that central arterial stiffness is an independent predictor of cognitive dysfunction and dementia (24–28). These studies, many of which were performed in epidemiologic cohorts including the Framingham Heart Study, the Maastricht study, and the PARTAGE study, found strong associations between stiffness and cognitive impairment. Interestingly, in the Maastricht study, the authors found a strong association with central stiffness (−0.018 SD [95% CI, −0.036 to −0.000]), but not with carotid stiffness (24). In addition, there are multiple studies establishing a cross-sectional association of central arterial stiffness to cognitive decline (29–32). Though there is relatively strong data supporting a link

TABLE 1 | Overview of feature of asymptomatic carotid atherosclerosis and their potential association with cognitive dysfunction and dementia.

Atherosclerosis feature	Imaging features	Potential mechanistic association with dementia	Supportive studies
Arterial stiffness	Central: Generally measured via pulse wave velocity Carotid: Generally measured directly with Ultrasound (US) based measurement of the carotid artery	Lack of vascular distensibility leads to increased flow load experienced by cerebral parenchyma	*Central* arterial stiffness may relate to cognitive impairment (24–32) *Carotid* stiffness is associated with cognitive impairment (33–38)
Carotid intima-media thickening	Measured via US in either the distal common carotid or proximal internal carotid artery	Similar mechanism as arterial stiffness and marker for generalized cardiovascular risk	Cross-sectional (39–43) and prospective (44–46) association between increased CIMT and cognitive impairment
Flow-limiting stenosis	Measured on either US, CT angiography, MR angiography, or digital subtraction angiography. Most commonly graded using NASCET criteria	Hypoperfusion from flow-limitations or potentially increased small infarctions	Association of flow-limiting stenosis to cognitive impairment (47–54); Changes to cognition after revascularization (55–59)
High-risk plaque features	Various features indicate "higher risk" including the presence of intraplaque hemorrhage, lipid-rich necrotic core, plaque ulceration, or increased plaque thickness/volume	Increased small covert brain infarctions or other markers of cerebral small vessel disease	High plaque volume and/or vulnerable plaque is associated with cognitive impairment (60–66)

TABLE 2 | Detailed study description for each feature of atherosclerosis.

Atherosclerosis feature	Key studies evaluating link to cognitive dysfunction
Carotid stiffness	Among 1,662 women (median baseline age = 41), greater carotid stiffness was associated with greater decline in neuropsychological test scores over 10-year follow-up (33)
	Higher carotid stiffness and lower compliance were associated with slower processing speed in 32 middle aged adults (mean age 64.2) (34)
	Higher carotid stiffness is associated with lower MMSE scores in 308 adults (mean age 63) without known vascular disease (35)
	Lower carotid artery stiffness in endurance athletes is associated with better neuropsychological outcomes (36)
	Higher carotid stiffness index is associated with reduced executive functioning processing speed in smokers (37)
	Carotid stiffness is associated with worse cognitive performance, primarily in processing speed and executive function and attention (38)
Carotid Intima-media thickening	In 8,208 participants (mean age 49.6 years), CIMT was inversely associated with memory function (39)
	CIMT ≥0.9 mm is independently associated with lower cognitive performance in 245 patients with asymptomatic HIV (40)
	In 3,227 participants (mean age 57.9 years), larger CIMT was associated with lower MMSE scores after adjustment for confounders (41)
	In 231 older adults, CIMT was associated with mild cognitive impairment after multivariate adjustment (42)
	In 1,826 patients with acute ischemic stroke, those with highest CIMT quartile were more likely to have cognitive impairments compared to the lowest IMT quartile (43)
	In 348 non-demented participants (mean age 71.7 years), greater baseline CIMT was independently associated with mild cognitive impairment and dementia diagnosis during a 5-year follow-up period (44)
	In 251 participants (mean age 78 years), there was a significant association between CIMT and change in executive functioning over a mean 2.3 year follow-up (45)
	Higher CIMT was associated with worse episodic memory after adjustment for vascular risk factors in 1,166 stroke-free participants being followed for about 5 years (46)
Flow-limiting stenosis	Asymptomatic participants with carotid stenosis had significantly lower levels of performance in tests of attention, psychomotor speed, memory, and motor functioning compared to those without stenosis (47)
	High-grade left carotid artery stenosis is associated with cognitive impairment and cognitive decline (48)
	Asymptomatic patients (n = 548) with high-grade carotid stenosis had worse performance on neuropsychological testing than healthy controls (49)
	Asymptomatic patients with high-grade carotid stenosis were found to have high rates of cognitive deterioration (51)
	Those with asymptomatic bilateral high-grade carotid stenosis had high risk of developing cognitive impairment (52)
	Those with severe asymptomatic unilateral carotid stenosis were found to have poor performance on neuropsychological exams (53)
High-risk plaque features	In a cross-sectional study of 284 patients with dementia, higher plaque volume is strongly associated with dementia (60)
	In 1,279 participants, those with carotid plaque (<40% stenosis) had a moderate association with poor cognitive performance (61)
	In 406 patients followed for 1 year, those with higher carotid plaque index were more likely to develop dementia (62)
	In 210 participants, the presence of carotid plaque was associated with abnormal cognitive function adjusting for confounders (64)
	In 2015 participants, those with carotid plaque were more likely have poor cognitive function (66)

between central arterial stiffening to cognitive dysfunction, there is less supporting evidence between carotid stiffness and dementia with some studies supporting this association (**Table 2**) (33–38), and other studies showing no association, after adjusting for other confounders (24, 67, 68). This is certainly an area worthy of future investigation to further our understanding of the role of carotid stiffness, an asymptomatic marker of vascular aging, to the development of dementia. Future longitudinal prospective cohort studies may be able to aid in clarifying this potential association.

CAROTID INTIMA-MEDIA THICKENING AND COGNITIVE IMPAIRMENT

Definition

Another marker of asymptomatic carotid atherosclerosis is thickening of the carotid intima-media. This subtle thickening of the arterial wall measured in either the distal common carotid artery or proximal internal carotid artery using ultrasound is a marker of subclinical atherosclerosis. Similar to arterial stiffness, both hypertension and smoking, along with other vascular risk factors, are known associations to CIMT. Since carotid intima-media thickening (CIMT) is a precursor for the development of atherosclerotic plaque, it is often considered an imaging marker of generalized cardiovascular risk. Though this thickening is asymptomatic, it is associated with cognitive dysfunction and dementia, along with stroke and overall increased mortality risk (47, 60, 69, 70).

CIMT and Imaging Markers Associated With Cognitive Impairment

There is evidence of an association of baseline increased CIMT to brain imaging markers of cerebral small vessel disease including white matter hyperintensities, covert brain infarctions, cerebral microbleeds, and also lower total brain volumes (71–76) (**Figure 2**). Specifically, a systematic review and meta-analysis of nine studies found that CIMT was associated with white

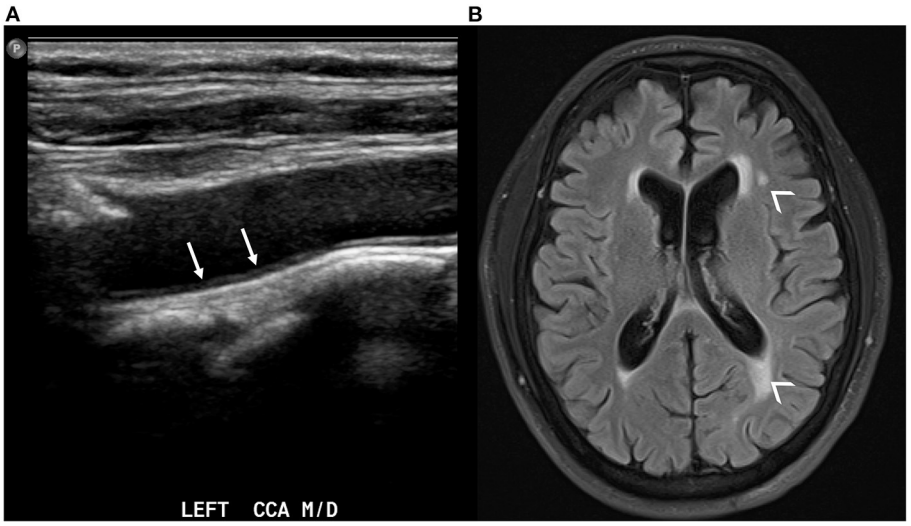

FIGURE 2 | Carotid ultrasound demonstrating thickening of the intima-media in the left common carotid artery [**(A)**, white arrows]. The same patient also has evidence of white matter hyperintensities in the periventricular white matter on axial T2 FLAIR brain MRI [**(B)**, small arrowheads].

matter hyperintensities [odds ratio (OR) 1.42, 95% CI 1.22–1.66, $p < 0.0001$], covert brain infarctions (OR 1.89, CI 1.46–2.45, $p < 0.0001$) (74). As for the association of CIMT with brain volume, there is evidence of lower total brain volume (−0.05 per SD, $P < 0.05$) in the Framingham Heart Study (77) and lower total brain and cortical gray matter (−0.29 per SD) in the SMART-MR study cohort (72). In addition, there is evidence that the progression of CIMT over time is also associated with lower hippocampal volumes in the Framingham Heart Study (78). As discussed previously, these imaging markers of cerebral small vessel disease and brain aging are independently associated with cognitive dysfunction and dementia.

CIMT and Cognitive Impairment

Several studies have evaluated the association between CIMT on ultrasound and the future development of dementia and cross-sectional association with cognitive function. Several studies from epidemiologic cohorts have found a positive association between increased CIMT at baseline and future development of cognitive decline (44–46). These studies followed cohorts of participants over time and found that having higher baseline CIMT on ultrasound was correlated with poorer future performance on cognitive testing and increased rates of dementia diagnoses. Hazard ratio for development of cognitive impairment based on elevated CIMT was 1.251 (95% CI 1.006–1.555, $p = 0.044$) in the Korean Longitudinal Study on Health and Aging after adjusting for basic demographics and baseline cognition (44). Further, in the Northern Manhattan Study, a cohort study of stroke-free participants, found that those with greater CIMT had worse performance on cognitive testing (ß $= -0.60$, $p = 0.04$ for episodic memory) (46). There are also many studies demonstrating a cross-sectional association between increased CIMT and poorer cognitive function (39–43).

Potential Mechanism

The exact pathophysiologic mechanism underpinning this association is unclear at this time, though it may be similar to the proposed mechanisms for arterial stiffness. Since CIMT is thought to be marker for systemic atherosclerosis, it may not necessarily be a direct contributor to cognitive dysfunction, but rather reflect general cardiovascular risk. Further evaluation of this association is necessary in order to identify potentially modifiable vascular contributions to cognitive dysfunction.

CAROTID STENOSIS AND COGNITIVE IMPAIRMENT

Definition

Flow-limiting carotid stenosis is a well-documented risk factor for stroke and is an established indication for carotid revascularization. Severe carotid stenosis is traditionally defined as 70–99% narrowing of the vessel lumen by various measuring methods, most commonly the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method in the United States (79). Moderate stenosis is defined as 50–70% stenosis. The degree of stenosis is a leading risk factor in the development of ischemic stroke with annual rates of ischemic stroke estimated to be around 1% (80). Though not nearly as well-studied, some have found that the annual rate of dementia in the presence of severe carotid stenosis to be around 1 (55).

Potential Mechanisms

The main mechanism by which carotid stenosis is hypothesized to contribute to cognitive impairment is via hypoperfusion (81). By limiting the flow to the brain parenchyma, some hypothesize that this may lead to end-organ damage, parenchymal atrophy, and neurodegeneration. Cerebral hypoperfusion is thought to accelerate amyloid and tau deposition, which is a potential

link between flow-limitation and cognitive dysfunction (82, 83). Other potential mechanistic explanations include via covert brain infarctions from embolization, which may act as an intermediate step between stenosis and cognitive dysfunction. Similar to many other features of carotid atherosclerosis, it is difficult to disentangle the complex associations between carotid stenosis, other vascular risk factors, and other findings of cerebral parenchymal damage. One potential method for clarifying these associations is by evaluating individuals with unilateral stenosis to determine if there are varying degrees of parenchymal damage downstream from the affected side. Currently, the exact mechanism by which flow-limiting stenosis contributes to cognitive dysfunction is not clearly established.

Stenosis and Cognition

Several studies have shown an association with carotid stenosis and poorer performance on cognitive testing (47–52), while others have failed to find an association. There are several studies finding that asymptomatic individuals with severe carotid stenosis with evidence of altered perfusion are more likely to develop cognitive impairment (51, 84, 85). In one of the largest studies evaluating this association in over 4,000 participants, the authors found that high-grade carotid artery stenosis was associated with cognitive impairment (OR 6.7, 95% CI 2.4 to 18.1) and cognitive decline (OR 2.6, CI, 1.1 to 6.3) (48). Some have found that left sided carotid stenosis is more likely to result in cognitive dysfunction than right-sided carotid stenosis, indicating that carotid stenosis may be an independent risk factor for cognitive impairment (48, 53). A systematic review and meta-analysis including over 760 subjects with asymptomatic carotid stenosis found an association between the presence of carotid stenosis and cognitive impairment (54).

Several studies have attempted to isolate the effect of carotid stenosis by assessing for changes in cognitive function after carotid endarterectomy with conflicting results (56). Overall, the majority of studies have found an improvement in cognition after CEA, but there are many studies showing either no change, and even a deterioration in cognitive function. In a large study of patients with asymptomatic carotid stenosis, there was no difference in mini-mental status examination scores in those who received medical therapy compared to those who underwent CEA (57). Another study based on patients from a randomized controlled trial with severe carotid stenosis without history of stroke or known dementia (ACST-1) found that carotid endarterectomy had no significant effect on the incidence of dementia (55). There is less data regarding cognitive changes after CAS, however, there are similarly mixed results with some studies showing an improvement in cognition after undergoing CAS (56, 58, 59).

Stenosis and Imaging Markers Associated With Cognitive Impairment

There is strong evidence that the presence of flow-limiting stenosis results in both cerebral atrophy as well as other markers of subclinical vascular injury, such as white matter hypterintensities and CBIs. There is evidence that severe carotid stenosis is associated with progression of brain atrophy, while the same link was not as pronounced in those with moderate stenosis (72). Further, there is strong evidence that carotid stenosis is associated with markers of parenchymal damage, including white matter hyperintensities and microstructural damage to both gray and white matter (86–88). In addition, there is strong evidence of an association between carotid stenosis and downstream CBI with a systematic review and meta-analysis of 11 studies reporting an OR of 2.78 (95% CI, 2.19 to 3.52, $p < 0.0001$) (89). Further, studies demonstrate that there are asymmetries in prevalence of CBI in cerebral hemispheres downstream from severe carotid stenosis, specifically with more cortical CBIs downstream from stenosis (90).

This role of flow-limiting stenosis in the development of dementia is an area worthy of further investigation. Though CEA and CAS procedures are primarily performed for stroke risk reduction, the potential added bonus of improved cognition may alter the risk calculus when identifying patients for carotid revascularization.

CAROTID PLAQUE AND COGNITIVE IMPAIRMENT

Definition

Carotid plaque is a specific marker of advanced atherosclerosis usually found in the carotid bifurcation. There are many different features of the plaque itself that carry varying degrees of associated embolic risk. There has been increased attention on individual plaque components and plaque volume in addition to the degree of stenosis when assessing stroke risk from carotid atherosclerotic disease. There is strong evidence that certain plaque components are more strongly associated with future and recurrent stroke, including intraplaque hemorrhage, lipid-rich necrotic core, and plaque ulceration (91). Many of these specific plaque elements are often more strongly associated with stroke than degree of stenosis which has led to a paradigm shift in stroke risk assessment (92). Though the major concern for carotid plaques is their leading to symptomatic strokes and/or transient ischemic attacks, many of these high-risk plaque features are also seen in asymptomatic individuals.

Though there is a strong association with high-risk plaque elements to stroke, there are fewer studies evaluating the association of plaque with the development of cognitive dysfunction and dementia. The current literature has shown mixed results with respect to the association of vulnerable plaque components and cognitive dysfunction.

Plaque and Cognition

Some studies have evaluated the association of increased plaque volume to performance on cognitive examinations and have found that there is worse performance on cognitive testing with higher plaque volume, even when accounting for education level and other confounding (60–66). For example, a study evaluating high risk plaque features on ultrasound found that those with more plaques were more likely to have poor performance on cognitive testing, including mini-mental status examinations (OR 1.72, 1.00–2.96) (61). Most of the studies evaluating this association used either ultrasound or CT imaging techniques

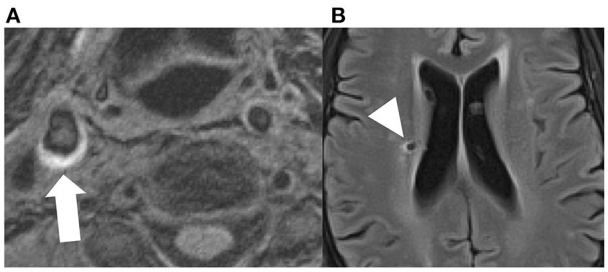

FIGURE 3 | Axial MPRAGE sequence demonstrating T1 hyperintensity in the right carotid bifurcation, compatible with intraplque hemorrhage [**(A)**, white arrow]. The same patient had a small covert brain infarction in the right periventricular white matter [**(B)**, arrowhead].

to evaluate plaque. Other studies have shown no significant difference in cognitive function when accounting for other cardiovascular risk factors (93).

Plaque and Imaging Markers Associated With Cognitive Impairment

There is evidence that vulnerable plaque features are associated with other markers of neurodegeneration and subclinical vascular injury. For instance, there is evidence that vulnerable plaque features contribute to cortical micro-infarcts detected on MR which are in turn associated with poor cognitive function (94). There are other studies which demonstrate an association with white matter hyperintensities and CBIs as well (74), though there are few studies explicitly looking at specific plaque features (**Figure 3**).

Potential Mechanisms and Future Directions

The exact mechanism behind this potential association is unclear at this time. Whether high risk plaque is directly associated with dementia due to repeated microembolic phenomena is not well established. Though there is evidence that high-risk plaque lead to increased risk of stroke, it is unclear if these plaque features may also contribute to microembolic phenomenon contributing to cognitive dysfunction. Other studies have found that there are increased markers of subclinical vascular injury which are associated with high-risk plaque features, including covert brain infarctions, cerebral microbleeds, and white matter hyperintensities which are independently associated with cognitive dysfunction. At this time, this exact association is unclear and further studies would be helpful in elucidating the exact contribution of high-risk plaque features to cognitive dysfunction and dementia.

CONCLUSION

Ranging from increased stiffness of the arterial wall to complex atherosclerotic plaques prone to rupture, there is a wide variety of manifestations of carotid disease. All of these manifestations can be seen in asymptomatic individuals. Though there has been a strong association between many features of carotid atherosclerosis and stroke, there has been less attention on the link to cognitive dysfunction. In this review, we present the existing evidence supporting this potential link.

There are many risk factors associated with the development of the presented types of carotid atherosclerosis, ranging from carotid stiffness to complex, vulnerable plaque components, including smoking and hypertension. A potential method for mitigating the association of asymptomatic carotid atherosclerosis and the development of cognitive impairment is to target these known contributors to atherosclerosis.

In the studies cited in this review, there are many definitions and diagnostic criteria for various types of cognitive dysfunction and dementia including mild cognitive impairment, vascular dementia, and Alzheimer's and Alzheimer's-related dementia. Future studies are needed with more streamlined diagnostic criteria and biomarker validation for the various forms of cognitive dysfunction. Future prospective longitudinal studies are necessary to further elucidate this relationship. As more studies confirm this link, we may expect changes to the risk-benefit assessment of pursuing surgical intervention in asymptomatic individuals with certain types of carotid artery atherosclerosis. In addition, with stronger scientific support, more targeted preventative strategies, including stringent medical management, could be considered directed at the development of carotid atherosclerosis as a means of dementia prevention. Currently, there is formal guidance not to perform routine screening for extracranial carotid plaque in individuals who are asymptomatic from the US Preventive Task Force. Though there is evidence of a potential link between asymptomatic carotid disease and cognitive impairment, the existing data is not strong enough at this time to reverse this recommendation. Further prospective observational studies confirming the link between carotid disease and cognitive impairment are necessary before making this recommendation. Additional evidence could warrant altering this recommendation including a randomized controlled trial comparing stringent medical management to those with less standard of care treatment with asymptomatic carotid artery disease showing that changes to medical management may decrease risk of cognitive impairment.

AUTHOR CONTRIBUTIONS

AG made substantial contributions to the conception or design of the work, drafted the work and revised it critically for important intellectual content, provided approval for publication of the content, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Association Between 18-FDG Positron Emission Tomography and MRI Biomarkers of Plaque Vulnerability in Patients With Symptomatic Carotid Stenosis

Nicola Giannotti[1], Jonathan McNulty[1], Shane Foley[1], John McCabe[1,2], Marey Barry[3], Morgan Crowe[1,4], Eamon Dolan[5], Joseph Harbison[6], Gillian Horgan[7], Eoin Kavanagh[1,8], Martin O'Connell[1,8], Michael Marnane[1,2], Sean Murphy[2], Ciaran Mc Donnell[9], Martin O'Donohoe[1,9], David Williams[10] and Peter J. Kelly[1,2,6]*

[1] School of Medicine, University College Dublin, Dublin, Ireland, [2] Neurovascular Unit for Translational and Therapeutics Research, Mater Misericordiae University Hospital, Dublin, Ireland, [3] Vascular Surgery, St. Vincent's University Hospital, Dublin, Ireland, [4] Department of Medicine for the Elderly, St. Vincent's University Hospital, Stroke Service, Dublin, Ireland, [5] Stroke and Hypertension Unit, Connolly Hospital, Dublin, Ireland, [6] Acute Stroke Service, St. James Hospital Dublin, Trinity College Dublin, Dublin, Ireland, [7] Health Research Board (HRB) Stroke Clinical Trials Network Ireland, University College Dublin, Dublin, Ireland, [8] Department of Radiology, Mater Misericordiae University Hospital, Dublin, Ireland, [9] Department of Vascular Surgery, Mater Misericordiae University Hospital, Dublin, Ireland, [10] Geriatric Medicine, Beaumont Hospital and Royal College Surgeons Ireland, Dublin, Ireland

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***Correspondence:**
Nicola Giannotti
nicola.giannotti@sydney.edu.au

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Purpose: Pathologic studies suggest that unstable plaque morphology and inflammation are associated with cerebrovascular events. ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) is a validated technique for non-invasive imaging of inflammation-related plaque metabolism, and MRI can identify morphologic features of plaque instability. The aim of this study was to investigate the association of selected imaging characteristics of plaque vulnerability measured with MRI and PET in patients with symptomatic carotid stenosis.

Methods: Patients from the BIOVASC study were selected based on the following inclusion criteria: (1) age $\geq$ 50 years; (2) recent (<30 days) ischaemic stroke (modified Rankin scale $\leq$3) or motor/speech/vision TIA; (3) ipsilateral internal carotid artery stenosis ($\geq$5 0% lumen-narrowing); (4) carotid PET/CTA and MRI completed. Semi-automated plaque analysis of MRI images was performed to quantify morphologic features of plaque instability. PET images were co-registered with CTA and inflammation-related metabolism expressed as maximum standardised uptake value (SUV_{max}).

Results: Twenty-five patients met inclusion criteria (72% men, mean age 65 years). MRI-measured plaque volume was greater in men (1,708–1,286 mm^3, $p = 0.03$), patients who qualified with stroke (1,856–1,440 mm^3, $p = 0.05$), and non-statin users (1,325–1,797 mm^3, $p = 0.03$). SUV_{max} was associated with MRI-measured plaque lipid-rich necrotic core (LRNC) in the corresponding axial slice ($r_s = 0.64$, p <0.001) and was inversely associated with whole-plaque fibrous cap thickness ($r_s = -0.4$, $p = 0.02$) and calcium volume ($r_s = -0.4$, $p = 0.03$).

Conclusion: This study demonstrated novel correlations of non-invasive imaging biomarkers of inflammation-related plaque metabolism with morphological MRI markers of plaque instability. If replicated, our findings may support the application of combined MRI and PET to detect vulnerable plaque in future clinical practise and randomised trials.

Keywords: PET, MRI, atherosclerosis, vulnerable plaque biomarker, carotid, plaque inflammation, plaque segmentation

INTRODUCTION

Recurrent stroke and coronary events occur in 4–6% of stroke survivors each year, despite guideline-based treatment (1). New approaches to address this residual vascular risk are urgently needed. The current assessment of carotid atherosclerotic lesions is based on luminal stenosis measurements and surface defects using *in vivo* imaging techniques including digital angiography, CT, MRI, and ultrasonography (2). However, histopathologic studies suggested that morphological plaque characteristics of instability and inflammation may be associated with an increased risk for cerebrovascular events (3, 4). The identification of carotid plaque containing a large lipid-rich necrotic core (LRNC) with intraplaque haemorrhage (IPH) and thin or ruptured fibrous cap (FC) may assist physicians to identify symptomatic or asymptomatic patients at higher risk for future stroke.

MRI is a validated technique for characterising luminal stenosis, plaque volume, and composition. Positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) has been validated for non-invasive imaging of inflammation-related plaque metabolism (5, 6). Almost no data exist on the association between plaque inflammation imaged with PET and biomarkers of unstable plaque imaged with MRI in patients with recently symptomatic carotid atherosclerosis. Therefore, using an imaging dataset of symptomatic patients recruited as part of a larger, multi-centre prospective cohort study Biomarkers Imaging Vulnerable Atherosclerosis in Symptomatic Carotid disease (BIOVASC), we aimed to investigate the association between plaque inflammation measured as SUV_{max} on ^{18}FDG-PET and MRI biomarkers of plaque vulnerability in patients with symptomatic carotid stenosis.

METHODS

Eligibility Criteria

Pre-specified inclusion criteria of the BIOVASC study were: (1) age $\geq$ 50 years; (2) presentation to medical attention with recent (<30 days) non-severe ischaemic stroke (modified Rankin scale [MRS] $\leq$ 3) or motor/speech/vision transient ischaemic attack (TIA); (3) ipsilateral internal carotid artery (ICA) stenosis ($\geq$ 50% lumen-narrowing) on admission Doppler ultrasound, magnetic resonance angiogram (MRA) or CT angiography (CTA) done for clinical care; (4) PET/CTA completed. The main exclusion criteria were: (1) possible haemodynamic stroke/TIA due to carotid near-occlusion; (2) contraindication to contrast-enhanced CT; (3) unsuitability for carotid PET/CTA, MRI, or research participation. For the current study, we selected patients who had high-resolution carotid wall MRI completed no later than 7-days from PET/CTA.

The study was approved by relevant Ethics Committees and patients gave informed consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Image Acquisition

PET/CT

F-fluorodeoxyglucose (^{18}FDG) PET/CT was performed using a Siemens Biograph 16 scanner (Siemens, Erlangen, Germany) after a minimum 6 h fast. Blood glucose level was verified for each patient and if above 11 mmol/L the PET/CT scan was not performed. Then, 320 megabecquerel (MBq) of ^{18}FDG was administered 2 h prior to image acquisition. The uptake phase was standardised with the patient resting. PET images were acquired in three-dimensional (3D) mode in two bed positions for 10 min each. Slice thickness of 3 mm and a 256 × 256 matrix were used. PET emission mode images were acquired and reconstructed by applying the OSEM2D4i24s algorithm and XZY Gauss 2 convolution kernel (Siemens Healthineers, Erlangen, Germany). A low-dose CT scan for attenuation correction was performed using the same scanner directly after PET; in addition, where the administration of a contrast agent (Omnipaque 350, GE Healthcare, Milwaukee, USA) was not contraindicated (serum creatinine level >1.5 mg/dl or estimated glomerular filtration rate < 60 ml/min) a diagnostic carotid CTA was performed using bolus tracking. The pre-monitoring slice was set at the aortic arch, and a circular region of interest (ROI) was drawn distant from any vessel calcification. CT images (1 mm slice thickness, with contrast enhancement) were acquired from the aortic arch to the skull base to identify carotid arteries and jugular veins. CTA parameters were 120 kVp, 104 mAs, 512 × 512 matrix, pitch 0.6 and 1-mm CT slice reconstructions following the acquisition. A smooth reconstruction kernel was used (b30f).

MRI

Carotid arteries were scanned from the common carotid artery to a point distal to the internal carotid artery stenosis where the vessel wall is parallel. Patients were scanned with Siemens

Abbreviations: LRNC, Lipid rich necrotic core; MDS, Most diseased segment; SHS, Single hottest slice.

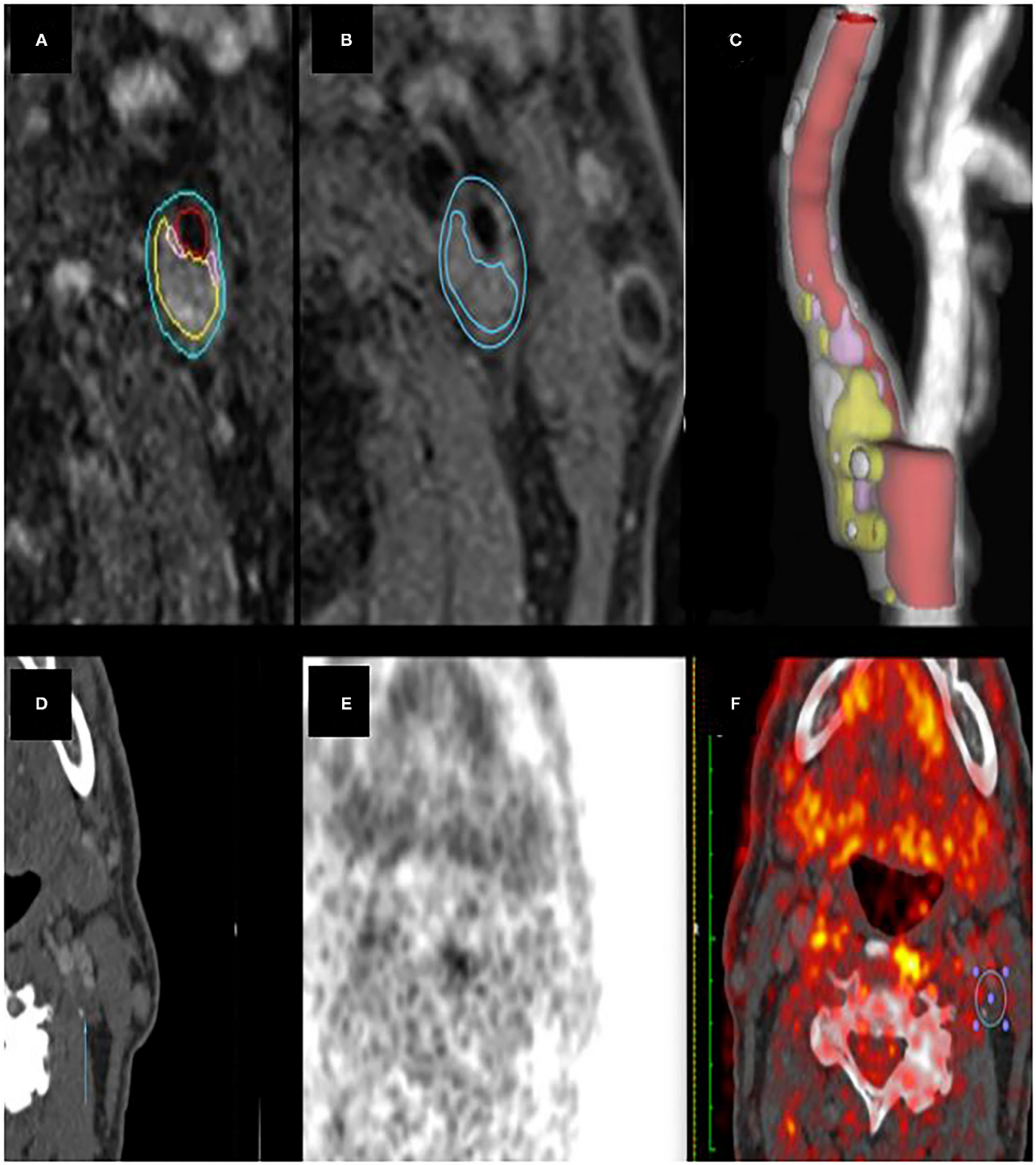

FIGURE 1 | (A) carotid MRI semi-automatic segmentation of lumen and vessel wall. **(B)** semi-automatic plaque characterisation of an LRNC area. **(C)** ICA plaque 3D Volume Rendering. **(D–F)** CT and PET images of the same plaque area. The ROI **(F)** shows where SUV_{max} was measured.

Avanto 1.5T MR (Siemens Healthineers, Erlangen, Germany) with a dedicated phased-array surface neck coil (Machnet BV, Netherlands). The carotid bifurcation of the symptomatic side was identified with the MR localiser. Following this, 3D time-of-flight (TOF) MR Angiography (MRA) and axial T1w, T2w, proton density-weighted (PD), and T1w post-contrast sequences were acquired along the length of the vessel wall. Double inversion-recovery (IR) sequences were used to allow

TABLE 1 | Patient demographics.

Characteristic	Patients
Total number	25
Age, years (mean, range)	65 (55–86)
Hypertension, *n* (%)	16 (64.0%)
Current Smoking, *n* (%)	13 (52%)
Statin at presentation, *n* (%)	11 (41%)
Aspirin at presentation, *n* (%)	11 (41%)
Diabetes mellitus, *n* (%)	3 (11%)
Type of index cerebrovascular event	
Stroke, *n* (%)	10 (40.0%)
TIA, *n* (%)	15 (60.0%)
Stenosis category (NASCET)	
Moderate 50–69%	15 (60%)
Severe > 70%	10 (40.0%)

blood signal nulling with cardiac synchronisation to reduce wall motion. T1w sequences were acquired prior to and post-injection of 20 mls of Gadobutrol (Gadovist, AG Bayer, Berlin, Germany).

Scanning parameters: field of view 256 × 256 mm; 2 mm slice thickness and 0.2 slice interval; time to repetition (TR)/time to echo (TE) were 978/12, 1,880/62, and 1,880/12 for T1, PD, and T2, respectively. Voxel size 0.5 × 0.5 × 2 mm and NEX of 1. Moreover, a 40° flip-angle and a short TE (< 7 ms) were used in the TOF sequence to maximise the contrast between stationary tissues and flowing blood. The total scan time was 23.2 min per patient.

Image Analysis

Quality assurance (QA) cheques were performed on PET/CT and MRI prior to commencing the study to ensure that the scanners were performing according to recommended international standards. Further QA cheques were performed on the MRI and PET/CT imaging datasets before commencing the image analysis.

All images were centrally analysed by a single trained reader, including re-measurement of CTA images to confirm the degree of stenosis according to the NASCET criteria (7). Intra-rater reliability assessment showed excellent agreement between carotid CTA measurements taken at different time-points (intraclass correlation $\alpha = 0.814$, $p < 0.001$) (8). Following semi-automated co-registration of PET and CT images (Osirix, Pixmeo, Geneva), carotid ^{18}F-FDG activity in 10 regions of interest (ROI) defined relative to the slice of maximal stenosis was quantified using standardised uptake values (SUV g/ml = measured uptake (MBq/ml) / injected dose (MBq) per patient weight [g]).

The whole plaque was defined as the volume of the carotid artery corresponding to 10 ROIs drawn on 10 1 mm CTA slices (1 cm length in total) using the point of maximal stenosis as the mid-point of the whole plaque segment. The whole-plaque SUV represents the SUV averaged across the 10 ROIs. Moreover, we defined the single hottest slice (SHS) as the axial slice with maximal SUV uptake (SUV_{max}) and most diseased segment (MDS) as SHS plus the adjacent proximal and distal axial slices, corresponding to a 3 mm long plaque segment (9).

Following a semi-automatic co-registration of MRI sequences (T1-weighted, T2-weighted, TOF, and proton density-weighted) and lumen-plaque boundaries segmentation, carotid plaque morphological features were semi-automatically measured with MRI-Plaque View 2 (VPDiagnostic, Seattle, WA, USA). MRI measures included plaque volume (mm^3), plaque thickness (mm^2), LRNC volume (mm^3), intra-plaque haemorrhage (IPH) volume (mm^3), fibrous cap (FC) thickness (mm), and normalised wall index (NWI). The NWI is defined as plaque wall area/(lumen + wall area).

Because inflammation may be non-uniformly distributed across carotid plaques, the association of SHS-SUV_{max} with MRI morphological features was first analysed and compared to the corresponding axial MRI slice (matching slice analysis) (**Figure 1**). The analysis was then repeated, comparing the MDS-SUV_{max} to MRI morphological features across the entire measured plaque (whole-plaque analysis).

Between-group characteristics were compared using pre-specified analyses which included *t*-tests, Mann-Whitney, or χ^2 tests. Non-parametric associations between continuous variables were analysed using Spearman's correlation test. Linear regression analysis was performed to investigate the strength of the association between plaque inflammation and clinical characteristics.

RESULTS

Clinical Characteristics

The study group consisted of 25 patients, among which 40% (10 patients) with severe ICA stenosis (**Table 1**). Furthermore, 10 patients presented with stroke (40%), while 15 patients (60%) with a transient ischaemic attack (TIA). One patient had stroke recurrence and four had TIA recurrence within 90 days. NWI was the only MRI metric that was significantly greater in patients with recurrent events (93 vs. 87.7, $p = 0.05$). MRI whole-plaque volume was greater in men (1,707.7 vs. 1,285.9, $p = 0.03$), non-statin users (1,325.3 vs. 1,797.3, $p = 0.03$), patients with stroke as index event (1,856 vs. 1,439.7, $p = 0.05$). LRNC volume was greater in men (121.1 vs. 39.3, $p = 0.03$) and mean plaque calcium volume was greater in patients with hypertension (209.3 vs. 64.6, $p < 0.01$) (**Table 2**). NWI was associated with plaque LRNC volume (rho = 0.49, $p = 0.01$).

Association of ^{18}F-FDG PET Plaque Inflammation With Plaque MRI Features

On analysis of corresponding axial slices, SUV_{max} SHS was associated with greater LRNC volume (rho = 0.64, $p = 0.001$), but not other MRI features of plaque instability (**Table 3**).

On analysis of whole-plaque MRI features, SUV_{max} MDS was inversely associated with plaque calcium volume (rho = −0.43, $p = 0.03$) and fibrous cap thickness (rho = −0.44, $p = 0.02$) (**Table 3**). SUV_{max} MDS showed a weak trend towards association with serum LDL-cholesterol ($r_s = 0.34$, $p = 0.09$).

TABLE 2 | Distribution of MRI plaque features and clinical characteristics.

	Mean plaque volume (mm^3)	*p*	Mean FC thickness (mm)	*p*	Mean IPH volume (mm^3)	*p*	Mean LRNC volume (mm^3)	*p*	Mean calcium volume (mm^3)	*p*	Mean NWI	*p*	Mean SUV	p	SHS-SUV	*p*	MDS-SUV	*p*
Gender																		
- Male	1,707.7		1.3		23.1		121.1		169.9		90		1.77		2.88		2.80	
- Female	1,285.9	0.03	1.0	0.18	10.1	0.81	39.3	0.03	124.5	0.85	85	0.1	1.93	0.39	2.81	0.79	2.75	0.85
Hypertension																		
- Yes	1,678.1		1.3		19.7		106.4		209.3		88.7		1.74		2.68		2.63	
- No	1,432.3	0.27	0.9	0.91	20.1	0.18	84.9	0.42	64.6	0.002	88.4	0.95	1.95	0.19	3.18	0.06	3.05	0.1
Current smoking																		
- Yes	1,558.3		1.2		26.8		117.4		136		89.9		1.72		2.99		2.91	
- No	1,623.5	0.76	1.2	0.99	12.3	0.36	78.4	0.23	180.2	0.53	87.4	0.25	1.90	0.26	2.71	0.29	2.65	0.3
Statin at presentation																		
- Yes	1,325.3		1.2		15.3		75.1		146.7		88.1		1.75		2.62		2.59	
- No	1,797.3	0.03	1.2	0.54	25.4	0.95	117.1	0.71	43.5	0.41	89.3	0.61	1.86	0.46	3.04	0.11	2.94	0.16
Diabetes mellitus																		
- Yes	1,256.3		0.9		23.4		101.9		97.6		88.3		1.63		2.53		2.53	
- No	1,635.1	0.26	1.2	0.86	19.4	0.92	98.2	0.8	165.4	0.93	88.8	0.93	1.84	0.39	2.91	0.35	2.81	0.45
Index event																		
- Stroke	1,856		1.0		28.1		137.3		200.1		86.5		1.74		2.65		2.60	
- TIA	1,439.7	0.05	1.3	0.15	15.2	0.33	76.9	0.21	133.1	0.25	89.9	0.14	1.86	0.45	2.98	0.22	2.89	0.27
Stenosis category																		
- Moderate 50–69%	1,778.3		1.2		22.5		104.1		189.5		87.5		1.77		2.77		2.69	
- Severe > 70%	1,349.5	0.04	1.2	0.82	17.6	0.69	90.6	0.74	108.8	0.35	90.3	0.22	1.88	0.5	2.99	0.42	2.91	0.38
Stroke recurrence																		
- Yes	1,494.2		1.5		5.56		105.4		85.1		92.9		1.79		2.72		2.65	
- No	1,613.5	0.66	1.1	0.63	23.4	0.52	97.0	0.59	175.3	0.15	87.7	0.05	1.91	0.54	3.42	0.14	3.30	0.13

TABLE 3 | Correlation between plaque FDG uptake and plaque MRI features (Spearman's correlation coefficient).

	Matching slice analysis		Plaque analysis	
	SUV_{max}-SHS	*p*	SUV_{max}–MDS	*p*
Calcium volume	−0.17	0.41	−0.43	0.03
FC thickness	−0.68	0.74	−0.44	0.02
IPH volume	−0.96	0.65	0.33	0.11
LRNC vol	0.64	0.001	0.09	0.64
Plaque volume	−0.15	0.49	−0.13	0.55
NWI	−0.30	0.14	−0.15	0.40

For analysis of FDG uptake and MRI features in matching slices, FDG is expressed as SUV_{max} in the corresponding axial slice. For analysis of FDG uptake and MRI features across the plaque, FDG is expressed as SUV_{max} in the MDS.

On linear regression analysis, plaque FDG uptake (measured as log-transformed SUV_{max} SHS to meet normality assumptions of regression analysis) was associated with LRNC area at the corresponding slice (R^2.5, $p = 0.001$, coefficient.016, standard error.003) suggesting that approximately half the variance in plaque SUV uptake was explained by LNRC area (**Figure 2**). No other associations between FDG uptake and MRI morphology were observed on linear regression analysis of corresponding slices.

DISCUSSION

In recently symptomatic patients with stroke or TIA, we investigated the relationship between morphological MRI biomarkers of unstable carotid plaque and inflammation-related plaque metabolism measured by ^{18}FDG-PET/CTA. We found positive associations between plaque inflammation and lipid-rich core volume in corresponding axial slices, and inverse (negative) correlations between inflammation and markers of plaque stability (plaque calcification and fibrous cap volume).

Few previous studies have investigated the combined use of carotid wall MRI and molecular imaging with PET/CT in patients with atherosclerosis. In non-stroke subjects who underwent serial whole-body combined FDG-PET/MRI, FDG uptake was associated with the number and volume of atherosclerotic plaques, and with plaque lipid content and positive remodelling (10). In 61 patients with carotid stenosis and recent symptoms,

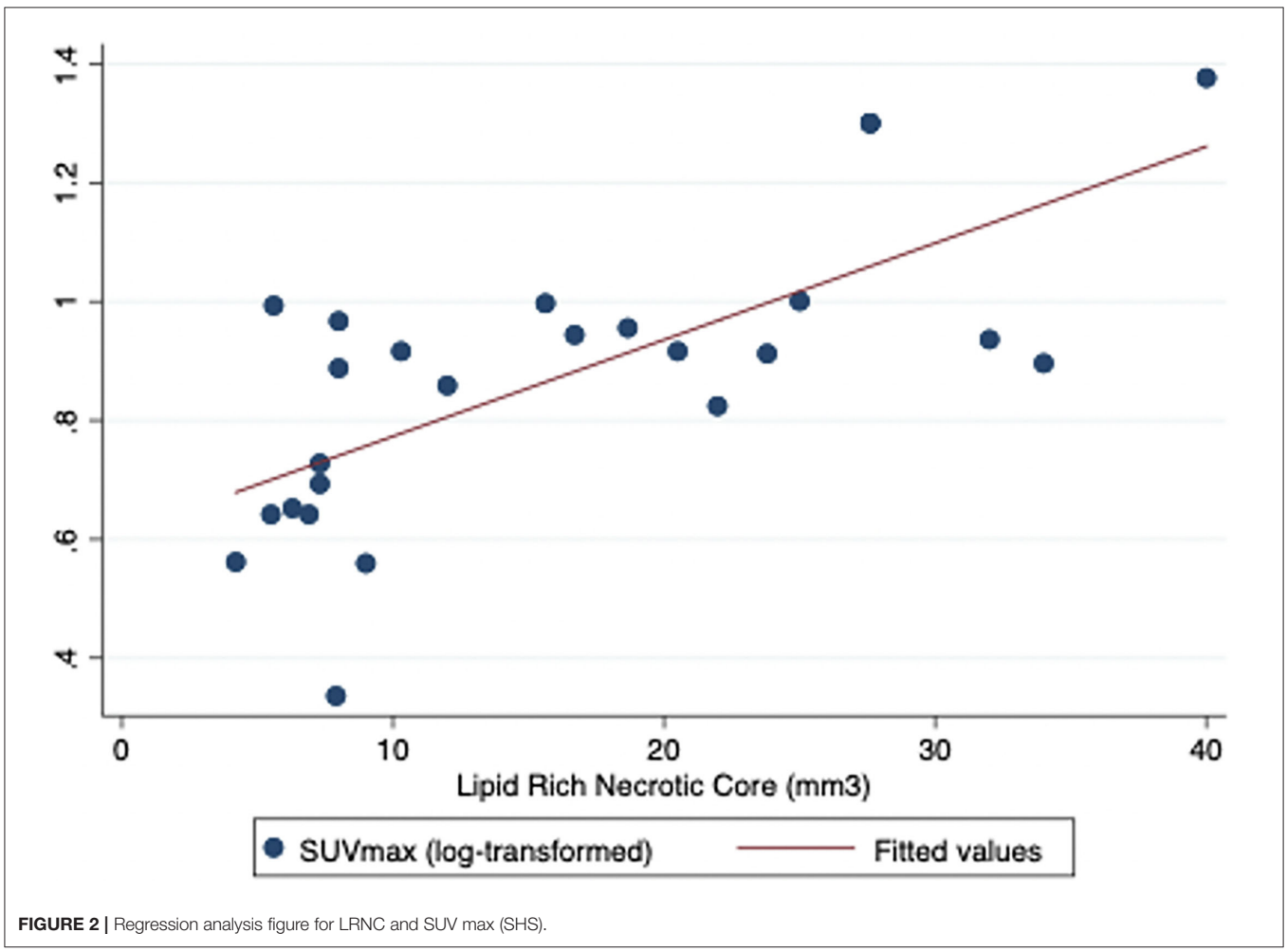

FIGURE 2 | Regression analysis figure for LRNC and SUV max (SHS).

plaque SUV_{max} was associated with serum LDL cholesterol, total cholesterol, and triglycerides, and inversely associated with HDL cholesterol (11). However, plaque lipid content was not measured in this study. In 18 patients with cryptogenic stroke and non-stenosing carotid atheroma, the presence and size of MRI-measured lipid core in ipsilateral carotid plaque were associated with FDG uptake (12). Similar findings were reported in a Chinese MRI/PET study of asymptomatic patients with non-stenosing carotid plaque (13).

Few data exist relating other MRI morphological features with FDG uptake. Inverse associations were observed between FDG uptake and ipsilateral carotid plaque fibrous cap thickness in patients with cryptogenic stroke and non-stenosing plaque, and in asymptomatic Chinese patients thicker caps and calcification were associated with lower FDG uptake (12, 13). We found no association between FDG uptake and IPH, unlike 2 earlier studies that reported positive associations (12, 14). Two other studies reported associations between plaque neovascularisation measured by dynamic contrast-enhanced MRI and plaque inflammation measured by PET (15, 16).

The main strength of our study is the novelty of its findings, as very little data exist on combined PET and MRI carotid plaque imaging datasets in recently symptomatic patients. Both unstable plaque morphology and inflammation are validated markers that identify patients at the highest stroke risk. If validated in further studies, our results may support a rationale for use of combined PET/MRI plaque imaging for improved risk stratification of patients in future randomised trials for carotid revascularisation or may improve the cost-effective targeting of next-generation anti-atherosclerotic medications towards high-risk patients (17).

The main limitation is the limited sample size, which may have resulted in insufficient statistical power for some analyses. The sample of data used in this study was collected from patients enrolled in the larger BIOVASC study where carotid symptomatic patients only were recruited. Although the SHS/MDS methods are standard for such studies, we also acknowledge technical limitations for spatial resolution of current PET scanners. Due to limitations of spatial resolution of PET, we cannot exclude the possibility that FDG uptake in the MDS may partially reflect spill-over of signal from adjacent proximal and distal plaque segments (∼1–1.5 mm in each direction).

Further studies involving a larger number of participants are needed. We acknowledge that some variability may exist in the matched slices analysis. Although the most optimal slice selection of PET/CT and MRI images was made using defined protocols and the carotid bifurcation as a reference, patient positioning and technical limitations of each imaging modality may introduce variability in the analysis of the two imaging datasets.

Summary

Although further research is needed, these initial findings suggest that inflammation-related plaque metabolism measured with PET/CT may be associated with morphological MRI biomarkers of plaque vulnerability, suggesting that the use of both PET and MRI may be a promising approach to assess new anti-atherosclerotic treatments to prevent stroke in patients with carotid stenosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Mater Misericordiae University Hospital, Dublin, Ireland. Ref 1/378/1131. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NG, JM, SF, and MB: contributed to study design, data acquisition, data analysis, and manuscript preparation. MC, ED, JH, EK, MO'C, MM, SM, CD, MO'D, and DW: contributed to the study design and manuscript preparation. GH: contributed to the study design, data acquisition, and manuscript preparation. PK is the principal investigator of the BIOVASC study, planned the study design and contributed to data acquisition, data analysis, outcome adjudication, and manuscript preparation. All authors have read and approved the final manuscript.

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REVIEW
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Extra-Cranial Carotid Artery Stenosis: An Objective Analysis of the Available Evidence

Anne L. Abbott [1,2]*

[1] Department of Neuroscience, Central Clinical School, Monash University, Melbourne, VIC, Australia, [2] Neurology Private Practice, Knox Private Hospital, Wantirna, VIC, Australia

Background and Purpose: Carotid stenosis is arterial disease narrowing of the origin of the internal carotid artery (main brain artery). Knowing how to best manage this is imperative because it is common in older people and an important cause of stroke. Inappropriately high expectations have grown regarding the value of carotid artery procedures, such as surgery (endarterectomy) and stenting, for lowering the stroke risk associated with carotid stenosis. Meanwhile, the improving and predominant value of medical intervention (lifestyle coaching and medication) continues to be underappreciated.

Methods and Results: This article aims to be an objective presentation and discussion of the scientific literature critical for decision making when the primary goal is to optimize patient outcome. This compilation follows from many years of author scrutiny to separate fact from fiction. Common sense conclusions are drawn from factual statements backed by original citations. Detailed research methodology is given in cited papers. This article has been written in plain language given the importance of the general public understanding this topic. Issues covered include key terminology and the economic impact of carotid stenosis. There is a summary of the evidence-base regarding the efficacy and safety of procedural and medical (non-invasive) interventions for both asymptomatic and symptomatic patients. Conclusions are drawn with respect to current best management and research priorities. Several "furphies" (misconceptions) are exposed that are commonly used to make carotid stenting and endarterectomy outcomes appear similar. Ongoing randomized trials are mentioned and why they are unlikely to identify a routine practice indication for carotid artery procedures. There is a discussion of relevant worldwide guidelines regarding carotid artery procedures, including how they should be improved. There is an outline of systematic changes that are resulting in better application of the evidence-base.

Conclusion: The cornerstone of stroke prevention is medical intervention given it is non-invasive and protects against all arterial disease complications in all at risk. The "big" question is, does a carotid artery procedure add patient benefit in the modern era and, if so, for whom?

Keywords: best practice, stroke prevention, carotid stenting, carotid stenosis, medical intervention, carotid endarterectomy, guideline standards, transcarotid arterial revascularisation

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Hege Ihle-Hansen,
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Seemant Chaturvedi,
University of Maryland, United States

***Correspondence:**
Anne L. Abbott
Anne.L.Abbott@gmail.com

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INTRODUCTION: KEY CONCEPTS

Carotid stenosis refers to atherosclerotic narrowing of the origin of the internal carotid artery (the main brain artery). The scientific literature and guideline recommendations tend to focus on ***advanced (50–99% or 60–99%) carotid stenosis***. This follows from randomized trials that showed an overall stroke risk reduction benefit from surgery (carotid endarterectomy, CEA) compared to ***medical intervention*** alone (lifestyle coaching and medication). That surgical benefit was only seen in ***highly selected*** patients with at least 50 or 60% carotid stenosis (1). There has never been direct comparison of any other so-called ***"carotid revascularization" procedure*** with medical intervention alone. Stroke prevention benefit with respect to other procedures, such as carotid artery angioplasty with stenting (CAS), are based on the assumption that randomized trials of CEA vs. medical intervention alone (that were conducted 3–4 decades ago) are still applicable.

In this article the ***definition of stroke*** is generally one based on an appropriate neurological deficit lasting at least 24 h, and a ***transient ischaemic attack (TIA)*** lasting <24 h (2). The risk of ipsilateral (same-sided) stroke in individuals with 50–99% or 60–99% carotid stenosis is approximately double the risk for individuals with lesser stenosis (3, 4). The ***main method of measuring carotid stenosis*** in previous trials and guideline recommendations is derived from conventional intra-arterial angiography and the North American Symptomatic Carotid Endarterectomy Trial (NASCET): the ratio of residual lumen at the point of maximal stenosis to the distal lumen where arterial walls first become parallel) (4, 5). This method (or similar methods) will be referred to in this article unless otherwise stated. Most arterial imaging is now done non-invasively, and measuring carotid stenosis is not an exact science (6–10).

Individuals with carotid stenosis are generally differentiated according to whether or not they have had previous stroke or TIA affecting the brain region or eye ipsilateral to (i.e., same-sided and, therefore, in the vascular territory of) the carotid stenosis. This distinction is made because carotid artery procedures are targeted interventions that focus on reducing the risk of stroke caused by the carotid stenosis. In addition, symptomatic patients have a much higher short-term stroke rate than asymptomatic patients and are more likely to benefit from CEA (4, 11–13).

The term ***"symptomatic carotid stenosis"*** has been widely used. However, it is a misnomer. It is inherently procedurally biased because it implies that the carotid stenosis was responsible for the stroke or TIA in any given patient. This implication of causality is inappropriate given that ∼50% of symptomatic individuals with ipsilateral carotid stenosis have another readily identifiable possible cause of their stroke or TIA and that cannot be treated by a carotid artery procedure (3). Thus, the presence of a condition, such as carotid stenosis, does not mean causation (14). The correct terminology, which encourages us to think holistically, is a ***symptomatic individual with ipsilateral carotid stenosis*** (ipsilateral to the affected brain region or eye).

Further, ***any stroke risk reduction benefit seen in past randomized CEA trials was an overall benefit***. Some patients were harmed, most did not benefit and some with asymptomatic carotid stenosis would have been included in analyses of symptomatic patients. In any given patient, it is usually impossible to be certain of the cause of stroke or TIA. Risk factors and probabilities are more applicable in diagnosis and management (2). By contrast, a person with ***asymptomatic carotid stenosis*** has never before had a clinically-defined ipsilateral stroke or TIA (2). However, such an individual may not be asymptomatic with respect to the rest of their brain or arterial system. Asymptomatic carotid stenosis may exist in a completely asymptomatic person or a symptomatic person with respect to past clinically manifest arterial disease complications.

Advanced asymptomatic carotid stenosis is common in older people, affecting about 10% of individuals by their eighth decade (13). Advanced carotid stenosis is easily detected using non-invasive imaging and causes about 10% of all strokes (13). Carotid stenosis also identifies individuals at higher risk of other preventable arterial disease complications, such as myocardial infarction (15–17). Therefore, knowing how to manage this lesion is very important.

Medical intervention is indicated for all individuals with carotid stenosis whether or not they have a carotid procedure. In contrast to carotid procedures, medical intervention reduces the risk of all arterial disease complications, including all stroke (ischaemic and haemorrhagic) and TIA affecting all parts of the brain, by addressing risk factors such as hypertension, hypercholesterolaemia, tobacco smoking, atrial fibrillation, diabetes, excessive weight and alcohol consumption and physical inactivity.

Medical intervention is fundamentally the same in individuals whether or not they have carotid stenosis. Therefore, determining current best medical intervention for carotid stenosis patients has implications for best preventing all arterial disease complications and best protecting all individuals with arterial disease risk. This is very important given that arterial disease is the lead cause of death worldwide and a leading cause of premature death and disability with huge social and economic consequences (18–20).

The stroke risk reduction benefit from medical intervention alone in carotid stenosis patients has improved significantly over the last 3–4 decades since past randomized comparisons with CEA were performed and is very effective (13, 21–28). ***The "big" question is, "Can a carotid artery procedure provide an additional stroke risk reduction benefit compared to current best practice medical intervention alone?"*** The evidence-base regarding each interventional approach for carotid stenosis will now be presented and discussed.

INTERVENTIONS FOR CAROTID STENOSIS AND REDUCING STROKE RISK

Currently there are four types of intervention done in the name of reducing stroke risk associated with carotid stenosis:

i. ***Carotid surgery or endarterectomy*** (CEA, surgical removal of the atherosclerotic plaque causing stenosis).
ii. ***Carotid angioplasty with stenting*** (CAS, balloon dilation of the stenosis, and stent placement *via* an intra-arterial catheter).
iii. A new CEA-CAS hybrid-type procedure, known as ***trans-carotid arterial revascularisation (TCAR)***.

iv. ***Medical intervention*** (risk factor identification and lifestyle coaching/healthy lifestyle habits and appropriate medication).

Worldwide, carotid artery procedures make up a multi-billion dollar per year international industry. **Table 1** shows published data from just a few countries with respect to use of CEA and CAS. The estimated procedural costs are based on 2007 estimates from the United States of America. There is notable heterogeneity in target populations for CEA and CAS between countries, as well as between hospitals within countries with respect to patient symptomatic status, age and sex (29). It is perhaps surprising to see such heterogeneity, given that all procedural centers should have access to the same evidence-base. Procedural intervention is more common in countries with "fee for service" reimbursement' where physician payment is proportional to the number of procedures performed (29).

Carotid Endarterectomy

Patients With Advanced Asymptomatic Carotid Stenosis

We have known for a long time from randomized trial evidence that CEA is inefficient for reducing stroke risk associated with advanced asymptomatic carotid stenosis (12). The Asymptomatic Carotid Atherosclerosis Study ("ACAS") remains the largest randomized trial of medical intervention plus CEA compared to medical intervention alone in patients with asymptomatic carotid stenosis (35). The Asymptomatic Carotid Surgery Trial ("ACST-1") is sometimes mentioned in this context (36, 37). However, ACST-1 was a randomized trial of early vs. deferred CEA with no medical-intervention-only-arm. In ACST-1, 24% of patients allocated deferred CEA had CEA by study end. In 2004 it was reported that the peri-operative rate of stroke or death in patients who had "deferred" CEA was 4.5% (36). Further, ACST-1 included patients who had been symptomatic more than 6 months before recruitment (making up 12% of participants). Ipsilateral stroke (the most relevant outcome with respect to carotid artery procedures) was not an outcome measure in ACST-1. The "SPACE-2" Trial was initiated to compare outcomes with medical intervention with or without additional CEA or CAS in asymptomatic carotid stenosis patients. However, it was stopped early due to slow recruitment (38). Meanwhile, the Veteran's Affairs Cooperative Study was a randomized trial only involving men and it was underpowered with respect to stroke as an outcome measure (39).

Therefore, ACAS remains the main trial for purported justification for CEA in patients with asymptomatic carotid stenosis. Patients were randomized into ACAS between 1987 and 1993, ∼3 decades ago. For every 85 patients with 60–99% asymptomatic carotid stenosis randomized to endarterectomy in ACAS, on average 3 patients had an ipsilateral stroke prevented over the next 12 months (see **Figure 1**) (35). However, that was at the expense of 2 patients who had a peri-operative stroke (or less commonly, peri-operative death). For the remaining 80 patients, CEA had no effect on their stroke risk over the next 12 months (35). The mean baseline age of ACAS participants was 67 years. They were all reasonably medically fit, as they were considered to be at low or average risk of major CEA complications and at low risk of death within the next 5 years.

Most patients did not have a stroke during follow-up in ACAS. For example, 89% of patients with 60–99% asymptomatic carotid stenosis in ACAS who were given medical intervention alone had not had an ipsilateral stroke by 5 years of projected follow-up (35). Only one subgroup of asymptomatic (or recently asymptomatic) carotid stenosis patients have ever been shown to have an overall statistically significant stroke reduction benefit from CEA. Using data from ACAS (with respect to CEA vs. medical intervention alone) and ACST-1 (with respect to early vs. deferred endarterectomy), it was only ***men aged <75–80 years with 60–99% stenosis*** (using conventional intra-arterial angiography or ultrasound and NASCET criteria) who benefited. In addition, such men had to be free of any major life-threatening condition, have a life expectancy of at least 5 years and satisfy all trial selection criteria. The overall stroke prevention benefit for these men was small, ∼1%/year (35–37). Women did not benefit from CEA in ACAS. Women coming closest to an overall stroke risk reduction benefit from early CEA compared to deferred CEA in the ACST-1 were aged <75 years. However, the result just failed to reach statistical significance (37).

The overall 30-day peri-operative rate of stroke or death was 1.7% in ACAS when the angiographic stroke risk was excluded and 2.3% when the angiographic risk was included (35). The overall 30-day peri-operative rate of stroke or death in ACST-1 was 3.1% (36, 37). Arguably, because ACAS was the most relevant trial, it should have been used for procedural hazard standards in routine practice. In addition, since the publication of ACAS in 1995, conventional intra-arterial angiography has not been accepted as best practice for identifying or assessing patients with asymptomatic carotid stenosis. It has generally been replaced by safer non-invasive methods (41). Hence, it could be argued that a 30-day peri-operative rate of stroke or death of 1.7% (rather than the generally accepted 3% rate) should have been used in routine practice as the standard for inferring an overall procedural benefit for asymptomatic carotid stenosis patients (1, 12).

Adding to evidence of net patient harm in routine practice, CEA outcomes in routine practice (when measured) are often, if not usually, worse compared to those seen in ACAS or ACST-1 (13, 42, 43). For example, in a meta-analysis of 30-day stroke or death rates associated with CEA in 47 high volume registries of asymptomatic carotid stenosis patients, it was only by about 2003 (8 years after ACAS was published) that the average 30-day CEA stroke or death rate in those registries averaged 2.3%, and only by about 2010 (15 years after ACAS was published) that this rate averaged 1.7% (42). Moreover, and as explained below, 30-day stroke or death rate standards derived from ACAS and ACST-1 have been increasingly outdated and excessive since they were published due to ongoing improvements in the stroke prevention effectiveness of medical intervention alone (12).

Symptomatic Patients With Advanced Carotid Stenosis

It has been known for a long time from randomized trial evidence that CEA is inefficient for stroke risk reduction in symptomatic patients with advanced ipsilateral carotid

TABLE 1 | The multi-billion dollar per year global carotid procedural industry (29–34).

Country	Procedures done/Year	Asymptomatic stenosis patients (%)	Procedural cost	Procedural complication cost^
United States of America	135,000*	92	2.7 billion	+ More
Germany	33,000*	57	0.7 billion	+ More
United Kingdom	5,700**	15	0.1 billion	+ More
Australia	3,200*	0–79	64 million	+ More
Total			3.6 billion	+ More

**CEA & CAS; **CEA only; 2005–2007 US estimates for procedural cost: $20,000/CEA, $35,000/stent. ^Complications such as death (∼1%), stroke (∼1–10%) and myocardial infarction (∼1%).*

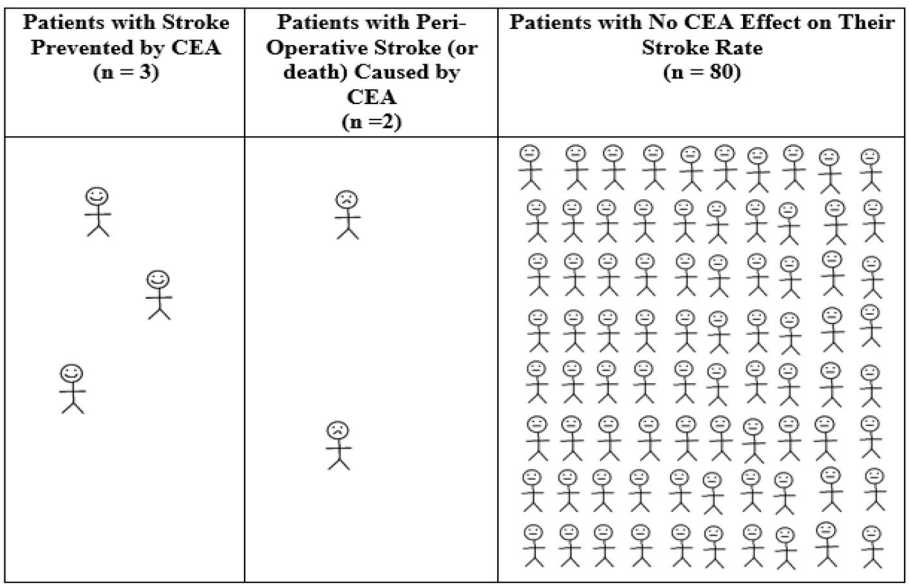

FIGURE 1 | Average 12-month outcomes for every 85 patients with asymptomatic carotid stenosis randomized to CEA in ACAS (35). Calculated from ACAS data regarding patients with 60–99% asymptomatic carotid stenosis (using "NASCET" criteria), the overall absolute annual ACAS stroke risk reduction from CEA and the 2.3% 30-day CEA rate of stroke or death in ACAS (35). There was a 5.9% reduction in any peri-operative stroke/death or later ipsilateral stroke in ACAS with CEA over 5 years using Kaplan Meier analysis (11.0% with medical intervention alone vs. 5.1% with CEA, or 1.18%/year risk reduction with CEA). Therefore, the number needed to treat by CEA to be ahead by 1 ipsilateral stroke over 12 months of study follow-up was 100/1.18 = 85. Derived from a figure originally published in Fast Facts, 2012 (©S. Karger AG, Basel) (40).

stenosis. There were 3 sufficiently large randomized trials of medical intervention with or without additional CEA to be impactful on routine practice: Veterans Affairs 309 Trial (VA309), North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST) (44–46). Patients were randomized into these trials between 1981 and 1994, ∼3–4 decades ago. Symptomatic patients with advanced carotid stenosis were more likely to benefit from CEA in randomized trials than patients with advanced asymptomatic carotid stenosis. However, the overall ipsilateral stroke risk reduction benefit for symptomatic patients with 70–99% carotid stenosis (using NASCET criteria and in the absence of near occlusion) was modest, 3.2%/year (4). Most patients did not have a stroke during follow-up in these trials. For example, 74% of symptomatic patients with 70–99% stenosis in NASCET who were given medical intervention alone had not had an ipsilateral stroke by 2 years of follow-up (47).

Using pooled data (4), for every 31 patients randomized to CEA across NASCET, ECST, and VA309, on average 3 patients had a stroke prevented over the next 12 months of follow-up (see **Figure 2**). However, that was at the expense of 2 patients who had a peri-operative stroke (or less commonly, peri-operative death). For the remaining 26 patients, CEA had no effect on their stroke rate over the next 12 months (40). The average baseline age of participants in these trials was 60–66 years. All were reasonably medically fit, as they were considered to be at low or average risk of major CEA complications and at low risk of death within the next 3–5 years.

Very few subgroups of symptomatic patients were shown to have a statistically significant (overall) benefit with respect to reduced stroke rate from CEA in these randomized trials. They

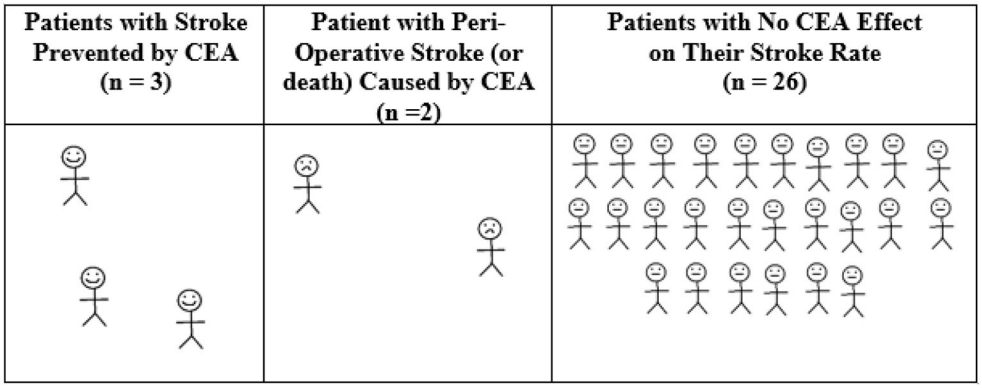

FIGURE 2 | Average 12-month outcomes for every 31 symptomatic patients randomized to CEA in NASCET, ECST, and VACS. Calculated from pooled randomized trial data regarding symptomatic patients with 70–99% stenosis (using "NASCET criteria" and excluding near occlusion), the overall absolute stroke risk reduction with CEA and the overall 30-day CEA rate of stroke or death of 6.2% (4). There was a 16% reduction in any peri-operative stroke/death or later ipsilateral stroke with CEA over 5 years using Kaplan Meier analysis (∼27.0% with medical intervention alone vs. 11.0% with CEA, or 3.2%/year risk reduction with CEA) (4). Therefore, the number needed to treat by CEA to be ahead by 1 ipsilateral stroke over 12 months of study follow-up was 100/3.2 = 31.25 (40). Derived from a figure originally published in Fast Facts, 2012, and now with a correction (©S. Karger AG, Basel) (40).

satisfied all the trial selection criteria, had a life expectancy of at least 3–5 years, did not have near carotid occlusion [angiographic evidence of severe stenosis and reduced distal flow (4)] and fit into one of these three groups:

i. ***Women with 70–99% stenosis*** *(by way of conventional intra-arterial angiography and NASCET criteria)* having CEA ***within 2–3 weeks*** of their last same-sided stroke or TIA.
ii. ***Men with 50–69% stenosis*** *(by way of conventional intra-arterial angiography and NASCET criteria)* having CEA within ***2–3 weeks*** of their last same-sided stroke or TIA.
iii. ***Men with 70–99% stenosis*** *(by way of conventional intra-arterial angiography and NASCET criteria)* having CEA within ***3 months*** of their last same-sided stroke or TIA. However, the benefit fell rapidly over this time and was highest ***within 2–3 weeks*** of their last same-sided stroke or TIA (1, 48).

Overall, in these randomized trials, the 30-day peri-operative rate of stroke or death associated with CEA was ∼6%. This is the standard that has been used in routine practice to infer an overall CEA benefit for symptomatic patients with advanced carotid stenosis compared to using medical intervention alone. However, because of advances in medical intervention since these randomized trials were conducted, 6% is now excessive as a procedural standard, fewer symptomatic patients are now likely to benefit from CEA and the window of opportunity for procedural benefit might now be shorter (49). New randomized trials of CEA vs. medical intervention alone in suitable symptomatic patients are a priority (see below).

Patient Subgroups and CEA Harm

Different sample sizes, patient selection criteria, patient risk factor profiles, procedural risks, standards of medical intervention, follow-up duration, definitions, and reporting methods cause heterogeneity between studies in detecting significant subgroup treatment differences.

Information From Individual Randomized Trials

Past randomized trials have shown that ***symptomatic patients*** are more likely to suffer peri-operative stroke or death than patients with ***asymptomatic*** carotid stenosis (see **Figures 1**, **2**) (50). Further, ***women*** were more likely to experience stroke or death after CEA than men in ACAS and ACST-1. However, these trials were not sufficiently powered to test the influence of patient sex on procedural complication rates (they had sample sizes of 1,662 and 1,320, respectively) (35–37). These trials were similarly underpowered to test the effect of ***age*** on procedural risk. The mean baseline age in ACAS and ACST-1 was 67 and 68 years, respectively. Patients over 80 years were excluded from ACAS and patients over 75 years at baseline comprised only 650 of all patients randomized in ACST-1 (36).

Symptomatic women had a significantly higher peri-operative rate of stroke or death in the pooled analysis of NASCET and ECST (OR 1.50, 95% CI 1.14–1.97, $P = 0.04$, 5,893 total patients) (51). Using the same pooled data, a higher peri-operative rate of stroke or death was not found according to ***age*** (<65, 65–74, and >75 years) (51). However, the average baseline age of patients in NASCET and ECST was 66 and 63 years, respectively (45, 46). There were only 409 (14.2%) NASCET and 176 (5.9%) ECST patients aged ≥75 years at baseline, indicating under powering for the analysis of age as a risk factor for CEA complications (51).

Information From Meta-Analyses of Randomized and Non-randomized Studies

In a meta-analysis of 25 studies of mixed symptomatic and asymptomatic patients, Bond et al. documented ***women*** had a higher rate of peri-operative stroke and death with CEA than men (OR 1.31, 95% CI = 1.17–1.47, $P < 0.0001$) (52). Bond et al. also reported a higher operative mortality in combined male and female patients of mixed symptomatic status ***aged ≥ 80 years*** compared to younger patients in a meta-analysis of 15 studies (OR = 1.80, 95% CI = 1.26–2.45, $P < 0.001$) (52). The authors

noted that, unfortunately, there were too few reports in the literature that stratified outcomes by both sex and symptomatic status for detailed patient subgroup analyses (52).

Since then, registries have provided outcome data for larger samples. For example, multivariable regression from the Nationwide German Statutory Quality Assurance database of 142,074 CEAs done for asymptomatic and symptomatic patients from 2009 to 2014 showed that more ***advanced age*** was associated with a higher procedural rate of any stroke or death until discharge (relative rate per 10 year increase 1.19 between ages <65 and ≥80 years; 95% CI 1.14–1.24) (50). Meanwhile, Khatri et al. found that ***age ≥70 years*** was a predictor of stroke, mortality and cardiac complications after both CEA and CAS in a multivariate analysis of 495,331 patients of mixed symptomatic status included in the Nationwide Inpatient Sample database (NIS) between 2005 and 2008 (OR 1.3 for both procedures, 95% CI 1.1–1.7 for CAS and 1.2–1.4 for CEA) (53). ***Female sex*** was not associated with a significantly increased CEA peri-procedural risk in the German database analysis or a 2000–2009 analysis from the NIS involving 221,253 CEA patients (50, 54). However, female sex was associated with a higher rate of peri-operative mortality in analysis of 21,597 symptomatic patients in the Vascular Quality Initiative (55).

Carotid Angioplasty and Stenting

CAS was introduced as a less invasive alternative to CEA. However, it is clear that CAS (by the transfemoral/transaortic approach) is more dangerous for patients than CEA. CAS has not yet been compared to any standard of medical intervention in a trial. However, the SPACE-2 Trial was a notable missed opportunity and new randomized trials are underway with this objective (see below) (38). Past randomized trials of CEA vs. CAS (none of which included a medical-intervention-only treatment arm) and recommendations for CAS have evidently been based on the misconception that medical intervention has not changed since the earlier randomized trials of medical intervention with or without additional CEA. In every adequately powered randomized trial comparison, CAS was associated with about 1.5–2.0 times as many peri-procedural strokes or deaths as CEA (see below) (12, 49, 56, 57). This excess CAS peri-procedural rate of stroke or death is also seen in meta-analyses of randomized trials, registries and administrative databases, and it is not compensated by the peri-procedural rate of clinically-defined myocardial infarction (see below) (12, 31, 43, 49, 56–63).

Severe carotid re-stenosis is also more common after CAS than CEA and CAS tends to cost more (31, 56, 62). Complications (apart from stroke and death) that are more likely with, or particular to, CAS compared to CEA include hemodynamic instability (severe hypotension or bradycardia, including the need for a permanent pacemaker) and retroperitoneal hemorrhage (64–66). Cranial nerve injury and myocardial infarction are less common with CAS than CEA. However, overall in past randomized trials, peri-procedural stroke, death, and clinically defined myocardial infarction were more common after CAS than CEA (see below) (12, 56, 60, 65). Differing results have been reported with respect to "protection devices" for lowering the CAS associated peri-procedural rate of stroke or death (56, 67).

TABLE 2 | Peri-procedural rate of stroke or death with CAS compared to CEA in the largest randomized trials of patients with asymptomatic carotid stenosis.

Randomized trial	*n*	Follow-Up (years)	30-Day peri-procedural stroke/death rate (%)		CAS excess	*P*
			CAS	CEA	OR/HR, 95% CI	
ACST-2 (68)^	3,625	5 mean	3.5	2.6	OR 1.35 (0.91–2.03)*	0.12
ACT-1, 2016 (69)	1,453	0–5	2.9	1.7	OR 1.69 (0.70–4.10)*	0.24
CREST-1, 2010 (65)	1,181	2.5 median	2.5	1.4	HR 1.88 (0.79–4.42)	0.15
SPACE-2, 2016 (38)	400	1–5	2.5	2.0	OR 1.30 (0.34–4.90)*	0.70
SAPPHIRE, 2004 (70)	237	1	5.4	4.6	1.2 times higher (no raw data published to allow statistical calculations)	?

*Individually each randomized trial was statistically **underpowered** to exclude a clinically significant difference in the rate of peri-procedural stroke or death with CEA and CAS.*
**OR calculated from published raw data.*
^Analysis using intention to treat figures.

CAS and Patients With Asymptomatic Carotid Stenosis

Table 2 summarizes the results of randomized trials of CAS compared to CEA in patients with advanced asymptomatic carotid stenosis (or at least asymptomatic in the 6 months prior to randomization) with a sample size of >200 (range: 237–3,625 total subjects per trial). Each of these trials was underpowered to exclude a clinically significant difference in the peri-procedural rate of stroke or death between CAS and CEA, as indicated by 95% confidence intervals (CIs) which overlap 1. These trials include the second Asymptomatic Carotid Surgery Trial (ACST-2) (68). The 95% CIs in these trials extend to 4.9. This means that with a larger sample size, as would occur if the randomized trial methods were rolled out into routine practice, it is within the realms of probability that CAS could cause up to 4.9 times as many peri-procedural strokes or deaths as CEA in patients with asymptomatic carotid stenosis. Such adverse outcomes with CAS would be clinically significant.

The direction of effect in each of these randomized trials was for 1.3–1.9 times as many 30-day peri-procedural strokes or deaths with CAS compared to CEA. This excess CAS harm in asymptomatic carotid stenosis patients reached statistical significance in a 2019 meta-analysis of randomized trials by Batchelder et al. (57) (7 randomized trials and 3,467 asymptomatic carotid stenosis patients). Registries and administrative databases of procedures performed on

TABLE 3 | Peri-procedural rate of stroke or death with CAS compared to CEA in the largest randomized trials of symptomatic patients.

Randomized trial	*n*	30/120 day stroke or death rate (%)		CAS excess OR/HR/RR, 95% CI	*P*
		CAS	CEA		
ICSS, 2010^ (72)	**1,713**	**8.5**	**4.7**	**HR 1.86 (1.26–2.74)**	**0.001**
CREST-1, 2010 (65)	**1,321**	**6.0**	**3.2**	**HR 1.89 (1.11–3.21)**	**0.02**
SPACE-1, 2006 (73)	1,183	7.7	6.5	OR 1.19 (0.75–1.92)*	0.4
EVA-3S, 2006 (74)	**527**	**9.6**	**3.9**	**RR 2.5 (1.2–5.1)**	**0.01**
CAVATAS, 2010# (75)	504	10.0	10.0	OR 1.00 (0.56–1.81)*	0.98
Wallstent, 2001 (76)	**219**	**12.1**	**4.5**	**OR 3.00 (1.01–8.61)***	**0.046**

Bolded font indicates trials with sufficient statistical power to compare the peri-procedural rate of stroke and death with CEA and CAS.
^120 day event rates.
#90% were symptomatic.
**OR calculated from published raw data.*

asymptomatic carotid stenosis patients also show excess peri-procedural rates of stroke and/or death with CAS compared to CEA (31, 43, 59). This excess procedural rate with CAS compared to CEA in asymptomatic carotid stenosis patients is consistent with the more clearly demonstrated statistically significant excess CAS stroke rate in randomized symptomatic patients (see below). For a given sample size, it is easier to show statistically significant differences in symptomatic compared to asymptomatic patients because of higher event rates in the symptomatic patients (71).

CAS and Symptomatic Patients With Carotid Stenosis

Table 3 summarizes the results of randomized trials of CAS compared to CEA in symptomatic patients with advanced carotid stenosis with a sample size of >200 (range: 219–1,713 total subjects per trial). Four of these trials were adequately powered to compare the peri-procedural rate of stroke or death between the procedures (as indicated by bold font in **Table 3**) (65, 72, 74, 76). These 4 trials showed that CAS was associated with approximately twice as many peri-procedural strokes or deaths as CEA. The direction of effect was similar in the underpowered trials. The comparison reached statistical significance in meta-analyses of randomized trials (56, 57). Registries and administrative databases of procedures performed on symptomatic patients with carotid stenosis likewise show higher peri-procedural rates of stroke and/or death with CAS compared to CEA (31, 43, 59).

The Harm (Not Benefit) From CAS Is Durable

Table 4 summarizes the results of randomized trials of CAS vs. CEA in ***asymptomatic and/or symptomatic patients*** with a sample size of >400 and participant follow-up of ≥12 months. In every adequately powered comparison (as indicated in bold font) stroke in the longer term was significantly more prevalent in patients who had undergone CAS compared to CEA. As seen above, the results of these randomized trials show that patients experience more strokes and deaths in the ***peri-procedural period*** with CAS compared to CEA. However, rates of stroke ***beyond the peri-procedural period*** were similar with CAS and CEA. This observation, regarding the post-procedural period, is important because it means that most patients experiencing peri-procedural stroke live long-term with their strokes. It is inappropriate to exclude peri-procedural complications when making treatment choices (see below).

There has been no adequately powered randomized trial of ***long-term outcomes of CAS compared to CEA in patients with asymptomatic carotid stenosis alone.*** Underpowered trials include ACST-2 (68). However, as seen in **Table 4**, in an analysis from CREST-1 (comprising the 1607 asymptomatic and symptomatic patients remaining in follow-up), the 10 year rate of peri-procedural death or any stroke was significantly higher with CAS (11.0%) compared to CEA (7.9%): HR 1.37, 95% CI 1.01–1.86, $P = 0.04$) (80). This finding was consistent with the excess peri-procedural rate of stroke or death with CAS in CREST-1. Considering all CREST-1 2502 asymptomatic and symptomatic patients, the peri-procedural rate of stroke or death was significantly higher with CAS (4.4%) compared to CEA (2.3%): hazards ratio [HR] 1.90, 95% CI 1.21–2.98, $P = 0.005$ (65).

As also seen in **Table 4**, the 2006 EVA-3S randomized trial (79) and 2014 ICSS (International Carotid Stenting Study) (77) of ***symptomatic patients with carotid stenosis***, each found a statistically significant higher rate of ***peri-procedural stroke or death or later ipsilateral stroke*** at median 4.2 and 3.5 years of follow-up, respectively, with CAS compared to CEA. A higher rate of peri-procedural stroke or death or later ipsilateral stroke during study follow-up with CAS compared to CEA in symptomatic patients was also seen in a meta-analysis of randomized trials (OR: 1.59, 95%CI 1.16–2.16 in trials with the longest follow-up) (56).

Patient Subgroups and CAS Harm

CAS has *not* been shown to be more beneficial than CEA or medical intervention alone in any subgroup of carotid stenosis patients. In fact, as mentioned above, in every adequately powered randomized trial comparison to CEA, CAS caused significantly more peri-procedural strokes (with or without peri-procedural deaths or myocardial infarctions) and was associated with more strokes in the long-term (12, 49, 56, 57).

Particularly vulnerable to the stroke risk of CAS compared to CEA are:

- ***The most senior patients (aged ≥ 70 years).*** Randomized trial comparisons in younger patients have been underpowered (53, 56, 60, 82–85).
- ***Those who are most recently symptomatic (especially within the previous 7–14 days,*** which is when best practice CEA is most likely to be beneficial) (63).
- ***Women*** (55, 56, 86, 87). However, men are also at higher risk of stroke or death from CAS compared to CEA (56).
- ***Those with certain carotid anatomical features,*** such as longer, angulated, or tandem lesions (67, 88, 89).
- ***Those who have CAS in low volume centers or outside trials*** (56, 90, 91).

TABLE 4 | Longer-term outcomes with CAS compared to CEA in the largest randomized trials of symptomatic and/or asymptomatic patients.

Randomized trial	*n*, symptomatic status	Follow-up (years)	Outcome measure (%) CAS vs. CEA		CAS excess: HR/OR & 95% CI	*P*
					30-Day peri-procedural stroke/death or later ipsilateral stroke	
CREST-1, 2010 (65)	**2,502 SPts + APts**	**4 by KMA (median 2.5)**	**6.2**	**4.7**	**HR 1.44 (1.00–2.06)**	**0.049**
CREST-1, 2010 (65)	1,181 APts	4 by KMA (median 2.5)	4.5	2.7	HR 1.86 (0.95–3.66)	0.07
CREST-1, 2010 (65)	1,321 SPts	4 by KMA (median 2.5)	8.0	6.4	HR 1.37 (0.90–2.09)	0.14
ICSS, 2015 (77)	**1,710 SPts**	**5 by KMA (median 4.2)**	**11.8**	**7.2**	**HR 1.72 (1.24–2.39)**	**<0.01**
SPACE-1, 2008 (78)	1,214 SPts	2 by KMA	9.5	8.8	HR 1.10 (0.75–1.61)	0.62
EVA-3S, 2008 (79)	**527 SPts**	**4 by KMA (median 3.5)**	**11.1**	**6.2**	**HR 1.97 (1.06–3.67)**	**0.03**
					30-Day peri-procedural death or any stroke	
ACST-2 (68)^	3,625 APts	5 mean	8.6	7.1	OR 1.23 (0.96–1.59)*	0.09
CREST-1, 2016 (80)	**1,607 SPts + APts**	**10 by KMA (7.4 median)**	**11.0**	**7.9**	**HR 1.37 (1.01–1.86)**	**0.04**
CAVATAS, 2009# (81)	504 SPts + APts	8 KMA (median 5)	29.7	23.5	HR 1.35 (0.94–1.93)*	0.10
					Any stroke free survival#	
ACT-1, 2016 (69)	1,453 APts	5 by KMA (median/mean not published)	93.1	94.7	Insufficient raw data published to calculate HR/OR	

KMA, Kaplan Meier analysis; SPts, symptomatic patients with advanced ipsilateral carotid stenosis; APts, patients with advanced asymptomatic or recently (for at least 6 months) asymptomatic carotid stenosis.

Bolded font indicates trials with sufficient statistical power to compare longer term stroke and death rate with CEA and CAS (including and beyond the peri-procedural period).

#90% were symptomatic.

**OR calculated from published raw data.*

^Analysis using intention to treat figures.

#These figures on any stroke free survival in ACT-1 appear to exclude 30-day peri-procedural strokes (69).

Trans-carotid Arterial Revascularisation

There is a push to roll out a new hybrid procedure called ***"trans-carotid artery revascularization"*** (TCAR) into routine practice, despite no comparisons with current medical intervention alone and an unlikely benefit for at least the vast majority of patients (12, 92, 93). Currently, TCAR is only being assessed in registries and compared against CEA and transfemoral/transaortic stenting. Presently, there are no randomized trials comparing TCAR with current best medical intervention alone. However, ***a routine practice indication for TCAR (or any other arterial disease procedure) cannot be established without first showing that the procedure provides additional patient benefit compared to current best medical intervention alone***. Further, it is insufficient to simply show that a procedural risk is low, or zero, even if that was universally possible (see below).

Medical Intervention

It is now well-recognized that the stroke prevention benefit of medical intervention alone (risk factor identification, lifestyle coaching or healthy lifestyle habits and appropriate medication) has improved significantly over the last 3–4 decades in both ***asymptomatic and symptomatic patients with advanced carotid stenosis*** (13, 21–28). Indication of this improvement in relation to asymptomatic carotid stenosis patients was first published in 2007 and was then confirmed in more detail and by several independent groups across multiple countries (13, 21–25). Latest reported average annual ipsilateral stroke rates associated with advanced asymptomatic carotid stenosis patients treated with medical intervention alone approximate 0.8%. This is lower than with either CEA or CAS in previous randomized trials (see **Figure 3**, **Table 4**) (2, 12). Further, the most recently reported quality measurements of stroke rate with medical intervention alone were published around 2013 (2, 12). These latest studies likely underestimate what can be now achieved because medical intervention has continued to improve since they were performed and published.

Furthermore, recent studies have shown that aggressive medical intervention in specialized stroke/TIA clinics can dramatically reduce the early risk of recurrent cerebral ischaemic events in symptomatic patients awaiting CEA or CAS (26–28). These studies include a 2021 comparison of stroke rates among symptomatic patients awaiting a carotid procedure in three older randomized trials of CEA vs. medical intervention (recruitment between 1981 and 1996) and four more recent randomized trials of CEA vs. CAS (recruitment between 2000 and 2008). This analysis showed that symptomatic patients enrolled in the more recent trials had a lower rate of stroke after randomization than patients in the older trials (28). Improvements in medical intervention have also been demonstrated by ***better outcomes in other populations***, including symptomatic patients with intracranial arterial disease in the SAMMPRIS Trial (21, 96, 97).

Medical intervention consists of the diagnosis and management of leading arterial disease risk factors, including hypertension, blood lipids, diabetes, tobacco smoking, atrial fibrillation, physical inactivity, sleep disorders, and excessive weight and alcohol consumption. The nature of the medical intervention received in previous studies of carotid stenosis patients most likely reflected common practice at the time. However, this information was not reported or, at best, it was only partially reported (2, 12, 21). This lack of reporting probably

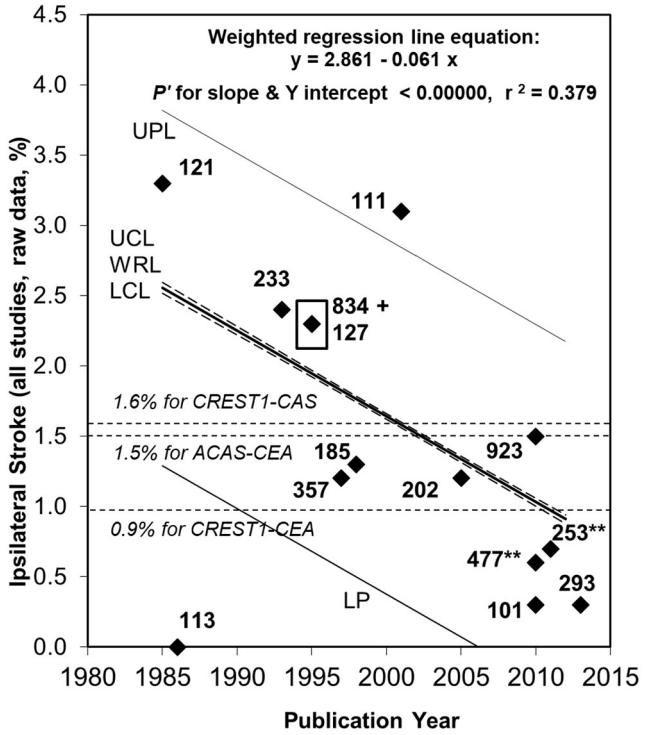

FIGURE 3 | Ongoing fall in ipsilateral stroke rate in patients with ≥50% asymptomatic carotid stenosis given medical intervention alone between 1984 and 2013 (2, 21). Sixty seven percentage relative (or 1.7% absolute) fall in the reported average annual ipsilateral stroke rate in patients with ≥50% ACS given medical intervention alone from 1984 to 2013. Fifty six percentage relative fall since ACAS was published in 1995 with 834 medically treated patients, ACAS result highlighted by a black box (35). Black diamonds are study results with corresponding sample sizes. As in 2009, the Ryan-Holm stepdown Bonferroni correction was made for multiple comparisons (converting raw *P*-values to *P'*-values, SYSTAT 13, SYSTAT Software Inc) (21). UPL and LPL, respectively, = upper and lower 95% prediction limits for new population rate estimates; UCL and LCL (dashed lines), respectively = upper and lower 95% confidence limits for the population regression line; WRL, weighted regression line; ACAS, Asymptomatic Carotid Atherosclerosis Study (35); CREST-1, Carotid Revascularization Endarterectomy vs. Stenting Trial (65). **Indicates two studies including a small minority with remote ipsilateral stroke/TIA at baseline (94, 95). These were included in this analysis because the regression line was not appreciably different with (y = 2.861–0.061x, *P'* for slope and y intercept < 0.00000 and $r^2 = 0.379$) (2) or without them (y = 2.720–0.051x, *P'* for slope and y intercept < 0.00000 and $r^2 = 0.275$) (12).

reflects a general under-appreciation of the value of medical intervention at the time. In addition, knowledge regarding how to best reduce arterial disease risk through medical intervention has evolved over decades and across many specialties, causing confusion and uncertainty (see below).

We are preparing an in-depth, multi-expert review of current best medical intervention for prevention of arterial disease complications with a focus on carotid stenosis patients. This will be submitted for publication shortly. Highlights include the importance of separating carotid stenosis patients into those who are completely asymptomatic with respect to arterial disease (in the absence of another indication, they do not need antiplatelet medication) (98) from those who have been symptomatic. Best use of antiplatelet and anticoagulant drugs is also heavily dependent on how long ago a patient was symptomatic, what kind of symptoms they had, and whether or not they have atrial fibrillation and/or metallic heart valves (99–109).

Generally speaking, the threshold for diagnosing the leading arterial disease risk factors has lowered over the last 3–4 decades (21). Target blood pressure and cholesterol levels have lowered and now tend to be influenced by the patient's overall risk factor profile rather than using a "one target fits all" approach. For example, some now recommend a target low-density lipoprotein (LDL) cholesterol for asymptomatic or symptomatic persons with carotid stenosis of 1.4 mmol/L (55 mg/dL) or less, or at least 50% lower compared to baseline (110). However, the lower the LDL, the lower the risk of arterial disease complications (111–116). For every 1 mmol/L reduction in LDL, there is an expected overall reduction in the absolute average annual rate of major arterial disease complications of 0.8% (a relative risk reduction of ∼20%) and 0.2% reduction in the absolute average annual rate of all-cause mortality (a relative risk reduction of ∼10%) (111, 112). There are no known risks of lowering LDL per say. There are similar benefits for men and women (112). Serious adverse reactions from statins and ezetimibe are uncommon (110).

A general definition of hypertension >140/90 prevails in Australian and European guidelines (117–119). Meanwhile, >130/80 is now used as the definition of hypertension in the USA (120). Benefits are proportional to the degree of blood pressure lowering, rather than class of drug used (121). Overall, meta-analyses have shown that for every 10 mm Hg reduction in systolic blood pressure, there is an expected 1.9% absolute (20% relative) risk reduction in major cardiovascular events (fatal and non-fatal myocardial infarction, sudden cardiac death, revascularisation, fatal and non-fatal stroke, fatal and non-fatal heart failure) over the next few years or so (122, 123).

CURRENT BEST MANAGEMENT OF CAROTID STENOSIS PATIENTS

Patients With Asymptomatic Carotid Stenosis

It can now be estimated that ∼0% of low/average surgical risk patients with advanced asymptomatic carotid stenosis (like those recruited into ACAS or ACST-1 and included in meta-analyses) (2, 12, 35, 37) could now overall benefit from a carotid artery procedure if they are receiving current best practice medical intervention. This conclusion is derived from the following observations:

i. ***The average annual ipsilateral stroke rate was ∼0.8%*** with medical intervention alone in the most recently published quality studies (2, 12, 21).

ii. ***About half the strokes occurring in the distribution of 60–99% asymptomatic carotid stenosis are not actually due to the stenosis*** (3). Therefore, the average annual ipsilateral stroke rate due to carotid stenosis (based on the most recently published quality studies of patients given medical intervention alone) is about ***0.4%.***

iii. ***The average age of diagnosing 50–99% asymptomatic carotid stenosis was 70 years*** in past quality studies of patients given medical intervention alone and their ***average survival was 10 years*** (2, 12, 21). Therefore, at most, about 4% (10 times 0.4%) will have an ipsilateral stroke due to carotid stenosis during their remaining life time following diagnosis and could possibly benefit from a carotid procedure were they to receive medical intervention to the standard in the most recently published studies (2, 12, 21).

iv. ***Medical intervention has improved*** since 2013. Therefore, the 4% estimate of the maximum proportion of average/low CEA risk patients with advanced asymptomatic carotid stenosis who could possibly benefit from a carotid procedure during their lifetime is probably an overestimate.

v. ***The procedural rate of stroke and death*** and other significant complications cannot always and everywhere be zero. This is expected to negate any possible overall routine practice benefit from carotid procedures in patients with asymptomatic carotid stenosis in the modern era, particularly given that routine practice carotid procedural outcomes are often, if not usually, worse outside trials (13, 42, 43).

The available evidence indicates that ***we have passed an era in which carotid artery procedures are likely to provide an overall benefit for this population***. Meanwhile, patients with a sufficiently high, average annual ipsilateral stroke risk (despite current best practice medical intervention) have not been identified. Such patients, if they exist, are rare. It is currently impractical and unethical to routinely screen to detect them if the purpose is to select individuals for carotid artery procedures (see below) (12). Therefore, the current best management of patients with advanced asymptomatic carotid stenosis is ***current best medical intervention alone***. It will remain that way unless at least one subgroup of this population is identified that benefits from the addition of a carotid artery procedure in appropriate randomized trials (which is unlikely), and the results of such randomized trials are at least as good in routine clinical practice.

Symptomatic Patients With Carotid Stenosis

Limited information is available with respect to outcomes of symptomatic patients with advanced carotid stenosis managed with current standards of medical intervention alone. This aspect of stroke prevention has not been properly retested, evidently based on the continuing false assumption that medical intervention has not changed and that CEA (or even CAS or TCAR) are indicated and beneficial for patients. However, as mentioned above, it is known that recurrent stroke and TIA rates in symptomatic patients awaiting a carotid procedure have fallen significantly over time as medical intervention has improved (26–28). Improvements in medical intervention over the last 3–4 decades mean that all past randomized CEA trials are outdated. In addition, the widely used 6% 30-day peri-procedural stroke or death rate "standard" used in routine practice, and derived from these outdated randomized trials, is presently excessive (1). As mentioned above, it is likely that fewer symptomatic patient subgroups will now benefit from a carotid artery procedure and the time window for procedural benefit is probably shorter compared to when NASCET, ECST-1, and the VACS were conducted 3–4 decades ago (49).

Symptomatic patients with carotid stenosis, however, have a higher stroke risk and are more likely to benefit from a carotid artery procedure than asymptomatic carotid stenosis patients. Symptomatic patients receiving current best practice medical intervention alone are the priority for stroke risk stratification studies (see below). Only those with a sufficiently high residual average annual ipsilateral stroke rate should be considered for future randomized trials involving carotid procedures vs. current best medical intervention alone. As explained below, the average annual ipsilateral stroke rate should probably be in the order of at least 3–4% despite current best medical intervention before randomized procedural trials are considered (71).

In the meantime, all ***symptomatic patients with carotid stenosis should receive current best practice medical intervention as soon as possible. Expertly performed CEA*** (not CAS or TCAR) ***could be considered for those who fit the profile of one of the 3 subgroups which had an overall benefit from CEA in NASCET, ECST and the VA309 (see above)***, so long as the 30-day stroke or death rate is "acceptable." The definition of acceptable is unclear. However, it should certainly be <6% (49). Independently of the surgical team, the 30-day peri-operative stroke or death rate should be systematically measured and adjusted for patient risk factors wherever CEA is performed. This information should be available at the point-of-care to allow clinicians and patients to make properly informed decisions. In addition, patients should be advised that the information for supporting this combined medical-surgical approach is based on highly selected patient subgroups and outdated, randomized CEA trials conducted 30–40 years ago.

Therefore, ***if consent for a carotid procedure is truly "informed" in a symptomatic patient,*** *several issues must be discussed with that patient and their carers:*

i. The option of current best practice medical intervention alone, given the lack of current randomized trial data with respect to CEA benefit, known improved outcomes with medical intervention alone since the VA309, NASCET and ECST, the modest overall benefit from CEA in those randomized trials (3.2%/year) and that most patients (for example, about ∼74% with 70–99% stenosis) did not have an ipsilateral stroke during follow-up in those randomized trials (4).

ii. The subgroups of carotid stenosis patients included and excluded in the VA309, NASCET, and ECST and the subgroups shown to benefit and not benefit in those trials.

iii. Identifiers of a particularly poor chance of procedural benefit and a particularly increased risk of procedural harm, such as advanced age and major comorbidity.

iv. Overwhelming evidence that CAS is more dangerous than CEA, while any TCAR benefit is unproven.

COMMON "FURPHIES" REGARDING CAROTID ARTERY PROCEDURES

According to Wikipedia, a furphie is Australian slang for rumor, or an erroneous or improbable story, but usually claimed to be absolute fact. A furphie is generally heard first or second

hand from a reputable source and, until discounted, is widely believed (see https://en.wikipedia.org/wiki/Furphy). This section provides an outline of five common furphies used to make CEA and CAS appear "similar" with respect to their outcomes (when they are not) or to make carotid procedures appear "indicated" (when medical intervention is the only currently proven effective treatment).

Omitting the Peri-Procedural Risk Furphie

Proponents of this first furphie imply that CAS and CEA are similar in outcome after a "successful" carotid artery procedure and/or emphasize only the outcomes beyond the peri-procedural period (36, 37, 68, 80, 81). By "successful," proponents generally infer a procedure not complicated by peri-procedural stroke or death. However, one cannot have a carotid artery procedure without the peri-procedural period and those who will have a peri-procedural stroke or death cannot be accurately predicted. It is inappropriate to compare procedures without including the peri-procedural period when making treatment decisions. As explained above, in every adequately powered randomized trial comparison, CAS was found to cause significantly more peri-procedural strokes (with or without deaths or clinically-defined myocardial infarctions) than CEA (12, 49, 56, 57). Stroke rate differences between CAS and CEA appear similar beyond that time. However, if the peri-procedural period is indeed included, the higher rate of stroke in patients who had CAS compared to CEA has been seen for as long as patients have been followed-up in randomized trials. This indicates that surviving patients who have peri-procedural stroke tend to live long term with their stroke (while those that die remain dead). Therefore, the harm caused by CAS in terms of stroke and death is durable. Short through to long term outcomes from CAS and CEA are *not* similar (124).

The Heart Attack Furphie

Proponents of this furphie imply that CAS and CEA are "similar" because the risk of stroke with CAS is compensated by the risk of myocardial infarction with CEA (70, 80, 125). Across the randomized trials of CAS compared to CEA, where the 30-day rate of stroke, clinically-defined myocardial infarction and death were reported, overall CEA was associated with nearly twice as many clinically-defined myocardial infarctions. However, CAS was associated with twice as many peri-procedural strokes and 1.5 times as many peri-procedural deaths than CEA (12). Moreover, in these randomized trials during the 30-day peri-procedural period, strokes and deaths (most associated with CAS) were 5.4 times more common than clinically defined myocardial infarctions (12). This means that, overall, CAS was associated with 1.6 times more peri-procedural strokes, deaths and clinically-defined myocardial infarctions than CEA (12). These comparisons reached statistical significance with respect to stroke, death, and myocardial infarction in symptomatic patients in meta-analyses of randomized trials (56, 57). However, there are still insufficient numbers of randomized asymptomatic patients studied to make an adequately powered comparison between CEA and CAS for this combined outcome measure. In summary, in randomized trials of CAS vs. CEA, CAS was overall associated with more peri-procedural stroke, death and myocardial infarction than CEA and the significantly elevated risk of stroke (or death) with CAS was not compensated by the smaller excess risk of myocardial infarction with CEA.

The Most Severe Stroke Furphie

Proponents of this furphie claim or indicate that CAS and CEA are "similar" because disabling strokes [with modified Rankin Scale (mRS) score $\geq$3] in the ICSS, or other randomized trials, were about as common with each procedure (68, 77). Such reasoning is inappropriate. ***Firstly,*** unless shown otherwise, all strokes should be assumed disabling. A modified Rankin score of 1 means able to carry out all usual activities of daily living despite some symptoms. A score of 2 means able to look after one's own activities of daily living without assistance, but unable to carry out all previous activities (126). For some patients, even this level of disability is likely be a significant infringement on their previous quality of life. In addition, the mRS only considers fundamental activities, mostly regarding mobility and self-care. It does not necessarily take into account more complex activities, such as the ability to return to one's previous employment.

Secondly, past randomized trials have been underpowered to exclude clinically significant differences in the rate of the most severe strokes associated with CAS and CEA. For example, as recently reported from ACST-2 (the largest randomized trial of CEA vs. CAS in ***asymptomatic/recently asymptomatic carotid stenosis patients***, with 3,625 total subjects), there were only 25 total 30-day peri-procedural strokes with a mRS score of 3–6 (13 with CAS and 12 with CEA, OR 1.09, 95% CI 0.46–2.61, $P = 0.84$) (68). The CI indicates that if the ACST-2 methodology was rolled out into routine practice, and thus involved a much larger sample size, it is within the realm of probability that CAS would cause up to 2.6 times as many of the most severe strokes as CEA. That excess harm associated with CAS would be clinically significant.

Meanwhile, the ICSS has been the largest randomized trial of CAS vs. CEA in ***symptomatic patients*** (1,713 total patients) (77). The ICSS was powered sufficiently to show that new diffusion-weighted lesions on magnetic resonance brain imaging (MRI) were more common after CAS (in an ICSS sub-study affecting 50% of the CAS patients and 17% of CEA patients, OR 5.2, 95% CI 2.8–9.8) (127). The ICSS was also sufficiently powered to show that *any* stroke (modified Rankin score of $\geq$1) by 5 years of follow-up was more common with CAS (affecting 15% of CAS patients and 10% of CEA patients, HR 1.7, 95% CI 1.3–2.3, $P < 0.01$) (77). However, the most severe strokes (with a modified Rankin score $\geq$3) occurred in only 6.5% of both CAS and CEA patients: HR 1.06, 95% CI 0.7–1.6 (77). The CI indicates that if the ICSS methodology was rolled out into routine practice, and thus involved a much larger sample size, it is within the realm of probability that CAS would cause up to 1.6 times as many of the most severe strokes as CEA. That excess harm associated with CAS would be clinically significant.

A trend with respect to more severe strokes with CAS compared to CEA was seen in meta-analyses of randomized trials of CAS vs. CEA in symptomatic patients (56, 57). Randomized trials have been underpowered with respect to comparing rates of severe stroke with CAS and CEA. Therefore, the procedural risk of severe stroke should not be used to justify CAS.

The Late Disability Furphie

Proponents of this furphie indicate that CAS and CEA are "similar" because the prevalence of late disability (poor functional outcome) with both procedures is similar (77, 128). This comparison was derived from the ICSS and involved disability from any cause, not just disability due to strokes caused by carotid procedures. Disability from any cause reportedly affected ∼60% of both CAS and CEA treated patients in the ICSS at 12 months post procedure and ∼70% of both groups by 5 years post procedure (77, 128). Disability from any cause is common in this elderly population. Combining disability from stroke with all other causes of disability statistically camouflages, but does not remove, the excess disability caused by stroke caused by CAS compared to CEA. As above, the excess rate of stroke (and therefore stroke caused disability) associated with CAS compared to CEA is measurable for as long as patients have been followed-up in randomized trials. It is, inappropriate to discount this excess stroke associated disability from CAS by mixing it with disability from any cause.

Limiting Carotid Procedures to "High Stroke Risk" Patients Furphie

This last featured furphie appears in recently published clinical guidelines for the management of patients with asymptomatic carotid stenosis (129–131). Proponents recommend CEA, or even CAS, for 50-99% asymptomatic stenosis patients if at least one of the following (or possibly other undefined) features, are present:

i. ***Silent infarct*** *on computed tomography brain imaging*
ii. ***Asymptomatic stenosis progression***
iii. ***Large plaque*** *area*
iv. ***Juxta-luminal black areas*** *on ultrasound*
v. ***Intraplaque hemorrhage*** *on MRI*
vi. ***Impaired cerebrovascular reserve***
vii. ***Plaque echolucency*** *on ultrasound*
viii. ***Transcranial embolic signals*** *with or without plaque echolucency*
ix. ***History of contralateral stroke or TIA***

However, for several reasons it is inappropriate to use these markers to justify carotid artery procedures in the routine management of asymptomatic carotid stenosis patients. ***Firstly***, not all of these markers have been shown to identify patients at higher than average ipsilateral stroke risk despite medical intervention (12). This includes detection of embolic signals (ES) with transcranial Doppler (TCD). Of the three studies investigating the association of ES detection and risk of subsequent stroke in asymptomatic carotid stenosis patients, two were flawed because nearly half the strokes that occurred during follow-up were in patients who already had an ipsilateral TIA during follow-up (94, 132, 133). Therefore, these were studies of mixed asymptomatic and symptomatic patients with carotid stenosis. The third study was negative (134).

Secondly, where measured, the average annual rates of ipsilateral stroke (12) and ipsilateral stroke or TIA (135) associated with such markers were generally too low to identify those likely to benefit from a carotid procedure. ***Thirdly***, no proposed stroke risk marker in carotid stenosis patients has been tested using current best practice medical intervention alone. Therefore, all past studies of these markers overestimate the current potential benefit of a carotid artery procedure (12). ***Fourthly***, most, if not all, proposed high plaque risk features are individually too common to identify the small proportion of patients who are now likely to benefit from a carotid artery procedure (a proportion which, as explained above, is close to zero, if such patients exist) (12, 135).

Moreover, as a group, proposed markers of high stroke risk may be used to cover just about any asymptomatic carotid stenosis patient, particularly when not all markers that may confer increased stroke risk are stipulated in guidelines (12, 130). Problems related to the lack of specificity of proposed stroke risk markers are compounded by guideline writers not providing reproducible definitions (129–131). For example, ∼10% of asymptomatic carotid stenosis patients will have at least 1–2 ipsilateral middle cerebral artery ES detected after 1–2 h of TCD monitoring (133). However, this proportion increases to over 60% with more frequent monitoring (133). By way of another example, at least some degree of ultrasound echolucency is very common in 60–99% asymptomatic carotid stenosis plaques, reported in at least 63% of carotid duplex studies in the "ASED Study" (136). Finally, no proposed marker of high stroke risk in asymptomatic carotid stenosis patients has been tested in randomized trials of CEA vs. current best practice medical intervention alone (12).

Another common mis-justification for procedural intervention for asymptomatic carotid stenosis is ***the presence of 80–99% (rather than 50–79%) stenosis*** (137, 138). However, past research has shown that the average annual ipsilateral stroke rate associated with 50–80% and 80–99% (using NASCET or unspecified criteria) is small (in the order of 1 and 3%, respectively) (139, 140). Such rates are particularly low considering we can expect to significantly lower these rates with current best, intensive medical intervention alone, perhaps to 0.5–1.5% or less (12). Meanwhile, the ACAS is still the dominant trial with respect to showing a potential routine practice procedural benefit in patients with asymptomatic carotid stenosis (35). Following on from ACAS results for patients given medical intervention alone, a population of patients with asymptomatic carotid stenosis with an average annual ipsilateral stroke rate of at least 2–3%, despite current best medical intervention alone, should be sought before a carotid artery procedure might be considered to provide additional benefit (35, 71). However, in order to provide a buffer against net patient harm, an average annual ipsilateral stroke rate over 3–4% is probably more appropriate given that 30-day procedural stroke and death rates in routine practice are often, if not usually, higher than in randomized trials (12, 42, 43, 71).

In summary, using proposed "high stroke risk" markers to select asymptomatic patients for carotid procedures in routine practice will continue the widespread use of risky, costly and unnecessary carotid procedures that started decades ago (1, 12, 29). As mentioned, symptomatic patients with carotid stenosis are much more likely to benefit from a carotid procedure

combined with current best medical intervention. Therefore, if the goal is to select patients who will benefit from a carotid artery procedure, ***symptomatic patients should be the priority for stroke risk stratification studies using the above markers and perhaps others.*** Only those with sufficiently high residual ipsilateral stroke rate, despite current best medical intervention, should be considered for randomized trials of current best practice medical intervention with or without an additional best practice carotid artery procedure.

ONGOING RANDOMIZED TRIALS INVOLVING CAROTID PROCEDURES

Currently three randomized trials involving carotid artery procedures (CEA and CAS) are known to be underway or are planned. They each have medical-intervention-only-arm ("ECST-2," "CREST-2," and "ACTRIS"). None of these trials is likely to identify a procedural indication for carotid stenosis patients in current routine practice.

ECST-2 is the only randomized trial that involves symptomatic patients with carotid stenosis (http://s489637516.websitehome.co.uk/ECST2/index2.htm). However, only those who are symptomatic and considered at low stroke risk on medical intervention are being randomized to medical intervention with or without CEA or CAS. Hence, outcomes are likely to be similar in the treatment arms, or possibly worse with a carotid procedure. In ***ECST-2 and CREST-2*** (https://clinicaltrials.gov/ct2/show/NCT02089217) patients with asymptomatic carotid stenosis considered at low or average surgical risk (similar to those recruited into ACAS and the ACST-1) are being randomized to medical intervention alone with or without additional CEA or CAS. However, as explained above, such patients are unlikely to have an overall benefit from these procedures.

By contrast, in ***ACTRIS*** (https://clinicaltrials.gov/ct2/show/NCT02841098) patients with advanced asymptomatic (or recently asymptomatic) carotid stenosis considered at higher than average ipsilateral stroke risk despite medical intervention are being randomized to CEA or medical intervention alone. Markers of "high stroke risk" being used include history of contralateral TIA or ischemic stroke due to atherosclerotic carotid disease, silent brain infarction on MRI, predominantly echolucent plaque on ultrasound, the presence of transcranial Doppler (TCD)-detected embolic signals, intraplaque hemorrhage on MRI, TCD-measured impaired cerebral vasomotor reserve or rapid stenosis progression. However, it is likely ACTRIS will be underpowered because stroke rates in such patients have not first been measured with current best practice medical intervention alone. As mentioned, all past stroke risk stratification studies in asymptomatic carotid stenosis patients given medical intervention alone are outdated and overestimate any current potential procedural benefit. As explained above, only asymptomatic carotid stenosis patients with a sufficiently high residual average annual ipsilateral stroke rate (in the order of least 3–4%), despite current best medical intervention, should be recruited into randomized trials involving carotid artery procedures.

Meanwhile, the ***ACST-2*** investigators relatively recently randomized only asymptomatic (or recently asymptomatic) carotid stenosis patients to either CEA or CAS (https://clinicaltrials.gov/ct2/show/NCT00883402) (68). ACST-2 investigators may find support for the notion that CEA and/or CAS are relatively safe. However, as mentioned above, there was a trend for more stroke and peri-procedural death with CAS (68). Moreover, the ACST-2 investigators cannot establish a procedural indication over current best practice medical intervention alone because the trial did not include a medical-intervention-only treatment arm.

WHAT THE GUIDELINES SAY

In 2015 we demonstrated many ways in which "evidence-based" guidelines for carotid disease management encourage overuse of so-called carotid artery "revascularization" procedures (1). We found 34 guidelines published between 2008 and 2015, from 23 different regions or countries and written in six languages with recommendations regarding the use of CEA and/or CAS in relation to symptomatic and/or asymptomatic patients. Many of these guidelines have not been reiterated. With respect to ***"average surgical risk" patients with 50–99% asymptomatic carotid stenosis***, 96% (24/25) of applicable guidelines endorsed CEA and 63% (17/27) endorsed CAS by recommending, respectively, that these procedures should or could be done. The endorsements were given despite no evidence of procedural benefit over contemporary medical intervention, underpowered randomized trial comparisons of CAS vs. CEA (with safety trends against CAS) and known clinically significant procedural risks (1). In addition, 48% (13/27) of the applicable guidelines endorsed CAS for patients with asymptomatic carotid stenosis ***considered at "high surgical risk"*** due to arterial anatomy, comorbidities or undefined reasons. This is despite safety trends against CAS, not measuring outcomes with any standard of medical intervention alone and the likelihood that many such patients would not live long enough to benefit from a carotid artery procedure (1, 141–144).

Our critical comparative audit of worldwide guidelines for carotid stenosis management also revealed that 100% (31/31) of applicable guidelines endorsed CEA for ***"average surgical risk" symptomatic patients with 50–69% or 70–99% carotid stenosis***. Just over half the guidelines [18/33 (55%) and 19/33 (58%), respectively], endorsed CAS for both moderate and severe carotid stenosis in average surgical risk symptomatic patients. In addition, 82% (27/33) of the applicable guidelines endorsed CAS for symptomatic patients ***considered at "high-CEA-risk"*** because of their vascular anatomy, comorbidities of undefined reasons. These endorsements were given despite no evidence of procedural benefit over contemporary medical intervention, clinically significant procedural risks (especially for CAS) and direct evidence that many "high-surgical-risk" patients will not live long enough to benefit from a carotid artery procedure (1, 141–144).

Other ways in which guidelines over-encourage carotid artery "revascularization" procedures include not limiting procedural

recommendations to subgroups shown to overall benefit from CEA compared to medical intervention alone in past randomized trials, not acknowledging that all past randomized trials involving CEA are outdated, and not clearly defining target populations and standards with respect to the 30-day peri-procedural rate of stroke and death (1). In addition, guidelines often omit recommendations for medical (non-invasive) interventions which are currently proven to reduce the risk of stroke and other arterial disease complications (1).

We are performing an updated critical comparative audit of guidelines regarding carotid "revascularization" procedures. Unfortunately, the ***procedural biases mentioned above are still common***, including in the most recently published guidelines (145–147). At least with respect to asymptomatic carotid stenosis patients, guidelines from Australia and Denmark discourage CEA and CAS or screening (148–150). Meanwhile, guidelines from the UK and USA were published which came at least part way in overcoming procedural bias in recommendations for asymptomatic carotid stenosis patients (151–153). However, unfortunately the improved UK guidelines were replaced by guidelines which omitted recommendations for asymptomatic carotid stenosis patients (154). Improved guidelines for symptomatic patients are even slower to emerge.

HOW TIMES ARE CHANGING FOR THE BETTER

Existing Changes

The good news is that stroke prevention has become much cheaper, more effective and less invasive over the last 3–4 decades (13, 21–28, 96, 97). This is testimony to the success of researchers, public health campaigners, policy advisors, educators, and the general public. Now it is clear that the individual has the most power to prevent their own stroke. Improvements in medical intervention provide hope not just for patients with carotid artery disease but for everyone. This is because medical intervention reduces the risk of all arterial disease complications in all at risk.

As indicated above, improved medical intervention in carotid stenosis patients has prompted some guideline updates and new randomized trials of carotid procedures to include a medical-intervention-alone arm (when previously only CEA and CAS were compared). There have been policy decisions that protect the public from unnecessary, risky and expensive carotid artery procedures (61, 62). Our successful campaign to advise US Medicare not to expand CAS reimbursement indications in 2012 led to the establishment of the Faculty Advocating Collaborative and Thoughtful Carotid Artery Treatments (FACTCATs) (61, 62). This is a growing group with currently over 365 clinicians and scientists of all career stages with an interest in stroke prevention. FACTCATs communicate and collaborate via simultaneous group email. Members with diverse views are welcomed and there is ongoing encouragement that opinions are substantiated by factual scientific evidence. This group, and the FACTCATs website (see https://factcats.org/), are effective and novel ways to provide large-scale education to professionals and the public. Moreover, rates of carotid procedures are falling in the USA and UK (155–158). Additionally, to drive further improvement in the field, two important new initiatives (or "emerging changes") are underway, as will be explained next.

Emerging Changes

The First "Evidence-True" Guideline for Carotid Artery Disease Management

The flaws in existing carotid disease guidelines are being used to define methods to ***maximize guideline objectivity and focus on optimizing patient outcomes***. These criteria will be utilized in the first "evidence-true" guideline for carotid artery disease management (159). These novel methods could be applied generally to clinical practice guidelines no matter the health condition. This new carotid disease guideline is being produced under the auspices of the International Union of Angiology (IUA, Abbott et al., in preparation, see: https://factcats.org/). The IUA provides focus for scientific endeavor across all specialties involved in vascular disease (see https://www.angiology.org). Existing good practice guideline methodology will be retained, including multi-specialty and consumer contribution (160, 161). ***Novel, generalizable methods include:***

i. ***Limiting guideline endorsements for interventions to subgroups that benefited in relevant trials*** and clearly distinguishing subgroups included and not included in such trials.

ii. ***Not treating subgroups the same*** (such as men and women) if the evidence clearly shows significantly different outcomes with the same treatment.

iii. ***Acknowledging when trials are outdated***, such as all past trials of CEA.

iv. ***Acknowledging when interventions cause excess harm,*** such as CAS.

v. ***Including recommendations for proven medical interventions,*** not just for procedures.

vi. ***Not automatically ranking randomized trial data as best, even if outdated or biased.*** Remarkably, evidence (research) appraisal is often lacking in guidelines, as well as guidelines for creating guidelines (1, 160, 162). However, the ***GRADE system*** is sometimes used, where evidence based on randomized trials begins as the highest quality evidence (163–165). Movement down levels is possible. However, the mechanism of movement is unclear, subjective and not inherently mandated (163–165). We have not noticed demotion of randomized trial evidence in any guidelines we have reviewed (1).

To facilitate objectivity, I have created ***a novel, 12-point scoring system with respect to point-of-care evidence applicability.*** This new ***"pertinence score"*** is a generic checklist of fundamental criteria required for research to be relevant to particular patients at their point-of-care. Factors to be considered include whether or not randomization is required for treatment decisions. For example, a randomized trial is not required to accurately measure a very low stroke rate with medical intervention alone and show, therefore, that a carotid procedure is not indicated. Other scored factors include whether or not study methods are current and key definitions are reproducible.

The CASCOM Study

Improvements in the effectiveness of medical intervention alone have made a welcome and dramatic impact on the management of patients with arterial disease. The highest priority in arterial disease is to properly document the nature of current best practice medical intervention and measure its impact in all kinds of patients, including those with carotid stenosis of any degree of severity. To help address this need, my collaborators and I are taking steps to establish the ***Carotid Stenosis Management During the COVID-19 Era with Best Medical Intervention Alone (CASCOM) Study***. The CASCOM Study is a prospective study of multiple cohorts of asymptomatic and symptomatic patients with carotid stenosis who do not undergo a "revascualrisation" procedure for any reason, including lack of resources caused by the coronavirus pandemic, situations of unproven procedural benefit, anticipated procedural futility or net harm or patient refusal. Hence, we will study patients for whom carotid procedures are not possible or considered unethical (see http://factcats.org/opportunities.php and https://www.anzctr.org.au/ACTRN12621001604897p.aspx).

To save clinician-researcher time, and therefore make the CASCOM Study feasible, we first need to enable the ***"Brainy Medicine" approach to healthcare***. This is where quality research data is produced as a by-product of usual patient reporting in clinical practice. Enabling Brainy Medicine involves innovative software programming and teamwork. We will separate CASCOM Study participants into those who would, and would not, have been eligible for past randomized trials of CEA versus medical intervention alone. Patients considered "eligible" for those randomized trials will be used for hypothesis testing. Given the available evidence (summarized above) we expect at least a 50% lowering of stroke rates with medical intervention alone in the CASCOM Study compared to that seen in past randomized trials of medical intervention with or without CEA. In addition, we plan to study patients in the latter randomized trial "ineligible" category and report their ipsilateral stroke rate over 5 years of follow-up. In contrast to the randomized trials of CEA or CAS presently being conducted, in CASCOM we will study low-, average- and high-surgical-risk patients. We will also independently check the quality of the medical intervention being used in other trials.

As mentioned above, we are preparing an in-depth, multi-expert review of current best medical intervention for prevention of arterial disease complications with a focus on carotid stenosis patients. This will be submitted for publication shortly and used to define standards for medical intervention in the CASCOM Study. This review also aims to address confusion over what constitutes current best medical intervention (49). The following are a few examples of confused issues to be addressed:

- ***Atrial fibrillation (AF)*** guidelines do not always limit anticoagulation recommendations to those with ***recent*** AND recurrent or persistent AF (166). Risk according to AF type is heterogeneous (167). Using anticoagulation beyond patient types who benefited in trials is over-treatment and exposes patients to a life-threatening bleeding risk (about 2–3%/year) without proven benefit.
- Major inconsistencies exist in guideline risk calculator recommendations on when to start ***lipid lowering therapy*** in primary prevention (168), implying error in evidence interpretation.
- "FACTCATS" discussions reveal variability in expert use of treatments, such as ***antiplatelet therapy*** for primary prevention (in asymptomatic patients). Some still inappropriately recommend it based on outdated trials (98).
- The Australian Pharmaceutical Benefits Scheme (PBS) has just announced subsidized use of ***low-dose rivaroxaban and aspirin*** in selected patients with asymptomatic carotid stenosis (see, https://www.pbs.gov.au/medicine/item/12192Q-12197Y|) However, there is no randomized trial evidence of significant benefit in patients with carotid stenosis (169). This PBS decision is likely to encourage exposure of patients to an unjustified risk of ***anticoagulant***-linked bleeding.

CURRENT PRIORITIES AND THE WAY AHEAD

Among the highest research priorities now is to properly ***document the nature of current best practice medical intervention*** for prevention of stroke and other arterial disease complications and ***measure its impact.*** Studies should include risk stratification with the goal of identifying asymptomatic and symptomatic patients likely to benefit from more aggressive or specialized medical and/or procedural interventions (41). Trials of new (and especially relatively high risk and/or expensive) interventions depend upon us first determining what can be achieved with the available effective interventions. Markers having the most promise with respect to carotid stenosis ***stroke risk stratification*** include standardized ultrasound characterization of plaque morphology combined with degree of stenosis and clinical features, MRI evidence of intraplaque hemorrhage and silent progressive stenosis toward occlusion (12, 139, 170, 171). As indicated above, it is more likely that such risk markers will identify symptomatic patients likely to benefit from a carotid artery procedure than asymptomatic carotid stenosis patients. Only patients with sufficiently high ipsilateral stroke rate, despite current best practice medical intervention alone, should be considered for randomized trials involving a carotid artery procedure. Meanwhile, we need to ***improve access to current best practice medical intervention***, establish ways to ***systematically measure outcomes from routine practice*** services using electronic health records and remove access to (or payment of) harmful and useless interventions (156, 159, 172). Resources saved should be redirected to better support effective services and more research (49).

Like it or not, and in ***answer to the "big question,"*** there is no current randomized trial evidence that a carotid artery procedure provides an additional stroke risk reduction benefit compared to current best practice medical intervention alone in any subgroup of carotid stenosis patients. To establish a current routine practice indication for a carotid artery procedure, at least one patient subgroup must be shown to benefit overall. This demonstration of overall patient benefit will depend on:

- Properly conducted ***risk stratification studies using current best practice medical intervention alone*** (to identify those with sufficiently high residual ipsilateral stroke rate), then
- ***Randomized trials*** of current best practice medical intervention alone with and without the addition of a best practice carotid artery procedure (only in those with sufficiently high ipsilateral stroke rate despite current best practice medical intervention alone) then
- Ensuring that favored randomized trial methods and results are ***duplicated at the point of care***.
- ***Acknowledging and addressing biases*** which continue to drive inappropriate carotid procedures, so we can provide only what is known to be effective treatment and perform the required research (1, 173, 174).

All things considered, we require a worldwide revolution in medical training, public education and resource allocation.

There is no current evidence that ***screening for asymptomatic carotid stenosis*** is beneficial for patients. Screening cannot be recommended if the intention is to identify patients for carotid artery procedures given the inherent procedural risks and no current evidence of procedural benefit. It is known that carotid imaging improves patient motivation to adhere to medical intervention and improves risk stratification compared to using clinically defined risk factors alone (175, 176). However, studies are required to determine if, and how, arterial imaging improves patient outcomes compared to managing clinically-defined risk factors alone (176). Currently, ***screening for carotid stenosis in stroke or TIA patients*** can only be justified for the 3 groups shown to have benefited overall in NASCET, ECST and the VA309 (as outlined above). However, this is while acknowledging that all past randomized trials of CEA vs. medical intervention alone are outdated and there is an urgent need for risk stratification studies and randomized procedural trials in symptomatic patients with sufficient residual ipsilateral stroke risk despite current optimal medical intervention.

Some cite or imply "improved," "acceptable," "comparable," "within guideline" standards or "similar" procedural outcomes, and "low risk" from CEA or CAS (such as in-hospital [rather than 30-day periprocedural] stroke or death rates below 2% for asymptomatic carotid stenosis patients) as sufficient justification for continuing carotid artery procedures (42, 65, 68, 145, 177–179). However, this is inadequate and inappropriate. ***A procedure must be shown to provide a clinically significant net patient benefit (that outweighs procedural risk)*** compared to current best practice medical intervention alone. The likelihood that a particular patient will overall benefit from, or be harmed by, a carotid artery at their point of care is the most important issue when advising patients with carotid stenosis. This is more important than other considerations, such as culture and ethnicity (180, 181). Further, patient preference is a prerequisite for any intervention (182). However, patient preference strongly depends on the way relevant information is presented (or omitted). This has already been demonstrated regarding the topic of asymptomatic carotid stenosis (183).

Patients should be advised that medical intervention is very powerful and the most effective proven way of reducing their arterial disease risk. Further, in at least the majority of patients, it is unlikely that a lack of adherence with current best practice medical intervention can be fully compensated by a carotid artery procedure, given the high level of effectiveness of medical intervention, the limited procedural benefit in previous randomized trials and the inherent procedural risks, particularly in routine practice.

Finally, it is essential everyone (including clinicians, patients, and carers) keep in mind that ***we cannot prevent all strokes or other arterial disease complications. The best that can be done is to choose the management strategy most likely to give the best chance of a favorable patient outcome*** (taking patient, intervention and service provider factors into account). Meanwhile, it is important to continue efforts to improve management strategies and improve patient access to the most effective management strategies. In the case of arterial disease prevention, medical intervention (lifestyle coaching/healthy lifestyle habits and appropriate use of medication) is the most effective strategy. ***Using the principle of "first do no harm," medical intervention is the gold standard by which invasive interventions must always be compared*** (184).

AUTHOR'S NOTE

AA is the founding member of the Faculty Advocating Collaborative and Thoughtful Carotid Artery Treatments (FACTCATS, see https://factcats.org/). FACTCATs have a shared goal of optimizing stroke prevention. By design, clinicians and scientists of diverse views are encouraged to be FACTCATs in this online environment which encourages substantiation of opinion with scientific evidence. The views of particular FACTCATs do not necessarily reflect the views of other FACTCATs.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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