



HHS Public Access

Author manuscript

Stroke. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

Stroke. 2020 January ; 51(1): 311–314. doi:10.1161/STROKEAHA.119.027272.

Carotid plaque with high-risk features in embolic stroke of undetermined source: systematic review and meta-analysis

Joseph KAMTCHUM-TATUENE, MD¹, Alan WILMAN, PhD², Maher SAQQUR, MD³, Ashfaq SHUAIB, MD³, Glen C. JICKLING, MD³

¹Neuroscience and Mental Health Institute, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada

²Department of Biomedical Engineering, University of Alberta, Edmonton, Canada

³Division of Neurology, Department of Medicine, University of Alberta, Edmonton, Canada

Abstract

Background and purpose: An ipsilateral mild carotid stenosis, defined as plaque with <50% luminal narrowing, is identified in nearly 40% of patients with embolic stroke of undetermined source (ESUS) and could represent an unrecognized source of athero-embolism. We aimed to summarize data regarding the frequency of mild carotid stenosis with high-risk features in ESUS.

Methods: We searched Pubmed and Ovid-Embase for studies reporting carotid plaque imaging features in ESUS. The prevalence of ipsilateral and contralateral mild carotid stenosis with high-risk features was pooled using random-effect meta-analysis.

Results: Eight studies enrolling 323 participants were included. The prevalence of mild carotid stenosis with high-risk features in the ipsilateral carotid was 32.5% (95% CI: 25.3 – 40.2) compared to 4.6 % (95% CI: 0.1 – 13.1) in the contralateral carotid. The odds ratio of finding a plaque with high-risk features in the ipsilateral versus the contralateral carotid was 5.5 (95% CI: 2.5 – 12.0).

Conclusions: Plaques with high-risk features are five times more prevalent in the ipsilateral compared to the contralateral carotid in ESUS, suggesting a relationship to stroke risk.

Keywords

embolic stroke of undetermined source; carotid plaque; intraplaque hemorrhage; echolucency; ulceration; stroke etiology

Correspondence: Dr. Joseph KAMTCHUM TATUENE, Neuroscience and Mental Health Institute, Faculty of Medicine and Dentistry, University of Alberta, 4-065 Katz Group Building, 114 Street & 87 Avenue, Edmonton, T6G 2E1 Alberta, Canada. Tel: +1 780 492 83 92. Twitter: @JTatune. kamtchum@ualberta.ca.

Authors' contribution: JKT and GJ conceived the study. JKT performed the literature search, selected the articles, extracted the data, performed the analyses and drafted the manuscript. AW, MS, AS, and GJ contributed to data interpretation and critically revised the manuscript. All authors approved the final version. JKT is the guarantor of the review.

Disclosures: none.

Subject terms

ischemic stroke; atherosclerosis; stenosis; computed tomography; magnetic resonance imaging; ultrasound

INTRODUCTION

Embolic stroke of undetermined source (ESUS) represents 17% (9–25%) of all ischemic strokes [1]. An ipsilateral mild carotid stenosis (plaque with <50% luminal narrowing) is identified in nearly 40% of patients with ESUS and may represent a source of athero-embolism [2, 3]. Vascular imaging is used to assess carotid plaque features other than degree of stenosis that may be important to estimate the stroke risk, notably intraplaque hemorrhage, large lipid-rich necrotic core, thin or ruptured fibrous cap, silent embolic infarcts, progression, irregularity or ulceration, echolucency, neovascularization, inflammation, large juxta-luminal hypoechoic area, large plaque volume, microembolic signals, and impaired cerebrovascular reserve [4]. Patients with ESUS that have a high-risk plaque may benefit from specific interventions to prevent stroke. We aimed to summarize data on the frequency of mild carotid stenosis with high-risk features in ESUS.

METHODS

This report is compliant with the Preferred reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The data supporting the findings of this study are available from the corresponding author upon reasonable request.

We searched Medline and Ovid-Embase for observational studies reporting carotid plaque imaging results in ESUS, from inception to July 15, 2019 (Table I, please see <https://www.ahajournals.org/journal/str>). The titles and abstracts were screened, and full-texts of potentially eligible records were retrieved for further assessment. Disagreements regarding study inclusion were resolved through consensus (JKT and GJ). The risk of bias was assessed using the Risk of Bias Tool for Prevalence Studies (Table II, please see <https://www.ahajournals.org/journal/str>) with the aim of excluding all studies with high-risk of bias from the quantitative synthesis.

We extracted first author's name, year of publication, study design, sample size, mean age, proportion of women, frequency of cardiovascular risk factors, type of index event (stroke or TIA), imaging modality, onset-to-imaging time, side and frequency of mild carotid stenosis with high-risk features.

Analyses were performed with STATA (version 13, StataCorp, College Station, TX, USA). Heterogeneity between studies was assessed using the χ^2 test on the Cochran's Q statistic and quantified by the I^2 index. The prevalence of ipsilateral and contralateral mild carotid stenosis with high-risk features was pooled using random-effect meta-analysis after stabilizing the variance of each study with the Freeman-Tukey double arc-sine transformation. Small-study effect was assessed by visual inspection of funnel plots and

formally tested using Egger's test. Statistical tests were two-sided and statistical significance defined as $p < 0.05$.

RESULTS

The initial search identified 181 records. Eight articles met the inclusion criteria [5–12] (Figure I, please see <https://www.ahajournals.org/journal/str>).

All studies were prospective and enrolled 323 participants with unilateral anterior circulation ischemic stroke (Table 1). Plaque imaging was performed within 14 days of stroke onset using MRI [5, 8–10], CTA [7] or ultrasound [6]. Ulceration, intraplaque hemorrhage, thrombus, fibrous cap rupture, echolucency, or plaque thickness ≥ 3 mm were the high-risk features considered.

The pooled prevalence of mild carotid stenosis with high-risk features was 32.5% (95% CI: 25.3 – 40.2) in the ipsilateral carotid (Figure 1) and 4.6 % (95% CI: 0.1 – 13.1) in the contralateral carotid (Figure II, please see <https://www.ahajournals.org/journal/str>). There was no small-study effect (Figure III, please see <https://www.ahajournals.org/journal/str>). The odds ratio of finding a mild carotid stenosis with high-risk features in the ipsilateral versus the contralateral carotid was 5.5 (95% CI: 2.5 – 12.0) (Figure 2). The odds ratio of finding a ruptured fibrous cap in the ipsilateral versus the contralateral carotid was 17.5 (95% CI: 2.2 – 140.1) (Table III, please see <https://www.ahajournals.org/journal/str>). In the sensitivity analysis, similar results were obtained after excluding studies with sample size < 20 or with potential population overlap [11, 12] (Figures IV and V, please see <https://www.ahajournals.org/journal/str>).

DISCUSSION

Mild stenosis with high-risk features were five times more prevalent in the ipsilateral compared to the contralateral carotid in ESUS, suggesting a relationship to stroke risk. Our findings align with the results of AF-ESUS study showing that patients with ESUS and ipsilateral mild carotid stenosis had a lower 10-year probability of atrial fibrillation detection, thus making a cardioembolic source less probable [2]. Moreover, in NAVIGATE-ESUS trial, patients with ESUS and ipsilateral mild carotid stenosis did not benefit from anticoagulation [3]. In COMPASS trial [13], Rivaroxaban-Aspirin combination was more effective than Aspirin or Rivaroxaban for prevention of non-cardioembolic strokes and represents a potential therapeutic option in patients with ESUS and an ipsilateral mild carotid stenosis. However, recent strokes were excluded and some participants had asymptomatic $\geq 50\%$ carotid stenosis [14]. Therefore, further trials are needed to investigate the benefit of Rivaroxaban-Aspirin combination in patients with recent ESUS and an ipsilateral mild carotid stenosis. Dual antiplatelet therapy with high-dose statins, endarterectomy or stenting also represent potential treatment options.

All studies used a single plaque imaging modality which may have led to underestimation of the prevalence of high-risk plaques in ESUS since various imaging modalities have different sensitivity and specificity for detection of high-risk features [4]. Besides features visible on plaque MRI, high-risk features identified by other imaging modalities may be useful:

microembolic signals (transcranial Doppler), large plaque volume (3D ultrasound), plaque neovascularization (contrast-enhanced ultrasound), and plaque inflammation (PET-CT) [4]. Combination of vascular imaging and blood biomarkers may also be useful to refine stroke risk stratification in patients with ESUS and ipsilateral mild carotid stenosis. RNA biomarker panels that predict stroke etiology with >90% sensitivity and specificity [15] can be integrated into multiparameter scores to predict causality of an ipsilateral mild carotid stenosis in ESUS and better stratify the risk of recurrence prior to inclusion in trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

GCJ receives research support from the Canadian Institutes of Health Research (CIHR), the National Institutes of Health (NIH), the Heart and Stroke Foundation (HSF), the Canada Foundation for Innovation (CFI), and the University Hospital Foundation.

REFERENCES

- Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic Stroke of Undetermined Source: A Systematic Review and Clinical Update. *Stroke*. 2017;48:867–872. [PubMed: 28265016]
- Ntaios G, Perlepe K, Sirimarco G, Strambo D, Eskandari A, Karagkiozi E, et al. Carotid plaques and detection of atrial fibrillation in embolic stroke of undetermined source. *Neurology*. 2019;92:e2644–e2652. [PubMed: 31068479]
- Ntaios G, Swaminathan B, Berkowitz SD, Gagliardi RJ, Lang W, Siegler JE, et al. Efficacy and Safety of Rivaroxaban Versus Aspirin in Embolic Stroke of Undetermined Source and Carotid Atherosclerosis. *Stroke*. 2019;50:2477–2485. [PubMed: 31401971]
- Saba L, Saam T, Jager HR, Yuan C, Hatsukami TS, Saloner D, et al. Imaging biomarkers of vulnerable carotid plaques for stroke risk prediction and their potential clinical implications. *Lancet Neurol*. 2019;18:559–572. [PubMed: 30954372]
- Bayer-Karpinska A, Schwarz F, Wollenweber FA, Poppert H, Boeckh-Behrens T, Becker A, et al. The carotid plaque imaging in acute stroke (CAPIAS) study: protocol and initial baseline data. *BMC Neurol*. 2013;13:201. [PubMed: 24330333]
- Buon R, Guidolin B, Jaffre A, Lafuma M, Barbieux M, Nasr N, et al. Carotid Ultrasound for Assessment of Nonobstructive Carotid Atherosclerosis in Young Adults with Cryptogenic Stroke. *J Stroke Cerebrovasc Dis*. 2018;27:1212–1216. [PubMed: 29307510]
- Coutinho JM, Derkatch S, Potvin AR, Tomlinson G, Kiehl TR, Silver FL, et al. Nonstenotic carotid plaque on CT angiography in patients with cryptogenic stroke. *Neurology*. 2016;87:665–672. [PubMed: 27412144]
- Freilinger TM, Schindler A, Schmidt C, Grimm J, Cyran C, Schwarz F, et al. Prevalence of nonstenosing, complicated atherosclerotic plaques in cryptogenic stroke. *JACC Cardiovasc Imaging*. 2012;5:397–405. [PubMed: 22498329]
- Gupta A, Gialdini G, Lerario MP, Baradaran H, Giambrone A, Navi BB, et al. Magnetic resonance angiography detection of abnormal carotid artery plaque in patients with cryptogenic stroke. *J Am Heart Assoc*. 2015;4:e002012. [PubMed: 26077590]
- Singh N, Moody AR, Panzov V, Gladstone DJ. Carotid Intraplaque Hemorrhage in Patients with Embolic Stroke of Undetermined Source. *J Stroke Cerebrovasc Dis*. 2018;27:1956–1959. [PubMed: 29571754]
- Gupta A, Gialdini G, Giambrone AE, Lerario MP, Baradaran H, Navi BB, et al. Association Between Nonstenosing Carotid Artery Plaque on MR Angiography and Acute Ischemic Stroke. *JACC Cardiovasc Imaging*. 2016;9:1228–1229. [PubMed: 26897689]

12. Hyafil F, Schindler A, Sepp D, Obenhuber T, Bayer-Karpinska A, Boeckh-Behrens T, et al. High-risk plaque features can be detected in non-stenotic carotid plaques of patients with ischaemic stroke classified as cryptogenic using combined (18)F-FDG PET/MR imaging. *Eur J Nucl Med Mol Imaging*. 2016;43:270–279. [PubMed: 26433367]
13. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med*. 2017;377:1319–1330. [PubMed: 28844192]
14. Sharma M, Hart RG, Connolly SJ, Bosch J, Shestakovska O, Ng KKH, et al. Stroke Outcomes in the COMPASS Trial. *Circulation*. 2019;139:1134–1145. [PubMed: 30667279]
15. Jickling GC, Stamova B, Ander BP, Zhan X, Liu D, Sison SM, et al. Prediction of cardioembolic, arterial, and lacunar causes of cryptogenic stroke by gene expression and infarct location. *Stroke*. 2012;43:2036–2041. [PubMed: 22627989]

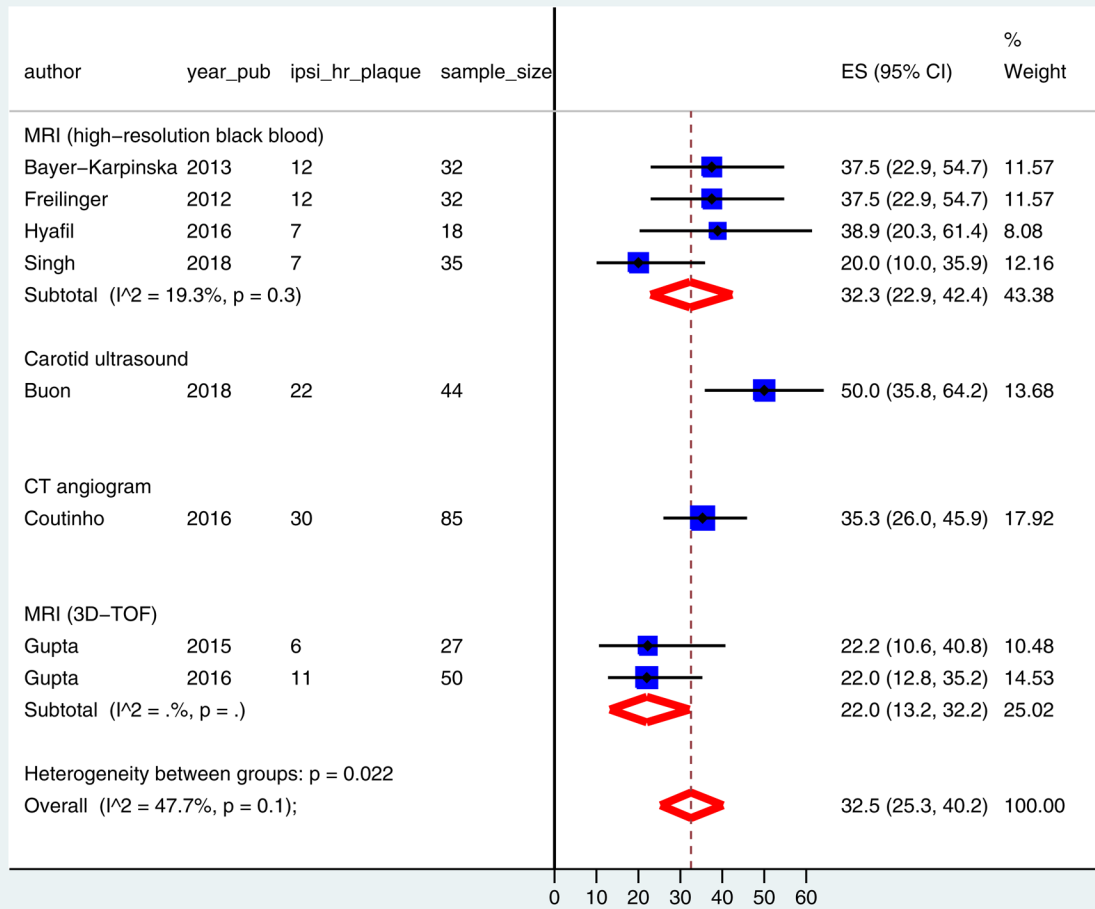


Figure 1: Prevalence of ipsilateral carotid plaque with high-risk features in ESUS
 3D-TOF = 3-dimensional time of flight, CI = Confidence interval, CT = Computed tomography, ES = Effect size, ipsi_hr_plaque = ipsilateral carotid plaque with high-risk features, MRI = Magnetic resonance imaging, sample_size = number of participants in the study, year_pub = year of publication

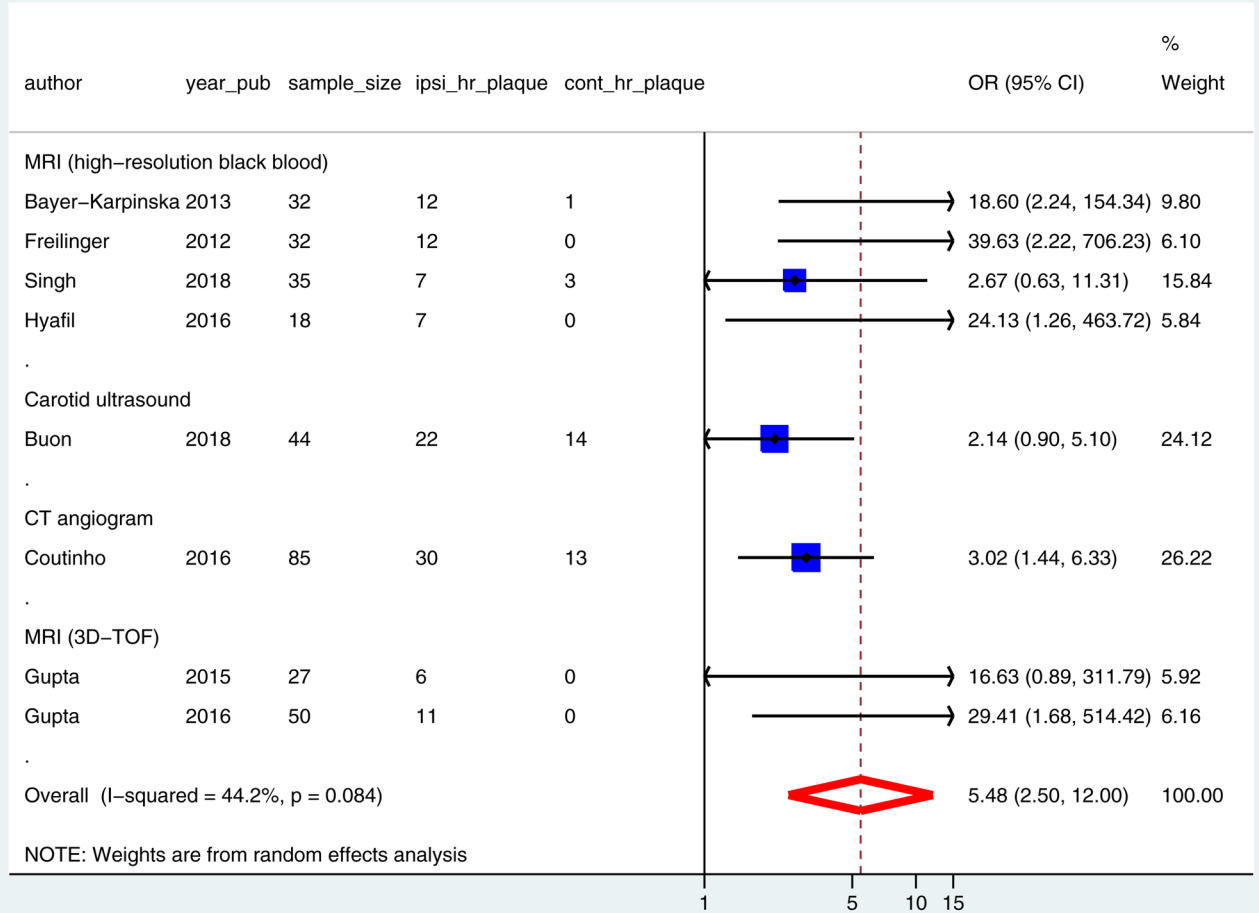


Figure 2: Odds-ratio of finding plaque with high-risk features in the ipsilateral versus the contralateral carotid in ESUS

3D-TOF = 3-dimensional time of flight, CI = Confidence interval, CT = Computed tomography, cont_hr_plaque = contralateral carotid plaque with high-risk features, ipsi_hr_plaque = ipsilateral carotid plaque with high-risk features, MRI = Magnetic resonance imaging, OR = Odds ratio, sample_size = number of participants in the study, year_pub = year of publication

Characteristics of the included studies

Table 1:

PMID	Author	Year	Sample size	Age (mean)	Age (median)	Women %	HTN %	DM %	Smoking %	DLP %	CAD %	Plaque imaging	Imaging delay (days)	High-risk features	ROB
24330333	Bayer-Karpinska [5]	2013	32	NA	74	32	72	22	49	28	22	MRI (HRBB)	< 7	ulceration, intraplaque hemorrhage, thrombus	9
29307510	Buon [6]	2018	44	NA	46.5	43	14	2	59	16	NA	Carotid US	NA	ulceration, echolucency, thrombus	9
27412144	Coutinho [7]	2016	85	NA	70	52	60	28	NA	34	20	CTA	< 10	plaque thickness 3 mm	10
22498329	Freilinger [8]	2012	32	71.7	NA	31	59	22	63	47	22	MRI (HRBB)	5.8	ulceration, intraplaque hemorrhage, thrombus	10
26077590	Gupta [9]	2015	27	71	NA	48	78	22	4	56	11	MRI (3D-TOF)	2.6	intraplaque hemorrhage	8
29571754	Singh [10]	2018	35	74.3	NA	54	74	29	6	80	49	MRI (HRBB)	NA	intraplaque hemorrhage	9
26897689	Gupta [11]	2016	50	69.5	NA	50	NA	NA	NA	NA	NA	MRI (3D-TOF)	1	intraplaque hemorrhage	9
26433367	Hyaifi [12]	2016	18	70	NA	63	72	22	17	28	22	MRI (HRBB)	< 14	fibrous cap rupture, intraplaque hemorrhage, thrombus	9

3D-TOF = 3-dimensional time of flight, CAD = Coronary artery disease, DLP = Dyslipidemia, DM = Diabetes mellitus, HRBB = High-resolution black blood, HTN = Hypertension, MRI = Magnetic Resonance Imaging, NA = Not available, PMID = PubMed accession number, ROB = Risk of bias score (maximum 10, 8–10 = low risk of bias/high-quality, 5–7 = moderate risk of bias/moderate quality, 4 = high risk of bias/low quality), US = Ultrasound